Foreword: Child Lung Health—A Global Priority

Respiratory disease is the major cause of childhood mortality and morbidity worldwide. The spectrum of disease ranges from infectious diseases like pneumonia, bronchiolitis, and tuberculosis to non-communicable diseases like asthma and chronic respiratory illnesses. The overwhelming burden of childhood respiratory disease and associated deaths occur in low and middle-income countries, where appropriate resources to prevent, diagnose and manage such diseases are often unavailable. In the last decade there have been encouraging advances in reducing childhood mortality and achieving the Millennium Development Goal 4 (which aims for a two thirds reduction in under-5 mortality by 2015 from mortality levels in 1990). Nevertheless, 6.5 million children still die each year before their fifth birthday, with approximately 20% of deaths due to pneumonia. Other associated respiratory causes of death such as pertussis, neonatal respiratory diseases and HIV-associated lung disease further contribute to mortality. Recent data suggest that nearly 1 million children acquire tuberculosis annually. Further, even in high income countries, where such infections have been effectively prevented and reduced, childhood respiratory diseases are a major cause for health care utilization and of chronic illness. As childhood mortality declines, so there is an emerging global focus on non-communicable diseases and morbidity. Importantly asthma is the commonest non communicable disease in children and adolescents globally.

The International Congress on Pediatric Pulmonology (CIPP) represents the main global meeting devoted solely to child lung health. It is therefore fitting that the abstracts for the 13th International Congress on Pediatric Pulmonology (CIPP XIII) are presented in this edition of Pediatric Pulmonology that has now expanded its focus to include global child lung health issues. These abstracts will be presented at the congress from June 26 to 29, 2014 in Bruges, Belgium. Reflecting the content of this global congress, the abstracts cover diverse areas of child lung health including physiology, neonatology, clinical science and laboratory based studies of childhood respiratory diseases from investigators around the world. The abstracts also reflect the divergent state of child health in high and low or middle income countries with unique challenges in different settings.

Child lung health remains an urgent and pressing priority globally. These abstracts and the conference offer the opportunity for considering child lung health in its global context, to further develop collaborations and to become stronger advocates within our own health systems to ensure that such global inequities are voiced and addressed. We have much work to do to advance child lung health globally and much to learn from each other, and CIPP can provide an excellent framework in which to do this.

—HEATHER ZAR
President CIPP XIII

PETR POHUNÉK
Chair, Science committee CIPP XIII

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Tobacco wars: the fruits of the victor

This presentation will review a personal selection of ten articles from 2013 onwards set in the context of other work. The focus is on papers addressing the long-term respiratory sequelae of extreme prematurity are well described, but the problems of the late pre-term are under-appreciated. Babies born at 33–34 weeks have airflow obstruction persisting into the teenage years, to a similar degree as 25–32 weekers. 44,173 women in Finland delivered 2661 babies between 1989 and 2008. Asthma was diagnosed in the children if they had a certificate of the diagnosis from a doctor and had been reimbursed for asthma medications [3]. There was an increased risk of asthma even in “early term” (37–38 weeks), with a stepwise greater risk for the late preterm (33–36 weeks) and the moderately (<32 weeks). We cannot be sure what the airway disease is from this manuscript, and we know that in BPD survivors the evidence for airway inflammation is minimal. Nonetheless, there are a lot of babies born just before term; look out for ongoing respiratory morbidity into adult life.

Is it asthma, Dr? What is the airway disease in Sickle cell disease (SCD)? Respiratory disease and a diagnosis of asthma are both common in SCD, but as is often the case, the diagnosis of asthma may be given out with more liberality than thought. Fifty SCD children who had previously been shown to have only minimal evidence of pulmonary vascular disease were shown to have obstructive spirometry compared to ethnic and age-matched controls [4]. However there was no difference in bronchial responsiveness or eosinophilic inflammation, at least as judged by exhaled nitric oxide, between the two groups, suggesting that another cause for airway disease must be sought. For sure, inhaled corticosteroids (ICS) should not be dispensed without careful thought to SCD children.

Inhaled steroids: a price to pay? But surely this is a lot of fuss about nothing? ICS are very safe, so if they are a little bit overprescribed, does it matter? We all know that high dose systemic steroids are immunosuppressive, and that asthma is a complex disease of multiple factors. The duration of the ill effects of SCD is not. The Brisbane group [2] reported the 14 year follow-up of 1129 SCD children in Western Australia. Long-term respiratory sequelae were common, and air leaks were common and there no response to treatment. Eighty (58%) had a history of household contact; and HIV status. Adding T-SPOT to chest radiography and tuberculin skin testing racked up costs but did not add diagnostic value. A really important message for high TB burden, low resource parts of the world.

I. INVITED SPEAKERS

I - Asthma and Allergy

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All I want is the air that I breathe: chILD This manuscript [7] reported on a novel interstitial lung disease (ILD) from Korea (there are also reports in adults). There were 138 cases between 2006 and 2011, with an increasing annual incidence. The mean age at presentation was 30.4 months, and symptoms were cough and fever for more than 2 weeks, night sweats, malaise and a history of household contact; and HIV status. Adding T-SPOT to chest radiography and tuberculin skin testing racked up costs but did not add diagnostic value. A really important message for high TB burden, low resource parts of the world.

Do old dogs need new tricks: Tuberculosis diagnosis in a resource poor area Continuing the theme of maybe the old being better, a manuscript from South Africa [6] examined whether T-spot added value to the diagnostic pathway of TB in 491 smear negative children. Culture confirmed TB was most associated with cough and fever for more than 2 weeks, night sweats, malaise and a history of household contact; and HIV status. Adding T-SPOT to chest radiography and tuberculin skin testing racked up costs but did not add diagnostic value. A really important message for high TB burden, low resource parts of the world.
such mild changes that most cannot be scored reproducibly [8]. This work sets a benchmark for the results of screening for CF, and also emphasises that (a) scoring systems suitable for moderate and severe disease may not apply to mild, and (b) it is essential to show that scoring is reproducible before introducing it as a clinical tool.

Another orphan: lung attacks and bronchiectasis “Exacerbation” has long been the expression used to describe an acute deterioration of a respiratory disease. This feeble phrase implies that these are benign and reversible, whereas “lung attacks” are in fact associated with a permanent decline in the context of many diseases including asthma and CF, and the prevention of lung attacks is seen as a priority and an end-point in clinical trials. Nearly 100 indigenous children with bronchiectasis were randomised to once weekly azithromycin (30 mg/kg) or placebo for 12–24 months [9].

The azithromycin treated children had a halving of bronchiectasis lung attacks (95% confidence intervals 0.35–0.7) albeit at the expected cost of increased macrolide resistance. This manuscript firmly establishes the role of azithromycin in those children with bronchiectasis requiring repeated courses of antibiotics.

To sleep, perchance not to wake up Snoring children have long been seen as a subject of mirth, but a recent paper highlights the morbidity and even mortality associated with paediatric sleep disordered breathing [10]. 2,998 children aged 0–19 with OSA were matched with 11,974 controls. There was increased morbidity in in a large number of organ systems in the three years before diagnosis, and a five year death rate of 70/10,000 for OSA compared with 11/10,000 for controls. We must do more to identify and treat these children from all over the world.

References

PREDICTORS OF ASThma IN YOUNG CHILDREN IN low AND MIDDLE income COUNTRIES

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The ISAAC phase-III study, 5–10 years interval from ISAAC phase-I, showed that asthma prevalence has peaked, and possible even begun to decline, in Western countries, whereas increases in prevalence are now occurring in many low and middle income countries where prevalence was previously low. For example, prevalence had increased by 0.16% per year in Africa, 0.32% per year in Latin America, and 0.07% per year in the Asia Pacific region, and prevalence had decreased by 0.07% per year in Western Europe. The ISAAC phase-II study reported that the fractions and prevalence of wheeze attributable to skin test reactivity were strongly associated with gross national income per capita (GNI), and the strength of the association between current wheezing and skin test reactivity increase with GNI.

The hygiene hypothesis had gained considerable support from researchers’ worldwide trying to explained asthma prevalence. However, at most one-half of asthma cases appear to be through allergic mechanisms; whereas the global increases in asthma prevalence appear to involve both allergic and non-allergic asthma. The declined prevalence observed in some European countries do not means that these became less clean countries. As we are going to describe below, for example asthma prevalence in Latin American countries (which appear unlikely to have lower infection rates or less exposure to microbe than European countries such as Spain or Portugal, which share the same language) has different risk factors to those involved in the hygiene hypothesis (generally explained by having protective effect of early exposures resulting in long-lasting health benefits). However, it is important to express that long-term continue exposure may be required to maintain an optimal protection.

A potential explanation of the high asthma prevalence in Latin America is that many asthma cases are non-atopic. A population-based cohort in Salvador, Brazil (n = 1445 children aged 4 to 11 years) showed that factors associated with wheezing in non-atopics were low maternal educational level (adjusted OR 1.49, 95%CI [0.98 to 2.38]), low frequency of room cleaning (2.49, [1.27 to 4.90]), presence of rodents in the house (1.48, [1.06 to 2.09]), and day care attendance (1.52, [1.01 to 2.99]). Recently, the same group reported that presence of minor psychiatric disorders in the mothers was significantly associated with the presence of asthma in the children, and this association was consistent with both atopic (1.72, [1.1 to 2.6]) and non-atopic asthma (1.7, [1.2 to 2.3]). Another population-based cross-section survey of 1132 children aged 6 to 59 months in Sao Paulo, Brazil reported prevalence recent wheezing of 12.5% (93% of these had medical diagnosis of asthma); and the risk factors identified were low income and conditions associates with poverty e.g. poor housing (3.10, [1.7 to 5.8]), low birth weight (1.93, [1.1 to 3.3]) and parasitic infections (2.84, [1.4 to 5.7]). In contrast, a population-based cohort in Cuba (n = 1042 children aged 4 to 14 years) showed that a family history of atopic diseases (2.19, [1.2 to 4.0]), and marginally allergic sensitization (1.83,[0.9 to 3.6]) and antibiotics use during the child’s first year of life (1.66, [0.89 to 3.11]) were predictors of the development of asthma. But poverty-related factors, such as low income and education and parasitic infections did not. In Esmeraldas, Ecuador, a cross study of 6821 schoolchildren living in tropical urban and rural areas showed no significantly greater prevalence of atopy, wheeze and eczema symptoms in urban versus rural samples. And a small proportion of symptoms were attributable to atopy (range 3.9

Pediatric Pulmonology
to 10.7%). Wheeze was associated with lack of access to potable water (1.44, [1.2 to 1.8]) and with birth order 3rd vs. 4th (0.75, [0.6 to 0.9]); but not with having pets, assist to day-care, father engaged in agriculture, farm animals and helminths.5

However, for clarifying the predictors of asthma in young children, the best way to do is through birth cohort studies. Unfortunately, few of them were conducted in low or middle-income countries. In Sao Paulo, Brazil, 144 infants from low-income families, at risk of asthma, were enrolled at birth. At 30 months, 51.5% had recurrent wheezing (3 or more episodes in the past year). Respiratory infection was strongly associated with recurrent wheezing (6.67, [1.96 to 22.7]), whereas exclusive breastfeeding for at least 1 month was a protective factor (0.009, [0.01 to 0.51]).4 In Cartagena, Colombia, 326 infants from low-income community living in the tropics under limited sanitary conditions and exposed to mites and helminth allergens were enrolled. Prevalence of recurrent wheezing (3 or more episodes in 12 months) was 17.5% at 6 months, 31% at 12 months and 38.3% at 24 months. Maternal asthma was the only prenatal factor associated with recurrent wheezing episode (4.42, [1.5 to 13.4]).5 Study from this same birth cohort reported that high cord blood total IgE was positively associated with higher Blomia tropicalis and Ascaris-specific IgE values during lifetime, but protected from recurrent wheezing (0.26,[0.08 to 0.88]). While, home dust mites or Ascaris sensitization showed no association with recurrent wheezing.6 Similarly, a birth cohort in Tanzania (n = 673), a tropical underdeveloped country, showed that total IgE in cord blood is a protective factor for current wheezing at four year of age (0.24, [0.07 to 0.85]). However, parasite in cord blood (10.2, [2.5 to 42.2]), maternal asthma (14.3, [3.5 to 58.1]), lower respiratory tract infection per each episode (2.70, [1.1 to 7.0]) and number of resident in household (1.12, [1.0 to 1.4]) were risk factors for persistent wheezing (having wheeze both at 18 months and 4 years). The reported prevalence of wheezing at 18 months was 22%, current wheezing at 4 years was 14% and frequent wheezing at 4 years (3 or more episodes) was 6.2%.9

Recently, a multicentre, cross-sectional, international, population-based study (EISL study) from 11 centres (n = 23624 infants) in Latin America (Chile, Brazil, Colombia & Venezuela)10 showed 23.7% of prevalence of recurrent wheezing (3 or more episodes) during the first year of life. The risks factors were: male (1.44, 95%CI [1.3 to 1.6]), parental asthma & rhinitis (1.91, [1.7 to 2.2] & 1.47,[1.3 to 1.7], respectively), infant eczema (1.66,[1.5 to 1.9]), maternal smoked in pregnancy (1.44,[1.2 to 1.7] ) , colds during the first 3 months of life (3.13,[2.6 to 3.1]), attended nursery school (2.5,[2.0 to 3.1]), mould stains on household walls (1.36, [1.2 to 1.6]), Afro-American ethnicity (1.26,[1.12 to 1.42]), per additional sibling (1.05,[1.0 to 1.1]) and person at home (1.04,[1.0 to 1.1]). And the protective factors were: university studies in mother (0.80, [0.7 to 0.9]) and exclusive breast feeding > 3 months (0.8, [0.7 to 0.9]). However, variability occurred among centres and within a single country, suggested influence of regional or local environmental/ecological factors as a plausible explanation for the variation found in the magnitude of those risk/protective factors. The highest population attributable fraction for recurrent wheezing were having colds during the first 3 months of life (25%, [23.1 to 27]) and infant eczema (15.8% [13.4 to 18.1]).10

Finally, it seems that as a result of the “package” of changes occurring early in the intrauterine and infant environment due to “Westernization” and/or “native” style of life in low and middle income countries increased the susceptibility to development allergic and non-allergic asthma. Many elements of this “package” (e.g. changes in maternal diet, smoke during pregnancy, increased fetal growth, smaller family size, increased or reduced maternal and infant infections [parasitic, viral and bacterial]), and the increased use of antibiotics/paracetamol/immunization) have been inconsistently associated with an increased risk of childhood asthma; probably because none of them could explain by itself the increase in asthma prevalence.

More research, especially large birth cohorts and studies involving the mechanistic (e.g. endotyping) of atopic and non-atopic asthmatics children need to be done in low and middle-income countries in order to find the predictors that could be modified through public politics.

References


ALLERGEN IMMUNOTHERAPY IS USEFUL IN THE TREATMENT OF CHILDHOOD ASTHMA

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Allergen specific immunotherapy can be considered an evidence based intervention for seasonal allergic rhinitis with pollen extracts applied subcutaneously or sublingually, as well as for insect venom allergy. (1.2,3) Unfortunately the evidence for efficicency in allergen driven asthma in both children and adults with sensitization to house dust mites and animals (cats and dogs) is less convincing. A variety of trials in allergic asthma have reported encouraging results, which led to Cochrane-metaanalyses concluding, that this intervention should be considered as effective. However, one of the problems with published metaanalyses is some confusion about endpoints related to asthma and a lack of consensus, there may also be a relevant publication bias. (4) Two years ago a German trial involving children as well as adults randomized for immunotherapy with house dust mites was able to demonstrate a steroid sparing effect of this intervention. (5) Seasonal allergic rhinitis in young children can be considered as a prodromal state of allergic asthma. Taking this into account subcutaneous immunotherapy with pollen allergen was applied in a large cohort of children with exclusive nasal, but no bronchial symptoms (PAT-study). After three years of immunotherapy the incidence of asthma was reduced by
50%, and it was demonstrated that this intervention effect remains stable for a whole decade. (6)

Currently a preventative trial with a grass pollen tablets (GAP-study) is still ongoing.

Since allergen specific immunotherapy has been demonstrated to be the only disease modifying intervention in allergic rhinitis it has been proposed that early intervention in preschool-age might turn out to be an effective intervention for secondary prevention of allergic asthma.

References


ALLERGEN IMMUNOTHERAPY IS USEFUL IN THE TREATMENT OF CHILDHOOD ASTHMA (CON)

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Although numerous trials have assessed the efficacy of allergen immunotherapy (AIT) for allergic rhinitis, few have been designed specifically to determine the impact of AIT on associated asthma. There are no trials in children that have been designed or powered specifically to look at the effect of AIT on asthma control or lung function as a primary outcome. Therefore, at present, with the current evidence base, it is not possible to determine whether AIT is useful for the treatment of childhood asthma.[3]

Potential benefits of AIT for the management of childhood asthma

One of the largest limitations of currently available asthma therapies is that they are not disease modifying. Inhaled steroids form the mainstay of therapy and do achieve symptom and disease control in the majority of children with allergic asthma. However, symptoms recur, exacerbations increase and lung function drops when treatment is stopped. In contrast, there is evidence to suggest that grass AIT in adults with moderate to severe grass pollen induced rhinoconjunctivitis with or without asthma is disease modifying[5]. The improvement in symptom scores 2 years after immunotherapy had been stopped was significantly better for the active group for rhinoconjunctivitis and in the sub-group that had asthma. However, this trial did not set out to show efficacy of immunotherapy in patients with asthma, the data for asthma formed a post-hoc analysis. In addition, this is data from an adult trial, and very few children with asthma are mono-sensitised to grass pollen, thus questioning the number of patients who would benefit.

Current data for the use of AIT in asthma

Although the data to date suggests allergen immunotherapy may be beneficial in paediatric asthma, this is based predominantly on data derived from results of current trials that have included children with and without asthma and seen benefit in both sets of patients. Both grass pollen and house dust mite (HDM) AIT have been investigated, but well designed, large studies exploring subjective and objective outcomes in asthma are needed. There is currently insufficient evidence for the effectiveness of HDM-sublingual immunotherapy (SLIT) in treating rhinitis or asthma in either adults or children. The GINA (Global Initiative for Asthma) guidelines state that the role of AIT in adult asthma is limited (and should be considered only after environmental measures and failure of pharmacological treatment), owing to the modest benefit compared with other treatment options, weighed against the risk of adverse events and the inconvenience of a prolonged course of injections for subcutaneous immunotherapy (SCIT). If 16 patients are treated with SCIT, one would be expected to develop a local adverse reaction (wheal and itching at the injection site), and if nine patients are treated, one would be expected to develop a systemic reaction of any severity (rash, wheezing and breathlessness). The implication is that patients must be observed long enough to deal with any major systemic reactions (typically within 30–45 min) and adequate resuscitation equipment and medications must be promptly available[3].

A recent proof of concept trial including 602 individuals to determine whether treatment of asthmatic patients allergic to HDM with sublingual immunotherapy can reduce the need of inhaled corticosteroids revealed promising preliminary results: a positive therapeutic effect on asthma control was demonstrated by a reduction in the dose of inhaled budesonide (mean: >80 mcg/day) for the active group compared with the placebo after 1 year of daily treatment. Overall, SLIT treatment was well tolerated, and only mild-to moderate local reactions were reported[8]. An ongoing study will be able to establish whether HDM SLIT can reduce the frequency and the time to first exacerbation after ICS reduction.

A limitation of assessing the efficacy of AIT in asthma is the consensus exists concerning the optimal endpoints, should they be asthma symptoms, use of medications, the number of asthma exacerbations, asthma-free days and/or lung function. As a consequence, to date, objective measurements have only rarely been recorded in trials, it is therefore not possible to provide fully evidence based answers relating to the role of AIT in asthma alone. Importantly, the majority of trials that assess the efficacy of AIT include only mono-sensitised patients. While most children with asthma, and certainly the majority of children with severe asthma, are poly-sensitised and have very severe sensitisation[5]. These are the patients that are clinically most in need of novel therapeutic approaches since they remain symptomatic despite maximal steroid therapy, yet there are no trials of efficacy in severe disease, and no convincing data of efficacy in multiple sensitization. In fact, almost all of the large surveys conducted in the United States have indicated that severe or uncontrolled asthma is the most important and independent risk factor for both non-fatal and fatal adverse reactions to AIT[9]. This suggests the group of children with asthma most likely to benefit and most in need of AIT would not even be eligible. Not only is multiple allergen sensitisation an issue, but perennial symptoms also cause difficulty. In children with perennial asthma, benefit from AIT has been much less easy to demonstrate. Small studies have demonstrated some benefit in pollen and animal dander allergy[1].

A recent meta-analysis restricted to children reported moderate effectiveness of sublingual immunotherapy on asthma symptoms and medication intake[8]. However, concerns were raised about shortcomings in the robustness of the systematic review, mainly because of substantial inter-study heterogeneity and because older randomized controlled trials had limitations in adequate sample size and methodology[9,10].

Summary

Much of the data relating to the clinical effectiveness of AIT in asthma, comes from open controlled or observational small studies. The variability of route of administration, patient selection, treatment duration and regimens among the studies is another major issue that affects the overall interpretation of results. More robust and adequately sized studies, specifically addressing asthma endpoints, are currently underway for HDM tablets; however, future research needs to extend to all other relevant allergens (grass, birch, ragweed, HDMs, cat and alternaria) in order to detect
eventual allergen-dependent differences in the expected clinical benefit. Evaluation of exacerbation rates in combination with objective outcomes such as pulmonary function, airway hyperresponsiveness and immunological changes is anticipated to be a key prerequisite in future research, as current data are inconsistent.

References


WHAT DOES THE PEDIATRIC PNEUMOLOGIST NEED TO KNOW ABOUT ALLERGY?

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Natural history of allergic airway diseases

For the last decades it has become increasingly clear, that chronic diseases like allergic rhinitis and asthma are not only associated, but preceded by allergic sensitzations and may be triggered by allergen exposure. During the first decade of life the incidence of skin or airway manifestations, their persistence as well as their remittance are considered as part of the “Allergic March”, which is characterised by the development of IgE-sensitizations to food, indoor and outdoor allergens. Early sensitization of children to indoor allergens like cats or house dust mites has been demonstrated to be a risk factor for persistent asthma and impaired lung function at school-age. (1,2,3,4,5)

Comorbidities

In most countries the majority of asthmatic children express atopic comorbidities (eczema, food-allergy). Their prevalence follows a characteristic sequence and it has been demonstrated, that infantile eczema predicts the later incidence of allergic asthma. (6,7)

Cross sensitization

Immunological cross reactivities may be relevant for certain fruit/vegetable and pollen allergens. Therefore as part of the diagnostic workup in asthmatic children specific allergy tests (skin-test and specific serum IgE-test) should always be considered and made available for every pediatric pneumologist.

Avoidance of allergens

As part of a therapeutic strategy for allergic asthma, complete allergen avoidance may have profound effects on the short and long term outcome of the disease and therefore should be considered as a first treatment of choice, even if complete elimination completely difficult to achieve. (8)

Immunotherapy

Allergen immunotherapy as a treatment of allergic asthma remains controversial and is not accepted in many treatment guidelines. However, immunotherapy to indoor allergens has been found useful in some trials. Clearly, more evidence should be provided on subgroups of patients where this intervention might be beneficial.

Biologicals of the future

During the next years new therapeutic tools for pathogenesis oriented interventions with a variety of biologicals beyond anti-IgE are expected to be available for asthmatic children and adolescents. The rationale for their application is a better understanding of the pathogenesis of allergic airway diseases which has been established during the past two decades. For pediatric Pneumologists it will be necessary to understand the immunological background of allergic sensitization in infancy and childhood in order to develop more targetted treatment in strategies for children with allergic airway diseases. (9,10)

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WHAT IS THE ROLE OF ALLERGY IN UPPER AND LOWER AIRWAY DISEASE

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Introduction

Allergy is classically considered to result from an IgE-mediated reaction associated with a cellular inflammatory and immune response of variable...
intensity [1]. However, at airway level, it is now also realized that some allergens, because of their enzymatic activity, may directly activate structural and inflammatory cells and, with the release of proteases and oxygen species, produce injury to the respiratory structures. The mechanisms involved in allergic reactions are multifaceted and although histamine, released by mast cells and basophils, is still recognized as one of the major effectors, many other mediators produced by inflammatory and immune effector cells, but also by structural cells are involved. These include cytokines, chemokines, neuropeptides and growth factors that may co-operate in a complex network, in different ways in the upper and lower airways, provoking symptoms and, eventually, complications. Crucial points of interest are the potential mechanisms by which allergic rhinitis and its associated conditions may interact. Indeed, it has been proposed that these relationships are consistent with a “united airway” model of respiratory disease [2]. In this integrated system the pathophysiological mechanisms that characterize the allergic reaction can affect the entire airspace, i.e. the nose, the sinuses, the middle ear, the nasopharynx and the lungs. Consequences of the integrated system are that, as compared with the general population, patients with allergic rhinitis should show a higher prevalence of lower respiratory disease, such as asthma, but also of disorders affecting sinuses, middle ear, nasopharynx. Similarly, patients with allergen-induced lower respiratory tract disease should have an increased prevalence of upper airway disorders and finally interventions directed at one component of the unified space should influence symptoms at the other components.

Allergic rhinitis and asthma: similarities and differences

Although the prevalence of allergic rhinitis and asthma varies all over the world, and allergic rhinitis is generally twice as prevalent as asthma, many epidemiologic studies have confirmed the link between the two conditions both in children and adults [1,3-4]. The structural characteristics of the nose and the bronchi are very much alike and allergic rhinitis and asthma are characterized by a similar inflammatory pattern, in which eosinophils, mast cells and T-lymphocytes are the predominant cells. However there are also significant functional and structural differences: a) acute nasal obstruction in allergic rhinitis is mostly the result of capillary vessel dilatation, while in asthma acute bronchial obstruction is mostly induced by smooth muscle contraction; b) there is a relative absence of myofibroblasts in the mucosa of allergic rhinitis patients while these cells are increased in the bronchial mucosa of asthmatic patients; c) in contrast to what happens in the bronchi of asthmatic patients, collagen deposition is not a typical feature of the upper airways in patients with allergic rhinitis [2].

Naso-bronchial interactions in allergic rhinitis and asthma

An important question is to what extent airway inflammation and hyperreactivity present in allergic rhinitis and asthma are due to the contemporary exposure to the allergens, to a systemic response or to naso-bronchial interaction. Experimental studies in patients with allergic rhinitis showed that nasal allergen provocation induced not only nasal but also bronchial symptoms, increased expression of adhesion molecules (ICAM-1 and VCAM-1) in nasal and bronchial mucosa and decreased peak nasal inspiratory flow and peak expiratory flow [5]. Elevation of the number of blood eosinophils and of serum IL-5 concentrations was also found after nasal allergen provocation, prove of a generalized airway inflammation through upregulation of adhesion molecules [5]. The inverse experiment, i.e. segmental bronchial instillation of allergen in patients with allergic rhinitis, induced bronchial and nasal symptoms, eosinophilic bronchial and nasal inflammation, reductions in pulmonary and nasal function, but also peripheral blood eosinophilia, reflecting again a “systemic” response [6]. Other mechanisms may explain the interaction between upper and lower airways in allergic patients. In allergic rhinitis, the nose can be obstructed with subsequent mouth breathing: the resulting reduced “filter” and “air-conditioning” functions of the nose may lead to inflammatory changes in the lower airways and increase in bronchial reactivity [2]. Aspiration of nasal secretions may stimulate pharyngo-laryngeal receptors and be responsible for a postnasal drip–related cough, but does not seem to have a contributory effect on naso-bronchial interaction in allergic patients [2]. Also neural naso-bronchial reflexes do not seem to explain the interaction between upper and lower airways. It is true that nasal provocation with allergen in patients with allergic rhinitis results in impairment of lower airway function [5], the temporal sequence of the events reflects a more delayed response than would be expected with a reflex induced by neural signals. Finally, the diffusion of the allergen in the blood after nasal inhalation challenge may induce an inflammatory reaction with elevation of IL-5 levels and increased numbers of eosinophils in blood, reflecting a generalized inflammatory reaction [5,6]. The role played by IL-5 in the migration of eosinophils toward the airway, together with the increased ICAM-1 and VCAM-1 expression by airway endothelium, could explain the influx of eosinophils that follows allergen challenge not only in the target organ but eventually also in other organs.

Other conditions associated with allergic rhinitis

Other conditions associated with allergic rhinitis are asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infections [1]. Some studies suggested that rhinosinusitis is a common complication of allergic rhinitis, however, there is no evidence of change in ostial patency or of increase in the incidence of purulent rhinosinusitis during the pollen season, that is present in similar proportions in patients with or without allergic rhinitis [1]. Experimentally, nasal instillation of allergens can produce mucosal oedema and sinus opacification; however, there is no prove that allergens deposited in the nose can reach the sinus cavities [1]. Allergy may be expected to result in inflammation and swelling of the nasal mucosa, leading to obstruction of the sinuses and acting as a precursor for both acute and chronic rhinosinusitis however, evidence is present only for the chronic and recurrent subtypes [7]. A relationship between allergy and polyposis has been presumed for many years but never firmly demonstrated. The prevalence of nasal polyposis in allergic patients is rather low and usually under 5%. No correlation has been demonstrated between positive skin prick tests and the number of repeat polypectomies, and, in another study, no association between the number of polypectomies in patients with at least one positive allergy skin test has been shown [1,8]. Finally, rhinitis and otitis media are common health problems and may appear together in a child but IgE-mediated allergic reactions represent only one aetiologic factor for otitis media, together with acute bacterial or viral infections [1,9]. There is a clear relationship between nasal allergic inflammation and otitis media, related to dysfunction of the Eustachian tube, but there is a difference in peak prevalence between these two conditions with respect to age distribution [10]. In addition, the middle ear mucosa itself is rarely a target tissue for allergic processes, although the biochemical mediators released during nasal allergic reactions may produce Eustachian tube edema and inflammation and, in some patients atopy may be responsible for the recurrence and maintenance of middle ear disease [1].

Conclusion

Allergic respiratory diseases and their associated disorders may cause significant morbidity with impaired quality of life in both young children and adolescents. They should be considered as part of a systemic allergic inflammatory process and should not be treated in isolation, with attention paid to comorbid disorders. A multidisciplinary approach, involving all pediatric specialists engaged in the diagnosis and treatment of allergic manifestations may be required to improve both patient care and quality of life and to prevent drug-related side effects, when long lasting treatments are necessary.

References

S8 Abstract


DIAGNOSTIC TESTS IN PAEDIATRIC ALLERGY

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Presence of IgE antibodies reflects a systemic immune response, which may or may not lead to the development of the symptomatic allergic disease. Consequently, within any population a proportion of “sensitized” individuals may have no symptoms of atopic disease (such as asthma, hay fever or food allergy). Similarly, in a proportion of sensitized, or “atopic” asthmatics, the presence of atopic sensitization may be just a chance finding which is not contributing to either presence or severity of their symptoms.

Defining allergic sensitization

Different levels of IgE antibodies and the size of the wheel on skin testing have been used as cut-offs to define the presence of allergic sensitization (e.g. >0.35 kU/L or >0.7 kU/L for specific IgE antibody levels; >0 or >3 mm in relation to negative control for a wheal diameter on skin prick testing), and the issue of what represents an optimal cut-off is a matter of considerable debate. We propose that labeling subjects as “atopic” or “non-atopic” based on largely arbitrary cut-off values may be an oversimplification of an atopic trait, which is not dichotomous in its’ relationship to either presence or severity of symptoms of allergic disease.1 For example, we have shown that the probability of asthma (both among pre-school children and young adults) increases with the increasing IgE antibody levels to inhalant allergens (mite, dog and cat), indicating that quantification of IgE-antibodies may improve confidence that sensitization has a role in the expression of symptoms.2,3 We observed similar quantitative relationships between the risk of allergic rhinitis in childhood and the level of IgE antibodies to grass pollen.4

Are there multiple phenotypes of atopy?

An additional level of complexity when interpreting “allergy tests” is added by our recent finding that atopy may have several different subtypes, with each subtype having different and unique association with symptoms of different allergic diseases.4 We applied a machine learning approach to all skin tests and sIgE data which we collected longitudinally from birth to school-age in our population-based birth cohort (Manchester Asthma and Allergy Study-MAAS), and identified four distinct subtypes of atopy.4 These subtypes (or phenotypes) of atopy were characterized by different patterns of responses to allergens (both with respect to the development of IgE response over time, and the IgE responses to different individual allergens). Most importantly, these different subtypes of atopy differed markedly in their associations with clinical disease such as asthma.4 These initial findings were subsequently validated in an independent birth cohort,5 suggesting that when investigating atopy, we need to incorporate allergen-specific patterns of IgE response and their developmental patterns (i.e. we need to take into account the diversity of specific IgEs, and the time component).6

Diagnostic tests in food allergy

Accurate diagnosis of food allergy is essential (but also challenging), and the oral food challenge remains the “gold standard” test. Skin prick tests and specific IgE tests to the whole food allergen extracts have low specificity, particularly in pollen-sensitised subjects. For example, based on the outcome of oral food challenge, we have recently shown that the majority of children who are sensitized to whole peanut extract do not have peanut allergy.7 Although ~10% of 8-year old children in our population-based birth cohort (MAAS) were sensitized to peanut using traditional tests (skin tests and/or sIgE to whole extract), only ~2% had clinical peanut allergy (i.e., ~8% were sensitized, but peanut-tolerant).7 Recent advances in biochemistry and molecular biology have led to isolation, characterisation and recombinant production of a number of allergenic proteins, which are increasingly used to investigate the IgE reactivity profile at the level of individual allergen components (in addition to or instead of the whole-allergen extracts). This new approach to allergy diagnosis has been termed molecular diagnosis, or component-resolved diagnostics (CRD). Such measurement of IgE responses to specific allergenic molecules may be more useful in predicting the presence (and perhaps severity) of true clinical allergy than currently used tests based on whole extracts. By using microarray CRD amongst peanut-sensitized children in MAAS cohort, we demonstrated marked differences in the component sensitization profile between peanut-allergic and peanut-tolerant subjects.1 Peanut-allergic subjects tended to have higher IgE to major peanut components Ara h 1–3; whereas the peanut-tolerant subjects had higher values to Cross-reactive Carbohydrate Determinant (CCD) and grass components Phl p 1, Phl p 4 and Phl p 5b. Peanut component Ara h 2 offered the best discrimination between peanut-allergic and peanut-tolerant subjects.1 In a follow-up study, we compared the diagnostic performance of sIgE levels to whole peanut extract and different peanut components (Ara h 1, 2, 3, 8 and 9) using the standard ImmunoCAP method.8 sIgE to Ara h 2 had the highest accuracy in differentiating between peanut-allergic and peanut-tolerant children, with cut-off of 0.35 kUA/L of Ara h 2 IgE conferring 100% sensitivity and 96.1% specificity. Using this cut-off point, 97.5% of subjects were correctly classified.8

Further studies from Europe, USA, and Japan have confirmed our findings that quantification of specific IgE to Ara h 2 may discriminate peanut allergy from tolerance (recently reviewed by Nicolau et al.).9 It is worth emphasising that due to the heterogeneity in component recognition patterns observed in different geographical areas, further studies are essential to identify and confirm potentially useful molecular diagnostic and prognostic markers for each geographic area and each age group. Until such markers are confirmed and, oral food challenge will remain the gold standard for accurate diagnosis.

High-resolution (multiplex) component-resolved diagnostics

Increasing availability of allergen components (either purified from the source or produced in recombinant form), has led to an expansion in the use of high-resolution multiplex CRD platforms in clinical practice. One such emerging technology is the ImmunoCAP® ISAC chip (Thermo Fisher Scientific), which measures specific IgE antibodies to >100 allergen components. We have recently reported that utilization of several linear and non-linear statistical learning models fit on ISAC® assay data may facilitate a more accurate assessment of allergic diseases such as asthma and rhinoconjunctivitis than currently used tests.10 However, our study has also identified that in order to fully capitalise on the potential of this exciting new technology, further improvements are needed in threshold ascertainment and/or value transformations for different allergen components, as well as carefully thought-out interpretation algorithms and selection of components.10

Pediatric Pulmonology
References

NOVEL THERAPEUTIC TARGETS FOR SEVERE-TREATMENT RESISTANT ASTHMA

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Monoclonal antibody therapies
The only evidence based novel treatment available for severe therapy resistant asthma (STRA) in children is the monoclonal antibody to IgE, omalizumab. There is good evidence to show it is effective in reducing acute exacerbations and hospitalization in children with moderate and severe asthma. However, this is when it is used as an adjunct to inhaled steroids. There is no convincing data in severe asthma to date that shows that it has an oral steroid sparing effect for those on maintenance oral steroids(3), although overall numbers of short courses of high dose oral steroids are reduced since exacerbations are reduced. Anti-IL-5 antibody therapy has been effective in reducing exacerbations in adults with severe asthma. However, no data is currently available in children. The DREAM trial which was a multi-centre double blind placebo controlled trial undertaken to determine the efficacy of mepolizumab in severe asthma did have an age-range of 12–75 years in the inclusion criteria(2). However, the mean age of subjects included was between 45 and 50 years, with a standard deviation of 10 years, suggesting few, if any children were actually recruited. Therefore this data, although showing a reduction in exacerbations, cannot be extrapolated to children. Paediatric STRA is characterized by pulmonary eosinophilia in both broncho-alveolar lavage and endobronchial biopsy(1), suggesting an antibody that can reduce eosinophil recruitment via blocking the action of IL-5 would be beneficial. But, the eosinophilia in children with STRA is present despite an absence of IL-5, thus the efficacy of such an agent in paediatric STRA is questionable(3).

Importantly, the criteria for eosinophilic airway inflammation in the DREAM trial included an elevated peripheral blood eosinophil count, or sputum eosinophilia or an elevated exhaled nitric oxide level. If these criteria were directly extrapolated and applied in a trial for children with STRA, recruitment would be very difficult, since we have shown that only a small proportion of children with STRA have elevated blood eosinophils(4), that the sputum inflammatory phenotype is not stable over time(5) and that there is little relationship between exhaled nitric oxide and either sputum or blood eosinophils(6). Therefore, although this novel therapeutic is available, its application in children with STRA is very uncertain. A monoclonal antibody directed against another T helper 2 cytokine IL-13 has also now been trialled in adults with severe asthma and been shown to improve lung function (FEV1), but only in those adults with a pre-defined treatment responsive immune signature(6). Patients that had a “Th2 high” phenotype, characterized by a serum biomarker, periostin, showed a clinical response to anti-IL-13 antibody therapy (lebrikizumab), but if all patients with severe refractory asthma were assessed together, the effect was lost. An important, although perhaps obvious, lesson that arose from studies of lebrikizumab was that not all patients even with severe refractory disease are likely to respond to the same treatments, but importantly it demonstrated that if IL-13 was not elevated, i.e. there was no evidence of a “Th2 high” signature, the therapy would not work. In a similar manner to this, we have shown that children with STRA do not have a “Th2 high” phenotype, since levels of IL-5 and IL-13 were not elevated in either broncho-alveolar lavage or biopsy in these patients. This emphasizing the very different underlying pathophysiology of disease in children compared to adults, and the importance of avoiding extrapolation of therapies designed for adult patients automatically to children.

The therapeutic targets for airway remodelling and steroid resistance in paediatric STRA
A limitation of current therapies for asthma is that they are not disease modifying. This may be because they do not effectively target underlying airway structural abnormalities, collectively termed airway remodelling. The main pathological abnormalities that are present in children with STRA include eosinophilic airway inflammation and airway remodelling, the latter is as severe as that seen in adults and established by school-age. There are two specific features of airway remodelling that are predominant in children with STRA, including increased thickness of the subepithelial reticular basement membrane and increased airway smooth muscle mass, and neither is affected by currently available therapies. Another important factor applicable specifically to severe therapy resistant asthma, is that symptoms persist despite prescribed high doses of inhaled, and frequently, maintenance oral steroid therapy. This occurs even when underlying modifiable factors such as adherence to therapy and allergen exposure have been addressed(5). However, there is little convincing evidence that the available novel monoclonal antibody therapies are significantly beneficial in their steroid sparing effects.

Vitamin D supplementation in paediatric STRA may impact smooth muscle mass and modulate steroid resistance
We have demonstrated that children aged between 6 and 16 years, with STRA have significantly lower levels of serum vitamin D than those with milder disease and age matched non-asthmatic controls(7). In addition, lower serum vitamin D levels correlated with lung function, and were inversely associated with symptoms and exacerbations. However, there was no relationship between underlying airway inflammation in either broncho-alveolar lavage or endobronchial biopsy, but intriguingly there was a negative correlation with airway smooth muscle mass. In children with STRA those with the lowest vitamin D levels had the most airway smooth muscle, and the most bronchodilator reversibility. These data suggest an association between smooth muscle, a feature of airway remodelling, and...


II - Pediatric Respiratory Infections

PROTRACTED BACTERIAL BRONCHITIS

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Protracted bacterial bronchitis (PBB) is a pediatric condition clinically defined as (a) the presence of isolated chronic (>4 weeks) wet cough, (b) resolution of cough with antibiotic treatment and (c) absence of pointers suggestive of an alternative specific cause of cough. While our original description1 included a criteria that required findings from bronchoalveolar lavage, we adapted the definition for clinical use.2 PBB has been officially recognized in chronic cough guidelines of many countries including the USA, Australia, Britain, Belgium, and China.
PBB is common among children seen in respiratory clinics. In a multicentre study in Australia involving 272 children newly referred for chronic cough, PBB was the most common (41.6%) etiology of the chronic cough.3 PBB is more common in boys and those who have attended child-care.4 Children with PBB are typically very young (median age ~2 years) and may have parent-reported wheeze. The reported ‘wheeze’ may actually be a rattle (reflective of airway secretions) and not a true wheeze.5 However, children with PBB may have co-existent asthma but in a prospective cohort study, we found that median peripheral blood eosinophils, total IgE and RAST testing for common allergens in children with PBB were similar to controls.6 The chest x-rays of children with PBB may be reported as ‘normal’ but usually show peribronchial changes (although in radiology studies, the reporting of peribronchial changes has poor agreement). In many children co-existent trachea-bronchomalacia7 is present although we found that no significant difference in the frequency of trachea-bronchomalacia between children with PBB and ‘non-PBB controls’ (children with respiratory symptoms but did not have PBB).8

Common respiratory pathogens found in the bronchoalveolar lavage (BAL) of children with PBB are H. influenza (mostly non-typable), S. pneumoniae and M. catarrhalis. In the original description of PBB,1 children who had the classical respiratory viruses detected by PCR were excluded, so as to obtain a ‘clean group’. More recently, using current definition, our prospective study showed that compared to controls, adenovirus was more likely to be detected on the BAL in those with PBB (OR 6.69, 1.50–29.80). Median CD56 and CD16 (natural killer T cells) cell levels in blood were elevated for age (0.7 x 109/L, IQR 0.5–0.9) in children with PBB.4 Thus it is likely, but
remains uncertain, that viruses play a role in the trigger and/or pathogenesis of PBB. Using the available clinical tests (immunoglobulin levels and responses to tetanus and *H. influenzae* type b vaccines), the adaptive immunity in children with PBB is normal. We have examined several aspects of innate immunity in children with PBB. The bronchoalveolar lavage (BAL) of children with PBB had marked airway neutrophilia and increased IL-8 and active matrix metalloproteinase-9 (MMP-9).7 Airway toll-like receptors (TLR)-2 and TLR-4 mRNA expression, as well as human β-defensin-2 and mannose-binding lectin levels were also elevated in children with PBB when compared to controls. In contrast, airway surfactant protein-A was not elevated and the ability of BAL cells to respond to various stimuli (lipopolysaccharide, lipoteichoic acid and polyinosinic-polycytidylic acid [poly(I:C)]) *in-vivo* were unlikely to be deficient. Children with PBB do not have an easily identifiable innate immune dysfunction but it remains unknown if those with recurrent PBB do. PBB is also characterised by increased IL-1β pathway activation in the BAL cells. IL-1β correlated with BAL neutrophilia, and the duration and severity of cough symptoms (unpublished).

In PBB, the child’s cough resolves only after a prolonged course (10–14 days) of appropriate antibiotics with resultant improved cough-specific and generic health related quality of life measures.3 Anecdotalexperience suggest that when shorter courses of antibiotics are used, the cough subsides but does not resolve and/or resolves but recures very quickly. Reasons for this are unknown but one postulate is that longer courses of antibiotics are required to overcome the bacteria associated with formation of biofilms, recently demonstrated in the BAL of children without cystic fibrosis or *Pseudomonas aeruginosa* infection.10 Some children with PBB have recurrent episodes (>3 per year) and some progress to chronic suppurrative lung disease. Thus, children with PBB should be clinically reviewed. Predictors of recurrence are currently unknown. Further, while chronic wet cough in children often signify PBB, wet cough could also be the marker of other conditions. Recurrent episodes of PBB and/or wet cough not resolving to simple therapies should prompt further evaluations of other causes of chronic wet cough (such as aspiration) as while most children with chronic wet cough have an airway infection, not all children do. The importance of wet cough in children relate to the implications of persistent endobronchial infection with the associated neutrophilic inflammation and the relationship with suppurrative lung disease. In a retrospective case series, we found that children who did not respond to a 4-week course of antibiotics were significantly more likely to have radiologically confirmed bronchiectasis, compared to those whose cough resolved (adjusted odds ratio 20.9; 95%CI 5.36–81.8).11 It is likely that PBB lies in a spectrum with radiological bronchiectasis at the other end of the spectrum, where on-going untreated infection and inflammation may cause irreversible airway and lung destruction in some people.

**References**


**EVIDENCE BASED MANAGEMENT OF VIRAL INDUCED WHEEZE IN THE YOUNG**

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The evidence base (such as it is) was summarised in the European Respiratory Society Task Force report [1], which was recently updated [2]. Although more evidence has accrued between the two reports, there are still considerable gaps in our knowledge. A recent practical approach has been proposed [3].

**Diagnostic Approach** Children with pre-school respiratory symptoms fall into one of four categories: normal child (the hardest diagnosis of all); significant diagnosis such as cystic fibrosis or tuberculosis (the differential will vary in different parts of the world); minor issues which may complicate or worsen wheezing syndromes, such as rhinitis or reflux; and a true wheezing syndrome (below). The first issue is to determine what noises are being described; the word wheeze is used very imprecisely by parents to describe a range of upper and lower airway sounds. Next a detailed history and physical examination is performed to alert the paediatrician to a possible missed diagnosis. For the vast majority of children, no further investigation is needed. If tests are performed they should be carefully targeted rather than adopting a scattergun approach.

**The normal child** There is often a lack of appreciation of the number and duration of viral colds in young children, in particular when first placed in a child care facility. 10% of pre-school children have more than 10 colds per year, and symptoms lasting more than two weeks with each are not uncommon. This succession of normal colds is all too often mis-interpreted as asthma or another unlikely diagnosis, and the child medicated with bronchodilators, inhalers and other therapies to which of course there is no response. I spend more time undiagnosing asthma in my practice than making this diagnosis.

**Phenotypes** Although epidemiological studies have taught us a huge amount about the natural history of wheeze, they do not, and never were intended to, guide the clinican about treatment options in the individual child. The proposed classification to inform treatment is:

- Episodic viral wheeze (EVW)—the child wheezes solely with (usually clinically diagnosed) viral respiratory tract infections, and is symptom-free between viral colds. This is not the same as transient wheeze—some of those retain an EVW pattern into late childhood.

*Pediatric Pulmonology*
Abstract

• Multiple trigger wheeze (MTW)—the child wheezes with viral colds, and also between colds with such triggers as excitement and allergen exposure. This is not the same as persistent wheeze—around 50% even of those with risk factors such as atopy lose their symptoms before school age.

This classification has been criticised because the phenotype in an individual may change over time, which is certainly true. However, there was never any intention to suggest that an individual child never changed phenotype, only that they could be used to guide treatment at the time the child was seen. The concept of changing treatment as the nature of the disease changes is, after all, commonplace in school age asthma. The lines of evidence giving external validity to this classification include that pure EVW (a) is not associated with airway eosinophilia, unlike MTW; (b) has less severe physiological disturbances than MTW; and (c) is associated with a much better prognosis for persisting symptoms in mid-childhood; indeed those with pure EVW in the pre-school age are no more likely to be or atopic or wheeze age 12 years than those who were symptom free in the pre-school years. Nonetheless it must be stated that this is a very crude classification, and we are in grave need of better biomarkers to guide therapy.

Treatment choices

We currently have no treatment which modifies the progression of pre-school wheeze to school age asthma, so a purely symptom based approach to treatment is justified. Both antihistamines and inhaled corticosteroids have been shown to be useless for this purpose. Before any treatment is started, the environment should be optimised, especially the effects of passive smoking eliminated. For EVW, before any treatment is started, the environment should be optimised, especially the effects of passive smoking eliminated. For EVW, treatment should be just at the time of symptoms. Options include Bronchodilators (β-2 agonists, anti-cholinergics) inhaled via a mask and spacer—and it is essential to ensure this is correctly used; intermittent leukotriene receptor antagonist; and intermittent ICS (e.g. Beclometasone 200 mcg bd). Some groups have advocated for the use of continuous ICS for pure EVW. There is no randomised controlled trial supporting this approach; however interval symptoms may be under-appreciated, and parents may realise after continuous ICS treatment that the child was more symptomatic than they realised. If continuous ICS are trialled, a small height decrement is to be anticipated [4] and the results should be monitored carefully. Children with MTW may benefit from continuous therapy, especially if there is a short term symptomatic response to short-acting β-2 agonists. A three-stage protocol is recommended, to avoid over-treating and wrongly labelling as asthmatic children with prolonged post-viral symptoms (Table). Whatever treatment approaches are adopted, critical is regularly to re-evaluate the child and the need for ongoing treatment, no matter who has commenced the therapy in the first place.

Traditionally, acute attacks of episodic viral wheeze in pre-school children have been treated with oral prednisolone. It is now clear that prednisolone is not useful in attacks so mild that admission to hospital is not necessary; and many preschool children admitted to hospital get better equally quickly whether or not they are treated with prednisolone. In the absence of a trial in really severe preschool wheeze, such children are likely to continue to be treated with systemic steroids, especially if they are close to admission to intensive care. However, it is clear that many unnecessary courses of prednisolone have been prescribed in the past.

Bronchiolitis

There are transatlantic differences in the use of this diagnosis; and therefore unsurprisingly, differences of opinion about treatment response. The UK definition is of an illness in a child less than a year of age, characterised by respiratory distress and showers of fine crackles on auscultation, quite different auscultatory findings from viral induced wheeze. In other parts of the world, episodes of viral induced wheeze have been labelled as bronchiolitis. Using the UK definition, bronchiolitis does not respond to any inhaled medications, and the very common prolonged post-bronchiolitis cough and/or wheeze also does not respond to any inhaled therapy. Leukotriene receptor antagonists also have no place. Recent trials of hypertonic saline have been negative. Management options have recently been summarised [5].

References


UNDERSTANDING DISTINCT RSV RELATED WHEEZING PHENOTYPES

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Respiratory syncytial virus (RSV) bronchiolitis is a major cause of childhood mortality and morbidity. Following malaria, RSV is the second most important cause of post-neonatal infant mortality. About 253,000 children die annually from RSV, virtually all in low income countries.1 About 10% of all children seek medical help for RSV bronchiolitis in the first year of life, about 1–2% of all children are hospitalized in the first year of life. Infected children at an increased risk for severe disease include children born prematurely with or without chronic lung disease as well as children with congenital heart disease, Down Syndrome or neuromuscular disease. The pathogenesis of RSV bronchiolitis is incompletely understood. Post-mortem studies show a paucity of mononuclear cells and bronchoalveolar lavages of mechanically ventilated children show a strong dominance of neutrophils. There are no effective treatments of RSV bronchiolitis. Potent anti-RSV antivirals are currently under development. When administered during the early phase of disease, perhaps in combination with immunomodulatory drugs, these drugs may improve the outcome of acute infection and decrease the risk of developing long-term airway disease.

Epidemiology shows that there are at least three wheezing phenotypes associated with RSV infection. First, during early infancy RSV bronchiolitis is characterized by the onset of upper respiratory tract symptoms in combination with signs of airflow limitation during infancy. Second, about half of children hospitalized for RSV bronchiolitis go on the develop recurrent episodes of wheeze during the preschool years. Post-bronchiolitis wheeze is a milder disease than RSV bronchiolitis, although associated with a general loss in health-related quality of life. Third, some studies report these wheezing episodes are the prelude to asthma at school age. Recently, Bacharier found in children with RSV bronchiolitis that 48% have an asthma diagnosis before age 7, and 35% percent has active asthma at age 7.2 However, the role of RSV in the pathogenesis of asthma remains unclear. Sigurs reported that RSV bronchiolitis is associated with subsequent persistent allergic asthma.3 Others were not able to confirm this.4,5 The three RSV-related wheezing phenotypes are characterized by distinct genetic mechanisms. RSV bronchiolitis is associated with variations in innate

Table three step proootocol for a trial of treatment in MTW

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<td>1</td>
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<td>2</td>
<td>Beclometasone or equivalent 200 mcg bd</td>
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<td>3</td>
<td>Discontinue therapy after 6-8 weeks</td>
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<td>If there has been no response, re-evaluate the diagnosis</td>
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<td>If symptoms have disappeared, you do not know if this is spontaneous or due to treatment</td>
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<td>3</td>
<td>Re-start therapy and titrate to lowest dose to control symptoms</td>
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Pediatric Pulmonology
immunity genes, such as Toll-like receptor (TLR) 4, IL-8, vitamin D receptor and vitamin D binding proteins. Post-bronchiolitis wheeze is associated with IL-10 production during RSV infection and variation in IL-10 family member genes, such as IL-19 and IL-20, which are known to be related to asthma. Asthma following RSV bronchiolitis is associated with family history of asthma and known allergy genes, such as IL-13. The relationship between RSV bronchiolitis and the development of subsequent recurrent wheeze, lung function abnormalities or asthma is a classical chicken or egg dilemma. RSV bronchiolitis and subsequent wheeze may be the result of a common predisposition, including genetic or pulmonary susceptibility (parallel hypothesis). On the other hand, RSV bronchiolitis may change the function of the immune system or the airways, perhaps by neutrophil-mediated damage of the airways causing recurrent wheeze, lung function abnormalities or asthma (serial hypothesis). These hypotheses are non-exclusive and likely co-exist. To conclusively determine the magnitude by which RSV infection contributes to recurrent wheeze, lung function abnormalities or asthma can only be addressed by intervention studies in which RSV infection is prevented. The MAKI trial is an investigator initiated study providing the first conclusive evidence of a causal relationship between RSV infection and recurrent wheeze in otherwise healthy late preterm infants. The trial enrolled 429 otherwise healthy children with prematurity 33-35 WGA. Patients were followed during the first year of life. Palivizumab recipients were less frequently hospitalized than placebo recipients (0.9 versus 5.1%) confirming the efficacy of the antibody. Primary outcome analysis showed that the burden of wheeze was about 60% lower in children receiving RSV prophylaxis. In the MAKI trial a post-prophylaxis effect on recurrent wheeze was observed, extending beyond 2 months after the last infection. Other non-randomized trials have confirmed that children prophylactically treated with palivizumab have decreased risk of developing recurrent wheeze during preschool age. Follow-up until school age will define which trial participants have developed asthma and, subsequently provide the answer to the critical question of whether RSV infection can cause asthma. So far, RSV intervention trials have only been performed in late preterm infants. These children are known to have decreased lung function at birth. Therefore, the generalization of these results may not be straightforward in healthy term infants. Currently, no palivizumab trials in this patient population are performed for practical reasons. However, a number of maternal and pediatric RSV vaccines have recently entered clinical trials. These vaccines will not only be important to prevent morbidity and mortality related to acute RSV infection, but also have the potential to answer the vexing question whether RSV infection in healthy term infants is causally related to long-term airway disease.

In conclusion, RSV infection during infancy is strongly and causally related to the subsequent development of preschool wheeze. Perhaps, RSV causes recurrent wheeze by a robust neutrophil-mediated inflammatory response in the airways. Additionally, there are likely genetic, immunological or pulmonary factors that predispose to both RSV and subsequent wheeze. There is less evidence to support a relationship between RSV infection during infancy and allergic or non-allergic asthma at school age. Final answers will come from long-term follow up in clinical trials investigating efficacy of RSV antibodies or future RSV vaccines.

References

THE RE-EMERGENCE OF PERTUSSIS.

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Is pertussis coming back?
The evidence for the increase of Bordetella pertussis infections comes from (public health surveillance) data in different countries throughout the world. Although pertussis has long been considered a disease of childhood, there is a growing awareness that adolescents and adults constitute rapidly increasing affected demographics. But how reliable are these data and are they comparable between different countries? A lack of awareness of the possibility of pertussis infection results in a situation that no effort will be made to test for it. The availability of diagnostic tools, such as culture, PCR, and/or serology are not equally distributed throughout world, leaving aside the financial stimulus or impediments to testing. To confuse matter further, the definition of a proven pertussis case varies from country to country. Finally, data collection on prevalence of infectious diseases in general and pertussis in particular varies within and between countries. Even in the light of all of these drawbacks to an equitable analysis, the increase in notifications for pertussis seems to be consistent throughout the world. Is the observed increase in pertussis cases real? There are several studies on the seroprevalence of pertussis antibodies in populations in different countries, and these studies show that there is an increase of pertussis infections. Interestingly, a majority of these people with positive serology for pertussis don’t recall any symptoms of respiratory infection. What is the cause of the re-emergence of pertussis? At first glance it was thought that the rise in prevalence was based on an increased focus on pertussis as the possible cause of prolonged coughing, especially in adolescents and adults. In addition, the availability of improved diagnostic techniques like PCR for pertussis have provided a fast and reliable tool to confirm or exclude a pertussis infection. Another explanation offered is that vaccination schedules are suboptimal in combination with vaccines (whole-cell as well as acellular vaccines), that are no longer capable of providing adequate immunity. The latter might be
caused by the observed changes in the Bordetella strains or the fact that whole-cell vaccines provide a Th1 reaction versus a Th2 reaction generated by acellular vaccines, resulting in a less effective immunity when using the newer, acellular vaccines.

In addition, the disappearance of natural pertussis circulating in the environment, that would have naturally boosted the immunity of adolescents and adults, might also play a role in the re-emergence of pertussis.

It has become clear that neither natural infection nor vaccination provide life-long protection against pertussis infection. Since vaccination protects against disease but not against infection or colonization, this waning immunity makes everyone, young and old, susceptible to re-infection with Bordetella pertussis, even after a few years post vaccination. After 10-15 years post vaccination, such a re-infection will cause disease, before that a re-infection might pass without any symptoms or mitigated complaints symptomatically resembling the common cold.

What can be done about it?

Since the unvaccinated newborns and the partly vaccinated infants are the most vulnerable population for Bordetella pertussis infection, the most attention has been paid to improving vaccine schedules. Most of these approaches, like cocooning, seem to be less effective or too costly, leading to a recently advocated strategy to vaccinate pregnant women in their third trimester. Most mothers, when well informed, would like to take part in such a vaccination program.

A new development in the fight against whooping cough is the creation of a new live, attenuated vaccine, which is administrated nasally. The first trial in healthy adults has been finished successfully.

References


The impact of Pneumococcal Conjugate Vaccine on Childhood Pneumonia

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Pneumonia is a major cause of morbidity and mortality in children globally. In 2011, there were an estimated 120 million episodes of childhood pneumonia, of which 14 million progressed to severe disease, with 1.3 million deaths. The incidence and severity of childhood pneumonia was highest in Africa and southeast Asia, which accounted for 30% and 39% respectively of the global burden of severe cases. Pneumonia remains the major cause of death in children, accounting for approximately 20% of deaths in children under 5 years. Identification of the etiology of pneumonia is challenging. S pneumoniae, estimated to cause 18% of severe cases and 33% of deaths, is the predominant etiologic agent identified in vaccine-probe studies. H influenzae type b (Hib) and pneumococcal conjugate vaccines (PCV) have reduced the burden of pneumonia. Data from six studies of the effectiveness of HibCV in low and middle income countries indicates a reduction of 18% in radiological pneumonia, of 6% in severe pneumonia and of 7% in pneumonia-associated mortality. PCV has led to a large decline in all-cause pneumonia hospitalization especially in children under 2 years of age. This included a 56% reduction following 7-valent PCV introduction in a middle-income country such as Uruguay, as well as a sustained reduction (43%) in children under 2 years in the USA, ten years following PCV introduction. However, pneumonia reduction among children 2-4 years has been more modest at approximately 12%. 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. PCV has also been associated with reduction in hospitalization for viral-associated pneumonia, suggesting that severe pneumonia results from bacterial-viral co-infection. Similarly, PCV immunization in children reduced hospitalization for pulmonary tuberculosis, suggesting that co-infection with M tuberculosis and pneumocococci may result in severe respiratory disease. PCV vaccination may also lead to substantial reductions in childhood mortality, especially in areas where there is poor access to care. In a rural setting in the Gambia, PCV9 reduced childhood mortality by 16%, translating into 7 deaths prevented per 1000 children immunized. PCV may also reduce mortality and pneumonia in HIV-infected children. Although the efficacy of PCV for prevention of invasive disease and pneumonia is lower in HIV-infected compared to uninfected children, the overall burden of disease prevented is much greater amongst HIV-infected children because of their susceptibility to severe disease and higher pneumococcal disease burden. Thus the overall vaccine attributable reduction in invasive pneumococcal disease was almost 60 times higher in HIV-infected compared to uninfected children, while the reduction in pneumonia was 15 fold greater. Further the use of concomitant antiretroviral therapy may result in greater vaccine efficacy.

With improved childhood immunization, the importance of vaccine-targeted pathogens can be anticipated to diminish, while viral pathogens and other bacteria, such as S aureus may increasingly emerge. Replacement disease, with non vaccine strains has not led to a widespread increase in incidence of pneumonia or severity of disease, especially following introduction of the 13 valent conjugate vaccine. Concern about replacement disease with non-vaccine serotypes due to an increase in non-vaccine serotype disease in communities with wide vaccine coverage has been
raised. However, a sustained and substantial reduction in invasive pneumococcal disease has occurred overall in populations with widespread use of PCV, especially since introduction of the 13 valent immunisation.60 Two large studies, a multicenter case control study, the Pneumonia Etiology Research for Child Health study (PERCH) and a birth cohort study, the Drakenstein Child Lung Health study are underway to investigate the etiology of childhood pneumonia in populations with high PCV coverage.

References

ADVANCES IN DIAGNOSING THE AETIOLOGY OF CHILDHOOD PNEUMONIA

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Current studies determining the aetiology of childhood pneumonia vary substantially with respect to factors that influence the diagnosis and ascribed microbial etiology. These factors include variations in case definitions, use and interpretation of chest x-rays (CXRs), peripheral blood white cell counts and inflammatory markers, depth of investigations, facility type, and patient characteristics.1 While procalcitonin is a promising biomarker in adults with pneumonia, its diagnostic thresholds in childhood pneumonia are less defined and its usefulness and safety in guiding management has not been established.2 Also, ascribing definitive etiology with confidence is exceedingly difficult unless lower airway specimens can be obtained and/or concurrent systemic infection is identified. Consequently, it is not surprising that studies describe different frequency and types of pathogens associated with pneumonia. The Pneumonia Etiology Research for Child Health (PERCH) project is the largest multisite study (6000 children, 7 African and Asian countries) of childhood pneumonia. It seeks to address the aforementioned limitations by using case-control methodologies and adopting a protocol that has standardized enrollment criteria, specimen collection, laboratory testing and molecular detection techniques.3 Further, despite advances in identifying microbiorganisms using highly sensitive molecular techniques, ascribing causation may be problematic. Nucleic acid amplification (NAA) techniques, such as polymerase chain reaction (PCR) assays, identify genetic material, but the implicated microbiome may no longer be viable or infectious and their presence may be from a recent, but unrelated respiratory illness. For example, the prevalence of respiratory viruses detected by molecular techniques in asymptomatic children is as high as 42%4 and strains of adenovirus C may remain latent in mucosal lymphocytes and be shed for months or even years.5 Even when the same molecular detection techniques for viruses are used, the site of specimen collection influences results. In paired comparisons of concurrently obtained upper and lower airway specimens for respiratory viruses in 75 children, we found significant discordance between nasopharyngeal aspirate and bronchoalveolar lavage (BAL) specimens.6 The discordance was dependent on the virus type and most marked for human rhinovirus (hRV) and adenoviruses. Nasopharyngeal aspirate (NPA) had a high sensitivity (92%) and low specificity (57%) for detecting hRV in BAL with poor kappa agreement value of 0.398 (95% CI:0.218–0.578, P < 0.0001), NPA had a fair sensitivity (69%) and good specificity (90.3%) for detecting adenovirus on BAL, kappa agreement was 0.561 (95%CI:0.32–0.80). Additionally, even when investigating viral infections from a single specimen collection site, detection of multiple viral types is common. This observation compounds the difficulty in determining the primary causative agent and presents new questions about the roles of these viruses in the aetiology of the disease. The ideal samples for determining etiologic agents in bacterial pneumonia are lower airway specimens. It is usually neither necessary nor feasible to obtain either BAL or needle lung aspirate specimens in acute pneumonia. Induced sputum is an alternative only in older children, and as potential respiratory bacterial pathogens commonly colonize the upper airways of healthy children, oropharyngeal contamination can complicate interpretation of culture results. Blood cultures are also infrequently (<10%) positive in children with pneumonia and as pneumococcal conjugate vaccines become incorporated into national immunization schedules their sensitivity is likely to be further reduced.2 PCR techniques have only modestly increased the yield of pathogen detection in blood samples,7 while with the exception of M. pneumoniae, serology is impractical in most clinical situations. Thus, it remains a challenge to determine the ideal, yet feasible, specimen for identifying the aetiologic agent(s) in children with pneumonia.

Increasingly, viral-viral, viral-bacterial and bacterial-bacterial interactions in the pathogenesis of respiratory infections are recognized with in-vitro and in-vivo animal and human studies.8 Thus, although viruses may initiate the respiratory infection, secondary bacterial infection may occur and simply identifying a virus at presentation (leading to antibiotics being withheld) may not indicate the sole etiology of the child’s acute clinical presentation or determine its long term outcomes. The complexity of the microbial contribution is further increased by introducing the world of ‘omics’ (e.g. metagenomics). While interest in this field is exploding, its use will likely further complicate ascribing etiology to a single organism. Microarray-based gene expression profiling (DNA
Abstract

microarray) i.e. comparing gene expression in infected to that in uninfected cells or tissues shows considerable promise for identifying causative pathogens of pneumonia. However, these and other nucleic acid amplification platforms (e.g. microbead arrays) are unlikely to be made available in the near future to resource-poor countries where the burden of childhood pneumonia is greatest. Nevertheless there are promising signs of improved diagnostic yields for pneumococcal pneumonia when using molecular techniques to detect pneumococcal gene sequences in blood or by combining elevated serum biomarker results (eg. C-reactive protein; CRP) with rapid pneumococcal urinary antigen testing.

References


PNEUMONIA IN CHILDREN: MANAGEMENT OF COMPLICATED PNEUMONIA

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Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality, especially in children under 5 years of age. The annual incidence of pneumonia in North American and European children under 5 years of age is approximately 36 per 1000. The microbiological diagnosis of pneumonia in childhood is complex and in most cases the cause is unknown. There is no standard diagnostic test for an etiologic agent in childhood pneumonia.

Epidemiology of complicated pneumonia

Complications associated with pneumococcal pneumonia include pleural effusion, pleural empyema, necrotizing pneumonia, and lung abscess. An increase in the incidence of complicated pneumonia has been reported in the last two decades in many studies from the United States and in Europe (1). Although the incidence of invasive pneumococcal disease has decreased since the use of pneumococcal conjugated vaccine (PCV), developed countries such as USA have seen an emergence of empyema and necrotizing pneumonia episodes caused by the nonvaccine serotypes (2). The reasons for this increase in the prevalence of suppurating complications in children with pneumonia have not been clearly identified. Suppurating complications were associated with age, recent chicken pox, infection with S. pneumoniae (especially serotype 1 and 19), and therapy with antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) prior to hospital admission.

Necrotizing pneumonia, also termed massive pulmonary gangrene, is a sequela of pneumonia in which the lung tissue becomes necrotic (3). Recent attention has focused on pneumococcal pneumonia as a causative agent in children, where with limited intervention the prognosis is good. Accumulation of fluid in the pleural space may follow the development of pneumonia in as many as 28% of children. The successful management of such fluid, which may either represent a parapneumonic effusion or be contaminated with micro-organisms, leukocytes, and fibrin to form an empyema, is a crucial component of the overall care of these patients.

Management of complicated pneumonia

The key components of the treatment of complicated pneumonia are the use of appropriate antibiotics, oxygen supplementation, proper hydration, provision of nutritional support, analgesia and antipyretics, and referral to a tertiary centre. However, inconsistency exists regarding the appropriate management strategy for empyema or complicated parapneumonic effusion in children.

Empyema - defined as accumulation of pus or infected fluid in the pleural space. The amount and type of fluid may vary. Fluid should be immediately tapped for diagnostic purposes. The importance of draining pleural effusions and empyema has been recognized since the time of Hippocrates. However, it has been realized that septations and loculations may hinder drainage of effusions and lead to lung entrapment and impair drainage. Current options include primary chest tube placement, either open or with radiologic guidance, and with or without fibrinolysis, or video-assisted thoracoscopic surgery (VATS) with removal of pleural fluid and exudate. Primary chest tube drainage may be favored by some clinicians because of the perceived advantages of radiographic drainage for localized fluid collections, avoidance of general anesthesia, and the smaller thoracostomy tubes used. However, the fibrinous pleural fluid in the setting of empyema often clogs these small drains, resulting in inadequate drainage. Intrapeural administration of fibrinolytics is believed to augment drainage, although this measure is not helpful in all cases. Two large double blind placebo controlled studies showed no advantage to fibrinolysis with reported complications. Primary VATS-assisted drainage of the pleural space in became more and more popular in pediatric patients with empyema and parapneumonic effusion. A VATS-based approach offers the potential for better lung expansion after removal of pleural debris and exudate, excellent magnified vision, optimization of the location of the chest tube, and reduced chest wall and muscle trauma compared with traditional thoracotomy. In comparison with historical cohorts it was associated with shorter hospital stay. However complications including prolonged air-leak and even death were reported (4). Furthermore, St. Peter et al. showed in a prospective controlled study that no therapeutic or recovery advantages between VATS and fibrinolysis for the treatment of empyema; however, VATS resulted in significantly greater charges (5). Therefore, our approach is chest drainage with no fibrinolysis. Most of the children will have complete cure even after a prolonged course. Shoseyov et al. reported that repeated needle aspirations had similar outcome as chest tube drainage (6). Furthermore, Carter et al. showed that some children with empyema can be treated with IV...
antibiotics alone and concluded that only those that required intensive care or had large effusions with mediastinal shift were more likely to require pleural drainage (7).

Choice of antibiotics

The antibiotic management of children with complicated pneumonia is usually empirical, as culture and antibacterial sensitivity test results are positive in only 5–15% of the cases at initial diagnosis. The pathogens commonly associated with complicated pneumonia are S. pneumoniae in the vast majority of the cases, Strep group A, and rarely S. aureus. Severely ill children are traditionally treated with parenteral antibacterials, usually with wider spectrum antibiotics. One of the reasons for this approach is concern of penicillin resistant pneumococci (PnP). However, PnP are not associated with more severe disease and it is not a factor in outcome from invasive S. pneumoniae community-acquired pneumonia. Furthermore, a number of studies demonstrated good clinical response to penicillin therapy despite in vitro resistance, and showed no adverse outcomes in patients infected with non-susceptible isolates [8-10]. Parenteral therapy with benzylpenicillin or an aminopenicillin should be used when pneumococcus is the likely pathogen and broader-spectrum agents have no additional benefit. For the severely unwell, toxic child with or without effusions, where rarer pathogens are a possibility, therapy should include a third-generation cephalosporin (e.g. ceftriaxone), or a penicilliniase-resistant beta-lactam (e.g. oxacillin) or vancomycin if Staphylococcus aureus or MRSA infection is likely. However, treating all children with complicated pneumonia with these antibiotics may change the microflora of pneumonia causing bacteria and increase the rate of infections with other less common and more resistant microorganisms.

References

supplementation must be systematic, particularly in the case of breast feeding and should be adapted to natriuresis (6). It should be increased during periods of hot weather and all other causes of high salt loss (diarrhea, fever, ileostomy…).

At initial diagnosis, infants must have pancreatic function assessed by stool fecal elastase. If elastase is normal, repeat assessment is recommended.

Pancreatic enzyme replacement therapy should be started at diagnosis in case of clinical symptoms of exocrine pancreatic insufficiency even before obtaining the results of the elastase assay. The initial dose could be 2,000 IU lipase per 100 mL of milk. In case of persistence of symptoms of pancreatic insufficiency despite a maximum dose of 10,000 UI/kg/day of lipase, it may be necessary to evaluate patient’s compliance and the methods of conservation and administration of the pancreatic extracts. In case of poor weight-for-height growth despite an adapted substitutive pancreatic oophylaxis, an evaluation is necessary including a dietetic review, a search for sodium insufficiency and other etiologies of malabsorption. In case of persistence of symptoms of exocrine pancreatic insufficiency despite a maximum dose of 10,000 UI/kg/day of lipase and in the absence of other etiologies, the administration of gastric secretion inhibitors may be envisaged.

Respiratory statements

Bacterial cultures of bronchial flora should be performed at each session of physiotherapy or in case of abnormal clinical status either on bronchial secretions (expectorated or obtained by sputum induction) or by pharyngeal swab (7).

A chest X-ray should be performed at baseline and annual assessment, and, in case of clinical abnormality. High Resolution Computed Tomography could complete the assessment in case of clinical or radiological abnormality and/or at initial assessment according to local practice to detect early bronchiectasis (8).

Systematic respiratory physiotherapy is recommended from the time of diagnosis. The frequency of sessions of physiotherapy depends on the clinical status of the infant. Regular therapy might be recommended even in the asymptomatic infant (3). Any evidence of respiratory infection justifies performing a respiratory culture and adapted antibiotic treatment of the isolated pathogens. Infection by Staphylococcus aureus sensitive to Meticillin should be treated by adapted antibiotherapy. In case of isolation of S.aureus resistant to Meticillin, a treatment aimed at eradication is recommended. Evidence of Paeruginosa justifies systematic antibiotic treatment aimed at eradication, even in the asymptomatic infant. Although there is still no consensus on the topic, treatment might begin with an inhaled antibiotic, eventually associated with oral Ciprofloxacine. In the case of persistence of P. aeruginosa after initial therapy, or if the infant presents with severe clinical signs, intravenous antibiotics should be considered (1,2,3). For other pathogens, there is less clear agreement and treatment should be guided by local policies. In the absence of clinical improvement despite an adapted antibiotherapy, bronchial sampling by bronchoalveolar lavage should be considered and non-infectious causes should be searched for, notably gastro-oesophageal reflux, asthma and an ENT cause.

Respiratory syncytial virus (RSV) may have adverse effects on respiratory status in patients with CF (9). There is insufficient evidence to support systematic recommendation of Palivizumab in the Cystic Fibrosis infant.

However, extrapolation of data from other populations suggests that there could be benefit from the use of RSV prophylaxis in infants with CF (10). US and French guidelines state that Palivizumab could be discussed, namely for the infant of less than 6 months of age during an epidemic period (2,3). Finally, dornase alfa, 7% hypertonic saline might be used in symptomatic infants according to the CF America, Foundation guidelines (2).

Conclusion

With increasing numbers of infants with CF being diagnosed by newborn screening across most of Europe and in North America, we will have the opportunity for large randomised controlled trials. There is an urgent need for best available evidence to harmonize therapeutic strategy in infants newly diagnosed with the final aim to improve clinical status at later ages.

References


NOVEL THERAPIES IN CYSTIC FIBROSIS. CAN WE CHANGE THE COURSE OF THE DISEASE?

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Since the discovery of the CFTR gene in 1989, the search for therapies that improve the basic defect in cystic fibrosis (CF) has been very intense. Initially, gene therapy was considered the ideal approach. However, the many challenges encountered quickly decreased the hope of ‘an easy cure’: the large size of the CFTR gene, the side effects associated with the use of viral vectors, the antigen response precluding repeated use of viral vectors, the difficult access to the basolateral surface the respiratory epithelial cell, the relative inefficiency of non-viral vectors.

In the meantime the basic pathophysiology of the disease CF was better understood and the era of translational medicine started (1). The CFTR protein functions as a chloride channel and ‘regulates’ the hydration status and height of the airway surface liquid with resultant normal mucociliary clearance. A framework of how the different CFTR gene mutations result in a defect in CFTR protein synthesis or function was created by grouping gene mutations in classes. This certainly helped the orderly progression of ‘small molecule therapies’ for CF. In class I mutation there is no protein production due to large deletions, frame shift mutations or premature stop codon mutations, the largest subgroup in class I. Class II mutations, including the most common mutation F508del, result in abnormal folding and trafficking

Pediatric Pulmonology
of CFTR in the endoplasmic reticulum (ER); the misfolded protein is retained and degraded. In Class III mutations (commonest example G551D) the protein is produced and inserted in the cell membrane, but there is impaired opening of the chloride channel. In Class IV the protein is present but has a decreased chloride conductance. In class V mutations less but normal protein is present. Understandably, patients with at least one class IV or class V mutation usually have a milder CF phenotype.

CFTR modulators include premature stop codon mutation read through drugs, CFTR correctors that improve CFTR protein folding and trafficking in the ER and CFTR potentiators that improve the channel opening. So far, most progress has been made for patients with at least one class III mutation. The CFTR potentiator ivacaftor, has been approved by FDA and EMA for use in patients with G551D class III mutation and recently FDA extended the approval for 8 more class III mutations. Indeed, after a successful preclinical program, ivacaftor also provided major benefit to the patient in subsequent phase 3 clinical trials: a mean improvement of about 10% in FEV₁, a large decrease in pulmonary exacerbations, improved weight gain, improved quality of life scores (2, 3). During open label extension, this benefit is being sustained. Unfortunately only about 3% of patients with CF do have a class III mutation. Several other compounds are currently in clinical trial. Furthest advanced in the pipeline are the combination trials with Vertex compounds lumacaftor (VX-809 CFTR corrector) and ivacaftor in patients homozygous for mutation F508del. Corrector VX-809 in monotherapy provided insufficient clinical benefit. The rescued mutated F508del protein is known to have defective gating and possibly also less stability at the cell membrane. Hence in the current clinical programs correctors lumacaftor and also VX-661 are combined with potentiator ivacaftor. After showing moderate benefits on sweat chloride in phase 2 trials and also a modest clinical benefit, the lumacaftor/ivacaftor combination is now in phase 3 clinical trial. Since many molecules are involved in normal CFTR folding and trafficking, it is not surprising that a combination of correctors working via different mechanisms of action further improves correction of the most common mutation F508del (4). This in vitro work on CFTR misfolding and trafficking and how it can be corrected will pave the way for further clinical trials. CFTR potentiators might also be of use for patients with class IV and V mutations, since in vitro ivacaftor potentiates normal CFTR as well as several mutated CFTR proteins associated with residual function (5).

Of particular interest are the premature stop codon read through drugs. Premature stop codon mutations occur in many if not all genetically inherited disorders. Hence, the compound under the trial ataluren is not only relevant in CF, but also in other disorders like hemophilia and Duchenne’s muscular dystrophy. In the context of CF, ataluren was associated with some improvement in CFTR biomarker function in open label phase 2 trials (6, 7), however in the phase 3 trial, the primary outcome parameter of improving FEV₁ was not met. A pre-planned post-hoc analysis demonstrated that ataluren had a modest but statistically significant benefit in patients not using inhaled aminoglycosides. A further evaluation of the efficacy of ataluren is therefore planned.

In parallel with the mutation class specific therapies, other routes of improving the basic CFTR defect are being tested: e.g. manipulation of other ion channels to circumvent the CFTR chloride dysfunction. Current efforts are concentrating on ENaC and calcium activated chloride channels. These therapies, if successful, would be applicable to all patients with CF, regardless of their specific mutation.

References


NONTUBERCULOUS MYCOBACTERIA IN CYSTIC FIBROSIS

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Cystic fibrosis (CF) lung disease is characterized by chronic bronchial infection caused by a wide variety of pathogens. Typical bacterial pathogens are Staphylococcus aureus and Haemophilus influenza, with Pseudomonas aeruginosa becoming more important with age. Emerging pathogens are Stenotrophomonas maltophilia, Acinetobacter xylosodanais and Burkholderia cepacia. The latter seems to gain importance in later life. In addition to these well-known CF pathogens, non-tuberculous mycobacteria (NTM) are increasingly recognized as important pathogens in CF microbiology. Since the nineties an increasing number of studies have reported isolation of NTM from the respiratory tract of patients with CF. It is still unclear whether NTM infections are more prevalent in the CF lung: maybe we pick up these pathogens more easily because of improved isolation techniques and improved awareness. Additional difficulty for clinicians is that isolation of NTM does not necessarily indicate active lung infection contributing to CF disease.

The two most common NTM species isolated in CF are Mycobacterium avium complex (MAC) and to a lesser extend) Mycobacterium abscessus. While M. abscessus can be found in CF patients of all ages, MAC is rarely recovered from patients below age 15 years. The large variation in incidence between studies may reflect a through in incidence but may also point to difference in surveillance systems and laboratory techniques used.

NTM is ubiquitous in the environment however with an important geographical variation. Age has been recognized as a risk factor for MAC infection. Studies looking at other risk factors have produced inconsistent results. Co-existence of other pathogens does not relate to an increased risk apart from Aspergillus fumigatus which has a higher prevalence in NTM positive patients. Systemic steroids and the use of antibiotics also have produced inconsistent results. There has been concern which has a higher prevalence in NTM positive patients. Systemic steroids and the use of antibiotics also have produced inconsistent results. There has been concern on the use of azithromycin since it may impair the autophagic and phagosomal degradation and inhibit the intracellular killing of mycobacteria. Again studies on this subject have shown conflicting results. Although traditionally it has been accepted that person-to-person transmission of NTM is unlikely, recent reports have been published on M. abscessus

Pediatric Pulmonology
transmission between CF patients. The risk for transmission may be related to the degree of mycobacterial burden in the index patient.

**Diagnosis testing**

Recovery NTM from CF sputum samples is technically difficult. The main issue is the risk of bacterial contamination and overgrowth. Therefore standard processing of sputum samples for mycobacteria cultures involves a digestion-decontamination method. The use of certain decontamination procedures however may inactivate NTM growth (for example after double inactivation processing). Recently alternative techniques for decontamination have been studied such as the use of 1% chlorohexidine (Ferroni 2006).

The use of novel growth media such as the B cepacia selective agar may improve the culture of mycobacteria when used with extended incubation. Also PCR techniques targeting 16S rRNA sequences have shown high sensitivity and specificity and can lead to more rapid identification of mycobacterial species. However data on the use of these techniques for CF sputum are limited (Devine 2004). Skin reactivity testing is less useful in the context of NTM infections. However measuring immunoglobulin titers against mycobacteria may be promising. IgG titers against mycobacterial antigen A 60 are higher in patients with high NTM load and active disease (defined according to the criteria of the American Thoracic Society and the Infection Disease Society of America) (Griffith 2007). These tests may thus allow to distinguish patients with active disease from those that were only colonized. In a small series of 6 patients undergoing bronchialveolar lavage, it has been shown that cough swabs should not be used to isolate NTM. On 6 patients positive on NTM on bronchoscopy a cough swab taken at the same time was negative for NTM (Ahmed B 2012).

**Clinical Course**

When mycobacteria are cultured in CF sputum it may be unclear if they represent an active disease process or mere colonization. Criteria as formulated for NTM lung disease (ATS, IDSA) may not be applicable to CF because the criteria such as ‘sputum production’ and the ‘presence of bronchiectasis’ may be part of the baseline symptomatology of CF. CF patients with positive sputum smears are more likely to have NTM disease if on HRCT there is cystic and cavitary lung disease. Other indications may be repeated growth versus single isolate and worsening symptomatology and lung function. Specifically M. abscessus rough (R) morphology isolate is felt to be more virulent than the smooth (S) variant.

**Management**

Monitoring for NTM is advised in CF patients especially in adolescents and adults. Most centers will routinely screen CF patients at least once a year for NTM infection. In patients with unexplained clinical deterioration, specific cultures for NTM should be requested.

The decision to treat or not to treat should depend on the number of positive cultures, the bacterial burden and the clinical evolution of the patients. A recent US study (Martiniano 2014) showed that the majority of patients with CF and a first positive NTM culture do not progress to active disease. Lower lung function at the start and accelerating lung function decline appeared to be indicators of the significance of an initial positive NTM culture. In a French study (Catherinot 2013) documented that MAC mainly affect adult patients with a milder form of CF (and often late diagnosis). M. abscessus infections however affect patients with more severe CF, high need for intravenous antimicrobial treatment and a medium age of 17 years.

Treatment for NTM should consist of a three or more combination drug schedule. Treatment is always lengthy with high risks of side effects and no guarantee of eradication or cure. In vitro drug susceptibility testing has a poor correlation with clinical response except for macrolide antibiotics. In general higher doses may be needed in CF patients due to a larger volume of distribution and rapid renal clearance of the drugs. Additionally there is an inconsistent drug absorption. Whenever possible routine serum monitoring levelling should be used.

For MAC usually a combination is used of a macrolide, Rifampicin and Ethambutol. For Mycobacterium abscessus a macrolide is combined with Ceftoxin and Amikacin. Alternative agents are Imipenem, Tigecycline, Linezolid and Amikacin. For the latter recent studies have reported on the use of inhaled Amikacin. Most guidelines for the duration of antymycobacterial therapy are derived for the non-CF population. ATS recommends to continue the therapy until 1 year following the first negative sputum. For refractory NTM disease, surgical resection may be considered if lung disease is localized.

Preexisting NTM disease is not an absolute contraindication to lung transplantation. Although the prevalence of NTM after transplantation will be higher, no overall survival difference has been documented between the two groups. For M. abscessus however, there is a high risk of morbidity and mortality due to M. abscessus disease under immunosuppression. In some centers M. abscessus disease may be a contraindication for transplantation. **References**


**IV - Pulmonary Systemic and Vascular Disorders**

**PULMONARY VASCULITIC DISEASES: “RARI NANTES” IN PEDIATRIC PULMONARY DISEASE**

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Childhood vasculitis is a rare disease. The prevalence is about 23 over 100000 children less than 17 years. Only in a small subgroup the pulmonary blood vessels are involved. Some times the diagnosis is missed or delayed. Early diagnosis is essential to prevent severe lung damage and even death. Vasculitic diseases can be classified in two groups: collagen vascular diseases and paediatric primarily vasculitic conditions.

The former group is a rare complication of collagen vascular or rheumatic diseases. The complication is suggested by the underlying autoimmune disease. Diagnosis is mostly not postponed and therapy adjustment of the underlying disease will help to control the vasculitic inflammation. In the latter group the vasculitic disease has a silent, many times not specific start with a slow and insidious progression. Severe pulmonary damage can already have occurred before a correct diagnosis is made!

This paper will focus on the latter group, children with primarily vasculitic disease.

1. Primarily vasculitic conditions in children form a troublesome nosocomial entity. The different diseases show confusing and overlapping definitions. An usable and clear classification was given by Dillon et al., they classified, during a consensus meeting, the different diseases relying on the size of the vessels involved.

Large vessels are affected in Takayasu disease, predominantly medium sized vessels in polyarteritis nodosa and Kawasaki disease. In predominantly small vessels disease a granulomatous form (Wegener’s granulomatosis, Churg-Strauss disease) and a non granulomatous group

Pediatric Pulmonology
(microscopic polyangiitis, Henoch-Schönlein purpura, pulmonary capillary-itis) are recognized.

Some of these systemic vasculitic syndromes have no specific lung involvement. In Takayasu's vasculitis mainly the aorta and its major branches are affected. Polyaerteritis nodosa (PAN) can disturb the blood supply to any organ, the lungs are typically spared.

Pulmonary involvement in Henoch-Schönlein purpura and Kawasaki disease is rare. In Henoch-Schönlein purpura few cases of fatal alveolar hemorrhage have been reported. Cough, respiratory distress, reticulogranular infiltrates, pleural effusions, atelectasis and airtrapping are occasionally present in Kawasaki disease.

We followed an infant with persistent fever, at day 3 there was a mild conjunctivitis and exanthema, at day 7 she was hospitalised. Beside fever there were no other clinical signs and a normal physical examination. A chest X-ray showed a fine reticulo-granular infiltrate over the right lung.

Inflammatory parameters were raised, viral and mycoplasma PCR's were negative. Chest X-rays deteriorated and HRCT-thorax revealed a pleural effusion. Hypo albuminemia suggested the correct diagnosis of atypical Kawasaki disease. Symptoms involved after intravenous immunoglobulin treatment. Severe and life threatening vasculitides belong to the so called ANCA disease. Symptoms involved after intravenous immunoglobulin treatment.

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Classical anti neutrophil cytoplasmic antibodies (C-ANCA) target. They were found to target conformational epitopes on a novel elastinolytic serine protease, proteinase 3 (PR3). PR3 can catabolize a number of human proteins, such as proteoglycans, elastin, and all four subclasses of IgG including the PR3-ANCA/PR3 complex. The latter activity suggests that PR3-ANCA is an inefficient inhibitor of the PR3 enzyme activity.

These paediatric pulmonary ANCA vasculitic diseases are classified by small or medium vessel inflammation, multi-organ system involvement and whether or not granulomatous microscopic appearance. Granulomatosis with polyangiitis, formerly known as Wegener’s granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome.

Pulmonary hemorrhage, respiratory failure, rapidly progressive glomerulonephritis and acute renal failure are the major co-morbid conditions in the acute phase of the disease.

Without treatment these diseases have a mortality of 100%. Compared to adults, children are more likely to develop multi-organ involvement and renal involvement.

Granulomatosis with polyangiitis affects the upper and lower respiratory tract and the kidney. Constitutional signs such as fever, malaise and weight loss are observed in 90% of the patients. Eighty percent have pulmonary symptoms (pulmonary haemorrhage, nodules, infiltrates, pleurisy, oxygen dependency, respiratory failure) and upper airway disease (nasal ulcerations, nasal septum perforation, recurrent epistaxis, sinusitis, mastoiditis, hearing loss and subglotic stenosis). Seventy five percent have renal lesions leading to hematuria, proteinuria, glomuromelephtritis and finely renal failure. The diagnosis relies on clinical presentation, biopsy and positive cytoplasmatic ANCA/pr3 (80-90% of patients).

Microscopic polyangiitis is a necrotizing, non granulomatous disease affecting the small vessels in lung and kidney. Beside constitutional symptoms, respiratory (cough, dyspnea, cracks on auscultation, occasionally hemoptysis) and renal impairment (100% hypertension, hematuria, proteinuria, 30% renal failure). In 30% necrotising vasculitic lesions in brain and skin are observed. A high titer of cytoplasmatic or peri-nuclear ANCA are measured.

Churge-Strauss syndrome is a granulomatous vasculitic disease affecting the small and intermediate vessels. The onset is insidious and primarily observed in children with severe asthma and allergy. The disease evolves progressively over a long period giving a broad spectrum of symptoms and signs: pulmonary infiltrates (85%), sinusits (77%), skin (66%), cardiac disease (55%), gastro-intestinal symptoms (40%), peripheral neuropathy (39%) and mild and rarely progressive renal impairment. Twenty five percent of the case are ANCA positive.

Treatment of ANCA-vasculitic diseases in children is adapted from adult studies or relies on papers from a small group of patients. Although there is a high risk of toxicity and relapse, corticosteroids and endoxan are the standard induction therapy. Recent studies looking for less toxicity and less relapse pointed at biologic drugs and plasmapheresis as an adjunct therapy. Infliximab, Rituximab and IVIG are options for refractory disease. In conclusion, vasculitic diseases with pulmonary involvement are rare but need our full attention. Whereas Pulmonary involvement in the more prevalent vasculitic diseases, Kawasaki and Henoch-Schönlein, is rare both diseases are not life threatening and treatment is simple and not harmful, diagnosis of the ANCA-vasculitis is urgent in order to prevent irreversible pulmonary and renal damage.

References

CHRONIC INTERSTITIAL LUNG DISEASES IN CHILDREN: WHAT’S NEW?

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This study was supported by the Kids-Lung Register Foundation and the EU-project “Orphans Unite: chILD better together—European Management Platform for Childhood Interstitial Lung Disease” was initiated in 2013 (Project No: FP7-305653-chILD-EU).

Chronic interstitial lung diseases in children (chILD), more appropriately called chronic diffuse parenchymal lung diseases in children, are a large group of mostly rare diseases which however may add up to a substantial amount of patients affected. Rare lung diseases are defined according to the European definition as entities which affect less than 1 in 2000 people. This is true for almost all diseases in Pediatric Pulmonology, where one excludes the frequent entities allergic asthma, chronic and recurrent bronchitis, acute bronchiolitis, pneumonias and tuberculosis.

The incidence of children’s interstitial lung disease (chILD) was prospectively estimated in Germany as 1.3 new cases/million/year (1). Although the instrument used for this, the monthly surveillance of all Children’s Hospitals, substantially will underreport the true frequency, as many entities will not be labelled appropriately and if labelled, will not all be reported appropriately due to the broad spectrum. Many of the entities are not considered to the group as the current categorization system (Fig. 1) is complex and not known to all physicians caring for this group of subjects. Here we present examples for these categories published in 2013 and will use the system to structure the txt in order to emphasized the utility and importance of the system in everyday care.

A1 - Diffuse developmental disorders
Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a rare and most frequently lethal condition, associated with nonpulmonary anomalies involving the gastrointestinal, cardiovascular, and genitourinary system in 80% of the cases. These children typically present initially as persistent pulmonary hypertension without ready explanation. About 65% of the children have a history of miscarriages. Common cause are mutations in the transcription factor FOXC1. The majority is sporadic, few being familial cases, showing a pattern of maternal inheritance consistent with paternal imprinting of the gene (2). Although ACD/MPV is rare a high percentage of cases is very likely missed due to lack of biopsies

Pediatric Pulmonology
and autopsies. As FOXF1 is a small gene, testing in refractory pulmonary hypertension is recommended.

A2 - Growth abnormalities, reflecting deficient alveolarisation

Subpleural cysts are believed to be caused by a decreased number of alveoli and alveolar enlargement. Patients with mutations of the filamin A (FLNA) X-linked gene are characterized by hyperinflation established as hyperlucent lung on chest films affecting all lobes. These infants have associated abnormalities including periventricular nodular gray matter heterotopia in the brain, skeletal dysplasia, Ehlers-Danlos variants and cardiovascular anomalies. Surgical resection of the affected lobes, if possible, may be curative and symptoms may improve with age (3).

A3 Infant chronic tachypnea and firm morphology

A cohort of nine infants diagnosed by open lung biopsy and chest CT findings was followed up to the age of 6 years (3.5 to 10). These mature infants presented with tachypnea (>60/min) and failure to thrive at age 4 months was biopsied at age 8 months and had symptoms for 18 months.

Histologically the disease was characterized by distension of distal airspaces, minor peribronchial accumulation of lymphocytes and Bombesin-staining increased neuroendocrine cells within the bronchioles; the diagnosis of NEHI, i.e. neuroendocrine cell hyperplasia of infancy, could be made (4). At the end of follow up, 4 were well and 5 had “non-atopic” asthma, i.e. recurrent episodes of wheezing.

A4 Surfactant dysfunction disorders

Mutations in the genes for surfactant protein B, C, and ATP-binding cassette subfamily A member 3 (ABC3A) result in the surfactant dysfunction disorders. Other causes include mutations in TTF1 and additional, not yet characterized genes. In the UK between 2006 and 2011, 427 cases of neonates and infants primarily with respiratory insufficiency were referred for surfactant mutation analyses to the North East Thames Regional Molecular Genetics Laboratory at Great Ormond Street Hospital, London. In 25 (7.5%) of these genetic mutations for surfactant dysfunction disorders were found: 6 cases with SP-B dysfunction, 7 cases with SP-C dysfunction and 12 with ABC3A dysfunction. Outcome in the majority was poor, indicating a significant bias towards severe cases (5). Several case reports on infants and children with ABC3A mutations report some response to a combined pragmatic therapeutic approach, treating with systemic steroids, hydroxychloroquine and azithromycin. Importantly all reports conclude that controlled studies are necessary to try an put such treatments on a rational ground. To reach such a goal and also to follow all these cases the EU-project “Orphans Unite: chILD better together—European Management Platform for Childhood Interstitial Lung Disease” was initiated in 2013 (Project No: FP7-305653-chILD-EU) to build a site to include all these children and also to investigate the mentioned treatments in a controlled fashion (www.childev.net). This platform offers a peer review of all cases included properly, the option to include into observational and interventional studies and also for long term follow up and combination of several cases to build up larger cohorts. All contributions are welcome (6).

B1 - Related to systemic disease processes

Antisynthetase syndrome is an autoimmune entity primarily described in adults. It is caused by antibodies against aminoacyl-RNA-synthetases causing fever, myositis, interstitial lung disease, “mechanic’s hands.” Raynaud phenomenon, and polyarthritis. Hayes Jr et al. (2012) report a 13-year-old Hispanic female in acute respiratory failure with underlying interstitial lung disease and pulmonary arterial hypertension (7). She had been healthy until 6 months earlier. At that time she presented with muscle weakness, creatine kinase elevation and anti-Jo1 auto-antibodies. Treatments with pulse corticosteroid steroids, cyclophosphamide, IVIG for 6 months did not halt continued decline. On extracorporeal membrane oxygenation she was a waiting lung transplantation. CT findings in this condition include pleural irregularities and/or prominent interlobular septa, subpleural lines, fibrosis with reticulation, consolidation, centrilobular nodular opacity, traction bronchiectasis, honeycombing, irregular peri-bronchovascular thickening, and ground glass opacity. If such a condition with an acute interstitial pneumonitis is faced, rapid listing for lung transplantation may be appropriate.

B2–Exposition and immune–intact

The most frequent interstitial lung disease in childhood is exogenous allergic alveolitis. It is important to note that cases may be familiar, mostly due to the same exposure. Presenting symptoms may include fatigue, weight loss, cough, dyspnea with exercise or later at rest, restrictive pulmonary function tests, decreased DLCO, ground-glass opacities on HRCT. BAL, lymphocytosis, and finally symptoms should improve after the children are evacuated from exposure, and the symptoms should recur on repeated exposure in both patients. Feathers and molds are the 2 most frequent allergens in pediatrics.

B3 - Immuno-compromised host or transplanted

Pneumocystis infection is frequently encountered during medication or therapy induced acquired or inborn immune suppression. It may also be superimposed to large range of interstitial lung diseases.

B4 - Related to lung vessels structural processes

In diffuse alveolar hemorrhage, idiopathic pulmonary capillaritis may be demonstrated on biopsy specimens and identify cases like the 9-year-old male who had a 6-year history of mild asthma and a 3-week history of dyspnoea on exertion, cough for 1 day and post-tussive hematemesis followed by recurrent hemoptysis over years (8). The young child was treated with oral cyclophosphamide, then monthly iv cyclophosphamide over 9 months until live time accumulated dose (infertility, malignancy).

Nevertheless she relapsed and remission was achieved by combination of plasmapheresis, rituximab, methylprednisolone, mycophenolate, and prednisolone. International and interdisciplinary case conferences, as well as long term follow up of the cases, appear mandatory to maximize learning and optimize treatment.

B5- Related to reactive lymphoid lesions

Many different entities can be diagnosed and differentiated only on the basis of histology. The most frequent entity appears to be follicular bronchiolitis, often associated with lymphoid interstitial pneumonitis. Treatment of this any most of the other rare interstitial lung diseases is best done in the frame work of the children’s lung register, recently established internationally in the chILD-EU program (www.childev.net).

The European Management Platform for Childhood Interstitial Lung Disease in order to better understand the natural course, risk factors, treatments and reasons for the development of childhood interstitial lung disease (chILD), a consortium of several specialized centers was formed in 2012, to analyze details of symptoms and quality of life, clinical data and also biological material of patients with the rare lung diseases indicated above in a Register and Biobank (www.childev.net)(6). In the long run, this Register will serve the improved understanding of the disease and will lead to the development of new and effective approaches to treatment. The goal of this open group is to determine the long term course of childhood interstitial lung diseases (chILD), optimize diagnosis as well as therapy, initiate quality assurance protocols and promote clinical and scientific progress. Interested centers are invited to participate.

References


A comprehensive discussion of the topic of lung bleeding is beyond the scope of this presentation; at a previous meeting of CIPP a limited discussion of the topic was offered with emphasis on diffuse alveolar hemorrhage (DAH), and a similar perspective will be taken with this updated talk covering:

- Definition, presentation, and diagnostic methods of hemosiderosis
- Incidence and causes of airway bleeding
- Classification
- Acute Idiopathic Pulmonary Hemorrhage of Infancy (AIPH)
- Diagnostic and Therapeutic Bronchoscopy in Pulmonary Hemorrhage
- Prognosis
- Clinical examples/Specific conditions

Definition and Clinical Presentation:
Hemosiderosis typically presents as the triad: hemoptysis, anemia and diffuse radiological alveolar infiltrates. However all three elements rarely coexist. In the absence of frank bleeding presenting as hemoptysis, fall in hematocrit (typically hypochromic, microcytic anemia) with respiratory failure. Fever and chest discomfort/pain are infrequently observed. Laboratory work up beyond the anemia is suggestive but nonspecific. Radiographic changes are non-specific and range from minimal infiltrates to massive parenchymal involvement; the feature that can separate hemorrhagic processes from other infiltrates is their fleeting nature, however, in patients with small frequent episodes of bleeding the radiographs may reflect chronic diffuse interstitial involvement and change only minimally with acute recurrence. CT scan is suggestive but also not specific. MRI is cited as offering more specificity on presence of blood with decreased signal on the T2-weighted images, but this is rarely recognized by radiologists. Pulmonary function testing is infrequently available at the age range under discussion and is non-specific. However, diffusion studies (DLCO) may result unexpectedly high because of rapid uptake of the tracer gas by hemoglobin in the alveolar spaces.

Incidence and Causes of Hemosiderosis:
Hemosiderosis is rare in infancy and childhood. The incidence varies by sites of reporting; in Sweden reported at 0.24 cases per million and 1.23 cases per million are reported from Japan. This low incidence also underlies the paucity of systematic information on the causality of bleeding. In a 10 year review from a large referral center, 228 children and young adults were reported: Cystic fibrosis (CF) represented 65%, Congenital heart disease 16%. The remaining 19% were infections (other than CF), neoplasms (2.6%), and other causes (typically classified as idiopathic). Classification: When lung bleeding is not easily diagnosed in relation to obvious causes such as cystic fibrosis or lung infection. The remaining cases, once defined as a hemorrhagic process, pose significant classification challenge and not infrequently lumped under “Idiopathic Pulmonary Hemorrhage” (IPH); it is important to understand that while a typical course of action is being undertaken in such cases, IPH is not a veritable diagnosis, and includes variable etiologies that are poorly understood. A systematic approach to classification of DAH in childhood separates disorders without pulmonary capillaritis; and among these ones with and without cardiovascular cause. The disorders with pulmonary capillaritis typically carry a more ominous prognosis and include idiopathic pulmonary capillaritis, Wegener’s granulomatosis, microscopic polyangiitis, systemic lupus erythematosus, Goodpasture’s syndrome, antiphospholipid antibody syndrome, Henoch-Schonlein purpura, IgA nephropathy, polyarteritis nodosa, Behcet syndrome, Cryoglobulinemia, Drug-induced capillaritis, and Idiopathic pulmonary–renal syndrome. Acute Idiopathic Pulmonary Hemorrhage of Infancy (AIPH) The Centers for Disease Control (CDC) have classified AIPH as a separate entity: a clinically confirmed case is an illness in a previously healthy infant aged ≤1 year; with a gestational age ≥32 weeks, and no history of neonatal medical problems that could cause pulmonary hemorrhage. The cases are characterized by abrupt onset of overt bleeding or evidence of blood in the airway, diffuse pulmonary infiltrates on chest radiograph and mostly severe presentation leading to acute respiratory distress or failure. Infantile airway bleeding is an uncommon occurrence but has historically emerged in clusters; first in Greece, and more recently in Cleveland and Massachusetts. The Cleveland outbreak in the mid 90s included over 30 cases of AIPH. Many of the infants came from the same geographic area, were African-American, male, with severe disease that appeared to be beneficially affected by use of corticosteroid that reduced the high mortality (16%). AIPH in five infants in the Boston area were reported in 2004 with no mortality. No similar report emerged in the literature since the Boston series but the clustered nature of the presentation points toward a common underlying cause of the bleeding. Indeed an initial association of the Cleveland series was made with Stachybotrys chartarum (atra), a mold that may be found in water-damaged homes; but ultimately, this association has not been substantiated. Similarly, in the Boston series the cause was assumed to be related to an underlying susceptibility to bleed, with von Willebrand's disease.

PULMONARY BLEEDING IN INFANTS AND CHILDREN
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The definitive diagnosis of bleeding in the lung in the non-hemoptysizing patient is challenging and eventually relies on bronchoscopy. Physical examination is non-specific and ranges from subtle tachypnea, dyspnea, variable crackles and wheezing to pulmonary hypertension or frank respiratory failure. Human and chest discomfort/pain are infrequently observed. Laboratory work up beyond the anemia is suggestive but nonspecific.
Willebrand Disease (VWD) being ultimately proposed in 3 of the infants. This underlying vulnerability was deemed to underpin the bleeding that would be precipitated by injury to the lungs, by a common environmental cause, possibly a viral infection. However, since no such direct trigger that could unify the cases was identified, no final etiology was identified and no further publications emerged from that series.

**Diagnostic and Therapeutic Bronchoscopy in Pulmonary Hemorrhage**

Flexible bronchoscopy is key in the initial diagnosis of DAH, in particular in cases without overt airway bleeding. In such cases bronchoalveolar lavage (BAL) results in persistently blood-tinted return fluid. Following the infantile epidemic bleeding in Cleveland, monitoring of the status of the bleeding via sophisticated scoring methods of the bronchoalveolar lavage fluid was developed to facilitate therapeutic decision-making and long-term follow-up. The use of flexible bronchoscopy for therapeutic interventions for bleeding while common in the adult literature has been limited in the pediatric practice. The largest report on a series of 14 pediatric patients with acute life-threatening pulmonary hemorrhage used CO2 laser bronchoscopy, Nd:YAG laser bronchoscopy, endoscopic balloon occlusion of a lobe or main bronchus, topical airway vasoconstrictors and endoscopic tumor excision. However, we may, however, be at the dawn of a new era for the pediatric interventional bronchoscopist in our ability to effectively control airway bleeding in DAH. Activated recombinant factor VII (rFVIIa) and tranexamic acid, a synthetic anti-fibrinolytic agent have been systematically administered to control recalcitrant bleeding in the lung, however, an extension of the concept by administering the agents directly into the airway has now been repeatedly documented. Intrapulmonary instillation of rFVIIa has been reported to dramatically control DAH with similar results using tranexamic acid in series of adult patients. Our group has reported successful use of the adult protocol in two children. Our procedures were undertaken as interventions of last resort; in both cases the hemorrhage was visualized during the procedure and its resolution following the treatment was immediate, unequivocal, and definitive. We are advocating this intervention as an attractive treatment of DAH in both adults and children considering its remarkable ease and efficacy and apparent absent side effects.

**Prognosis:**

There is limited information about long-term outcome of pulmonary hemosiderosis. Older studies suggest that the overall prognosis may not be favorable in the “idiopathic” cases. However, a more recent large multicenter French study is more promising in its outcomes. Clearly, these cases require careful follow-up and appropriate treatment that most often consists of corticosteroids and immunosuppressive therapies. Importantly, some cases with DAH may declare themselves in later life as having well-defined autoimmune diseases. While the infant population with AIPH discussed above likely reflects a different subclass within the “Idiopathic” group, individuals with recurrent bleeding and mortality have been reported.

**Clinical examples/Specific conditions**

The examples discussed will include metabolic disorders, specifically Lane-Hamilton syndrome (hemosiderosis associated with celiac disease), Pulmonary-renal syndromes, and cardiovascular structural abnormalities that present with pulmonary bleeding.

**References:**


Pediatric Pulmonology

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**CAUSES OF HYPERSENSITIVITY PNEUMONITIS IN CHILDREN—WHAT TO LOOK FOR IN THE ENVIRONMENT?**

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Exogenous allergic alveolitis (EAA), in the North-America also called hypersensitivity pneumonitis (HP), is a complex syndrome caused by numerous inhaled agents including agricultural dusts, bio-aerosols, fungal-, bacterial- or protozoan microorganisms, and certain reactive chemicals. In children two major inciting allergens must be considered primarily: (1) bird (avian) including down and (2) inhaled particles derived from fungi, like thermophilic actinomycetes, or rarely fusarium, aureobasidium and epicoccum. The condition is relatively uncommon however it is the most frequent interstitial lung disease in children, making up about 50% of all cases (1).

In a recent study we determined the current practice of diagnosis and therapy, using the Surveillance Unit for Rare Pediatric Disorders (ESPED), to identify incident cases of HP in Germany. The median age of the 23 children identified was 9.4 y (4.4–15.1). All presented with dyspnea at rest or with exercise, mean FVC was 39% of predicted, 7/23 children already had a chronic disease state at presentation. IgG against bird was elevated in 20, and against fungi in 15. Bronchoalveolar lavage was done in 18 subjects (41% lymphocytes), and lung biopsy in 6. Except 2, all children were treated with prolonged courses of systemic steroids. Outcome was not favorable in all cases. The problem consisted of late diagnosis in up to a quarter of the children with EAA and possibly inappropriate steroid treatment (2).

In countries with a high prevalence of tuberculosis and HIV, EAA is an unusual differential diagnosis. Vice versa, under Western European conditions, in children with nodular interstitial pattern on CT, tuberculosis and HIV should be kept in mind. Low values for hemoglobin, alterations of leukocyte count and differential; hypoalbuminemia and hyponatremia supports the diagnosis of TB.

For the diagnosis at least 4 of the following 7 criteria should be fulfilled: (1) History of appropriate allergen exposure, (2) Restrictive lung function (FVC <80% pred., FVC/FEV1 <1). (3) positive serum precipitins for allergens, (4) Lymphocytosis (>20%) in BAL, (5) HRCT (nodular, linear, reticular opacities; ground glass), (6) Biopsy (lymphocytic alveolitis, bronchiolitis,
V - Lung Development
NORMAL AND ABNORMAL LUNG DEVELOPMENT-RECENT ADVANCES
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Overview of lung development
Normal lung development is initiated by outpouching of the foregut endoderm to form two lung buds along with the trachea. The nascent lobes are then established, followed by repeated rounds of branching morphogenesis to produce the respiratory tree, which is comprised of thousands of branches. Following on from these reiterative rounds of stereotypical branching morphogenesis, the terminal branches undergo further morphogenesis, during the canalicular and then saccular phases. It is during these later phases that primitive epithelial sacs are formed which will subsequently develop into the alveoli. Elucidating the complex genetic and cellular processes that generate the lungs is vital for us to understand both congenital and adult onset lung disease. There is now a wealth of published evidence clearly linking perturbation of genes and pathways critical for lung development with the pathogenesis of lung disease. In addition, a number of laboratories are actively seeking novel ways of manipulating genes important for lung development to repair or regenerate damaged lung tissue and ultimately to treat disease (Rock and Konigshoff, 2012; Herriges and Morrisey, 2014). Much of the work to understand normal and abnormal lung development is undertaken in mouse because of the similarity to humans, the genetic tools and the advances in our understanding of lung development. In addition, a number of laboratories are undertaking in mouse because of the similarity to humans, the genetic tools and the advances in our understanding of lung development.

Wnt2/2b- role in specification of lung endoderm
Recent investigations have shed light on how the very early lung is specified and can be distinguished from other organs that are also generated from the foregut endoderm e.g. liver, esophagus. Defects in these early specification events can give rise to agenesis of specific foregut derived structures as well as incomplete separation of the osophagus and trachea, resulting in trachea-oesophageal fistula.

Detailed genetic analysis has shown that both Wingless-related MMTV integration site 2 (Wnt2) and Wnt2b are necessary for early lung specification. Mouse embryos that lack Wnt2 and 2b show complete lung agenesis and do not express Nkx2.1 (Goss et al., 2009). The authors went on to show that these Wnt ligands signal through the canonical (β-catenin) downstream signaling pathway; lungs fail to form following deletion of β-catenin in the endoderm. Tbx4/5 a view from the mesoderm

Much of the research in lung development is focused on epithelial derived factors, however the lung develops by reciprocal signaling interactions between the epithelium and the mesenchyme and both tissues are required for normal lung formation. One reason that less work has been done to define mesenchyme derived factors is that there are fewer genetic tools available to specifically manipulate gene expression in the lung mesenchyme alone. Despite this it has long been known that Fgf10 and Wnt2 are mesenchyme specific and both are absolutely required for lung development. Two T-box (Tbx) transcription factor genes have now been shown to be mesenchymally derived factors that are both required for lung development (Goss et al., 2009).

Cell adhesion and polarity
The establishment and maintenance of cell polarity is critical for normal lung development and function. A number of recent studies have examined the function of different polarity proteins in lung development and as expected, mutations in these genes cause profound morphological defects. Apical-basal (A/B) polarity is the most well studied polarity axis; investigations in vitro as well as in organisms such as Drosophila have elucidated that A/B polarity is maintained by an apical protein complex consisting of atypical protein kinase C, Par3 and Par6 and a complex of Par1, Dlg, Lgl and Scribble that maintains the basolateral membrane domain. Analysis of a Discs large homologue 5 (Dlg5) mouse mutant revealed that this protein is required for lung branching morphogenesis. Dlg5 mouse mutants show reduced branching during embryogenesis and post-natally show significant airspace enlargement reminiscent of emphysematous lungs (Nechiporuk et al., 2013). Crumbs homologue 3 (Crb3), another A/B associated protein that binds to the apical aPKC, Par3, Par6 complex has also been shown to be critical for lung epithelial morphogenesis and more specifically, has a key role in linking the apical membrane to the cytoskeleton (Whiteman et al., 2014). Orthogonal to the A/B axis is the planar polarity axis, sometimes referred to as tissue polarity. Our own studies have shown that this pathway is also critical for normal lung development highlighting the importance of polarity for normal airway morphogenesis (Yates et al., 2010; Yates et al., 2012). Cell adhesion complexes, such as adherens and tight junctions, are closely linked to polarity, for example, cell: cell adhesion is a pre-requisite to establishing polarity. In mammalian cells, the tight junctions are situated just below the apical surface of the cells and these protein complexes provide a barrier to regulate paracellular permeability of ions and solutes. Maintaining the epithelial barrier is essential for normal lung function and its breakdown has been shown to be a hallmark of a number of lung diseases including Asthma and COPD. Claudin 18 (Cldn18) is a tight junction protein that is highly abundant in the lungs and unlike other lung claudins, Cldn18 is found exclusively in the epithelium and not in the endothelium (Li et al., 2014). Ubiquitous deletion of Cldn18 revealed an important role in the alveolar epithelium. Monolayers of alveolar epithelial cells derived from these mutant mice displayed a decreased transepithelial resistance indicating disrupted barrier function. Consistent with this finding, the mice also showed increased permeability to ions and solutes along with increased alveolar fluid clearance.

Control of mitotic spindle orientation is another important area in regulating lung development. This aspect of cell biology, linked to polarity, is important for the self-renewal and differentiation of epithelial cells. Eyes absent 1 homologue (Eya1) has emerged as a key regulator of cell polarity and spindle orientation in the lungs (El-Hashash et al., 2011). In this study, the authors’ showed that a-symmetric cell division takes place in the distal lung epithelium and that Eya1 regulates

Pediatric Pulmonology
cell polarity and spindle orientation. Eya1 also regulates the localization of Numb, a protein that inhibits progenitor cell identity promoted by Notch signaling.

Epigenetic modifiers of lung development

An increasing number of reports are highlighting the effects that epigenetic factors, associated with diet or environment, can have on both lung development and disease. Epigenetic mechanisms, such as histone modification have been asociated with diseases like COPD and asthma and recently histone deacetylases (Hdac) have emerged as key regulators of lung development (Zhu et al., 2012). These genes, along with histone aminotransferases (Hats, Histone acetyl transferases in humans), are involved in regulating the modification of histones at specific amino acids. Hats regulate acetylation of the histone tail whilst Hdacs remove the acetyl group thereby leading to gene silencing. Maintaining a balance between the levels of Hats and Hdacs is necessary for normal lung development and in addition, these genes can directly target a variety of other proteins e.g. Bmp4 and the cell cycle mediators Rb1, p16 and p21. The functions of other epigenetic mechanisms such as methylation in lung development are not well understood and this is a subject that is likely to yield further interesting results.

The research areas discussed above illustrate just a few of the recent advances in our understanding of lung biology. Many of these key developmental genes have additionally been shown to be aberrantly expressed in congenital or adult lung diseases and on-going studies in ours and other labs are likely to discover many more important links between lung development and disease in the near future.

References


“sigh” to the infant, thus opening microatelectasis and recruiting more ventilation units. It was shown that synchronized NIPPV (SNIPPV) compared with NCPAP may improve the patency of the upper airway, could accelerate respiratory drive, improves thoraco-abdominal synchrony that stabilizes the chest wall, improves lung mechanics and decreases the work of breathing in premature infants. When NIPPV was compared to NCPAP for the different indications of NRS, it was shown to enhance the potential of NRS.

A recent meta-analysis demonstrated a relative risk reduction for intubation in the first 72 hours in the NIPPV group compared with NCPAP (RR 0.60, 95% CI 0.43, 0.83). The NIPPV trial was a large international multicenter randomized trial powered to study the important outcome of BPD, recruiting 1,009 extremely low birth weight babies, and it showed no difference between babies randomized to NIPPV compared with CPAP. Yet, the results of this study should be considered with caution because of several limitations. For example: There was no uniform experience and equipment used for NIPPV among participating centers; approximately 50% of the infants were supported with biphasic CPAP that is a limited form of NIPPV (maximal peak inspiratory pressure of 9–10 cm H2O in that study).

SNIPPV vs. NCPAP for later use, post extubation at RDS resolution, as a “bridge” to spontaneous unsupported breathing was shown to be more effective than NCPAP. A pooled meta-analysis showed that SNIPPV was more effective than NCPAP in preventing failure of extubation (RR 0.21 (0.10, 0.45)) and the number needed to treat was only 3 infants to prevent one extubation failure. SNIPPV vs. NCPAP, post extubation, also tended to decrease the rate of BPD. SNIPPV may be more effective than NCPAP also for apnea of prematurity. A meta-analysis, regarding apnea of prematurity, suggests that SNIPPV is more efficacious with apnea that is frequent or severe. However, the studies performed addressed short-term outcomes and as such could not address properly the incidence of requirement for reintubation. Thus, more studies are needed before recommending SNIPPV as standard of care for apnea of prematurity.

While non-invasive ventilation is probably safe, its success depends on gestational age. The data indicate that surfactant may still have a significant role in the treatment of RDS, especially in ELBW infants. Recently, Morley et al. and the SUPPORT study reported on an intubation rate of ~50% in their NCPAP group in ELBW infants. This leads us to the INSURE approach. This approach may allow the infant to benefit from both, surfactant and NRS. A Cochrane review concluded that the INSURE approach with NCPAP compared with later selective surfactant administration, continued mechanical ventilation, and extubation from low respiratory support was associated with less need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. Another option for surfactant application to the trachea without endotracheal intubation was described by using a thin catheter in spontaneously breathing preterm infants receiving NCPAP. This technique was reported to reduce the need for mechanical ventilation. There are ongoing trials with inhaled surfactant. To summarize, the available evidence supports the preference of early or later use of NIPPV/SNIPPV compared to NCPAP because of minimizing the use and the length of endotracheal ventilation. There are data to suggest that this approach may also reduce the rate of BPD, however this was not shown yet. The results of a large international RCT comparing both primary, and post-extubation use of NIPPV with NCPAP, with a composite primary outcome of death or BPD at 36 weeks’ corrected age indicate no additional benefit, or risk, conferred by NIPPV in comparison to NCPAP.

Whether NIPPV/SNIPPV is more beneficial than NCPAP within the INSURE approach needs to be shown. Recently, heated, humidified high-flow nasal cannula (HHHFN) is frequently used as a mode of NRS. High flows result in washout of anatomical and physiological dead space and contribute to improved fractions of alveolar gases with respect to carbon dioxide as well as oxygen and decrease the work of breathing and the energy cost of gas conditioning. HHHFN probably creates positive end expiratory pressure (PEEP) that may contribute to its beneficial effect. However, the PEEP that is not monitored, had raised concerns regarding the safety of HHHFN in terms of air leak. Recent prospective studies support the notion that HHHFNC is as effective as NCPAP for early stages of RDS, post extubation and for apnea of prematurity. Yet, more studies, especially in the initial treatment of RDS and in ELBW infants, are needed before adopting HHHFNC as an alternative mode of NRS in these conditions.

New modes of NRS such as neurally adjusted ventilator assist (NAVA), and nasal high frequency ventilation, need to be further studied before concluding on benefits for the short and long term outcomes in premature infants.

Non-ventilatory measures in the treatment of RDS, such as caffeine, nutrition, fluid and PDA management and postnatal steroids in certain conditions should be included in the care of premature infants with RDS in order to minimize the rate of BPD.

The noninvasive ventilator strategy needs to be confirmed by large prospective randomized controlled trials (with long-term follow up) in order to assure it is applicable to most ELBW infants. Furthermore, the strategy needs to be tailored to individualized infants according to the infant’s maturation; antenatal steroid treatment and severity of RDS; general condition; and to certain practical NICU conditions such as experience, personnel and timing during the day.

References


BPD- WHAT DO WE KNOW ABOUT THE LONG-TERM OUTCOME?

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Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects the mortality and morbidity of children born preterm. The original cases, now termed “old” BPD, were the results of aggressive ventilation strategies in relatively large, premature infants. Over the years, the quality of ventilatory treatment in neonatal care has improved (due to e.g. introduction of antenatal steroids and surfactant replacement). Clinically, however, only the incidence of severe BPD has decreased while the overall incidence of BPD has remained constant. [1] The increasing rates of survival among the smallest of premature infants, contribute to an increase in the incidence of the so-called “new” BPD. New BPD is closely associated with low gestational age and low birth weight. The most prominent features of new BPD are disruption of lung development, with decreased septation and alveolar hypoplasia leading to fewer and larger alveoli and dysmorphic pulmonary vasculature.

A recent systematic review of the published literature of general and respiratory health outcomes in adult survivors of BPD showed that survivors of BPD experience more problems during childhood, adolescence and adult age when compared to children born preterm without BPD as well as when compared to healthy controls. [2] These problems emerge in different areas of functioning. We will successively describe pulmonary outcome, neurodevelopmental outcome and growth and nutritional problems at school age and beyond.

Pulmonary Outcome at school age and beyond

Chest symptoms and pulmonary function abnormalities have been found in children as well as in adolescents and young adults with a history of “old” and “new” BPD. The symptoms are often described as recurrent episodes of wheezing, cough and reduced exercise tolerance (compared to peers). [2,3] Additionally, children with BPD describe symptoms due to airway hyperresponsiveness to exercise, that improve after bronchodilator administration. The pulmonary function abnormalities consist of airway obstruction, airway hyper reactivity and hyperinflation as well as an exercise restriction. [2] Some children with BPD have a lower diffusion capacity. [2] The prevalence of airway hyperreactivity is not different from that of children born prematurely without BPD. Children with BPD who have demonstrable airway hyperreactivity do not have elevated levels of exhaled nitric oxide (a marker for eosinophil-driven inflammation) or an increased incidence of atopy. [4] Therefore, although children with BPD and children with asthma have similar symptoms, the underlying pathophysiology of these two diseases seems to be different. The lungs recovered from older childhood and adult survivors of BPD demonstrate airway wall thickening similar to individuals with asthma. In addition there are morphologic changes noted on CT scans of the chest, which are compatible with a diagnosis of fixed peripheral airway narrowing (see below).[2,5] Children with asthma-like symptoms due to BPD may respond to inhaled corticosteroids, but the effect is less consistent than in children with asthma [6]. The majority of children with BPD show abnormalities on the CT-scan, including linear and triangular opacities, mosaic perfusion, air-trapping and/ or multifocal emphysema, and bronchial wall thickening both in the first year of life and at older age [2,5].

Cardiovascular complications

Because of increased vascular resistance in the lungs, children with BPD may develop right ventricular hypertrophy. Left ventricular hypertrophy is also seen, possibly associated with systemic hypertension which is commonly found in children with BPD. [7] A rare but serious complication is the development of pulmonary artery hypertension and the resultant right heart failure (cor pulmonale).[7] The incidence and prevalence of pulmonary hypertension in these infants, its risk factors and the outcome of BPD-associated pulmonary hypertension are insufficiently known. Little is known about the characteristics and outcomes of BPD-associated pulmonary artery hypertension in the current era. Severe BPD complicated by severe pulmonary hypertension is associated with an increased early mortality rate. In survivors, a recent global pediatric Pulmonary Hypertension Registry suggests that BPD-associated pulmonary hypertension is still present several years after birth and is associated with significant morbidity [8].

Neurodevelopmental

Children with BPD (compared with those without BPD) are at increased risk for neurodevelopmental impairment. Underdeveloped motor skills, both gross and fine, occur more often in patients with BPD Some studies show that more than one-half of the (severe) BPD group have abnormalities of gross and/or fine motor skills at 10 years of age. More attention deficit problems are seen and children with BPD are more often diagnosed with attention deficit hyperactivity disorder (ADHD). [9] Children with BPD have a lower intelligence quotient (IQ) and usually have more problems with progression at school.

Feeding and growth

Problems with growth and nutrition are common directly after birth, but are also seen later in childhood. Some studies found that growth remains delayed at older age, but more recent studies have found no difference in growth when correcting for confounders. [10] Various study designs have been used to study specific effects of BPD in children, adolescents and adults. It is currently unclear whether these provide a complete survey of relevant problems. This makes it difficult to ensure that long term follow up, which is of special importance in neonatal disorders, captures all aspects of medical, psychological and social importance to these patients. In general, an important finding from review of the adult literature is the relative absence of studies to determine non-pulmonary outcomes and consequently there is a need for a multidisciplinary research in this population.

References

The Importance of Tobacco Control in Promoting Child Lung Health

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In 2014, the world celebrated the 50th anniversary of the US Surgeon General’s report on ‘Smoking and Health’ which caused a paradigm shift in tobacco control. This report, 12 years after Doll and Hill’s landmark 1964 BMJ paper1 describing the clear association between smoking and lung cancer, triggered global attention and sowed the seed for tobacco control measures. Although reports of isolated tobacco control measures date from 1590 when Pope Urban VII threatened to excommunicate people anyone who took tobacco in a church vicinity,2 it was not until 1999 that the World Health Organisation made global tobacco control a priority.2 That tobacco control is vital in promoting child lung health is indisputable. There are numerous reasons for this, including:

(a) the unquestionable fact that second hand tobacco smoke (SHS) is harmful to the fetus and children,
(b) pro-smoking messages are highly effective marketing tools3 that continue to be pushed by the tobacco industry,
(c) young children are vulnerable to the adults’ actions and are unable to defend themselves,
(d) tobacco smoking is an addiction and adults who smoke often cannot or do not act in the interest of their children when it comes to tobacco smoking,
(e) smoking usually has its roots in adolescence. If individuals do not take up smoking during this period it is unlikely that they ever will.4 Once smoking becomes established, cessation is challenging; the probability of subsequently quitting being inversely proportional to the age of initiation.5 Thus it is not surprising that pro-smoking messages had been, and continue to be, often targeted at the young,
(f) the tobacco industry has a well-oiled machinery whose influence is not restricted to politicians. For example, when tobacco dependence as a diagnosis in DSM-III was viewed by tobacco companies as an adverse event, “the industry took steps to try to mitigate its impact. These actions mirror industry tactics to influence medical research and policy in various contexts worldwide. Such tactics slow the spread of a professional and public understanding of smoking and health that otherwise would reduce smoking, smoking induced disease, and tobacco company profits”.6

In addition to the above, the economic cost of SHS is large.7,8 A 2012 study based in the USA estimated that in 2006, “SHS-attributable deaths resulted in a loss of nearly 600 000 years of potential life lost and $6.6 billion of lost productivity, or $158 000 per death”.7 Based on two German birth cohort studies, the estimated smoking attributable total costs per child exposed to SHS “at home was $7 [10–165] (patio/balcony) and 144 [6–305] (indoors) compared to those with no exposure”.8

An emerging problem is the propagation of e-cigarettes (battery operated nicotine vapourisers) which is increasingly being adopted by big tobacco companies. Some have predicted that e-cigarettes will overtake the sales of conventional tobacco products within a decade. To entice young people, companies are using candy and fruit flavors in these products. In Sept 2013, the USA Center for Disease Control and Prevention press release highlighted the doubling of middle and high school students who use e-cigarettes and that “in 2012 more than 1.78 million middle and high school students nationwide had tried e-cigarettes”. <http://www.cdc.gov/media/releases/2013/p0905-e-cigarette-use.html>

Tobacco control encompasses public health science, policy and practice dedicated to restricting tobacco use and exposure. The 6 tobacco control policies identified by WHO as part of their ‘Tobacco Free Initiative’, abbreviated as ‘MPOWER’ are: (i) Monitor of tobacco use and prevention policies, (ii) Protect people from tobacco smoke, (iii) Offer help to quit tobacco use, (iv) Warn people about the dangers of tobacco, (v) Enforce bans on tobacco advertising, promotion and sponsorship, and (vi) Raise taxes on tobacco. The intervention points within these policies are outlined in the document that is available in many languages. <http://www.who.int/tobacco/mpower/package/> However, policies on tobacco control are most effective if accompanied by legislation that are enforced. A Cochrane review has shown that “legislative smoking bans does lead to a reduction in exposure to passive smoking”.9 Readers are also referred to a website which outlines tobacco control legislations around the world <http://www.tobaccocontrollaws.org/>.

As clinicians in respiratory medicine, we have a duty of care to support tobacco control measures in our own setting. We should take every opportunity in our clinical and research activities to limit children’s exposure to SHS and eliminate any propensity for children initiate tobacco smoking. There is still much to be done today (March 2014); e.g. plain packaging of tobacco is only legislated in a few countries (Australia) and even in advanced countries like the UK, the right of children not to be exposed to SHS in the car (through banning of smoking in the car) is only currently being debated.10

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Keywords: Pollution, airway disease, asthma, children

The relationship between ambient air pollution and asthma has been a major focus of research and debate over the past few decades. Children are more susceptible to the detrimental effects of air pollution as their developing lungs and airways may be more sensitive to damage by various environmental pollutants [1]. Children have higher exposure to ambient air pollutants because of their higher minute ventilation adjusted for body weight and they usually spend more time exercising outdoors than adults. Ambient air contains a wide variety of pollutants including gases such as ozone ($O_3$), sulfur dioxide ($SO_2$), carbon monoxide (CO), oxides of nitrogen (NOx), and particulate matters with different sizes. Because of the complexity of the pollutants in ambient air, it is not easy to determine the role of a specific pollutant in respiratory morbidity due to complex interactions between these pollutants. There have been many time-series and cross-sectional studies investigating the adverse effects of air pollution on children with asthma [2]. Increasing levels of air pollutants have been found to be associated with visits to accident and emergency departments, hospitalization, deterioration in lung function, and increase use of asthma medication. However, the effect of ambient air pollutants on the prevalence of asthma is not as clear.

The most important origin of various ambient air pollutants is from the combustion of fossil fuel. In industrialised nations, power plants and motor vehicles are the most important sources of pollution. Particular matter refers to a mixture of solid particles or liquid droplets which can be inhaled into the lung. Particles with an aerodynamic diameter greater than 10 µm are unable to reach the lower airways as they are deposited on the nasal pharynx. Fine particles are less than 2.5 µm in diameter (PM$_{2.5}$) and are produced during the process of combustion from motor vehicles, power plants and wood burning. Ultrafine particles have a diameter of less than 0.1 µm. Although these ultrafine particles contribute very little to the total particle mass, they are the most abundant in terms of number and offer a very large surface area capable of inducing inflammatory changes in the airways and alveoli. In experimental model of sensitized mice, inhalation of ultrafine particles was found to have an adjuvant effect in inducing airway inflammation [3]. Further studies are necessary to clarify the role of these particles in respiratory morbidities in humans.

Sulphur dioxide used to be a major air pollutant in many countries. It is released into the atmosphere as a result of combustion of high-sulphur containing coal and oil. With the restriction on sulphur content of fuel in most developed countries, the concentration of this pollutant has dropped significantly. In a time-series study of childhood asthma admission in Hong Kong carried out in the early nineties, daily asthma admission for childhood asthma would increase by 6% for every 10 µg/m$^3$ increase in $SO_2$ [4]. The increase in the concentration of air pollutants such as $NO_2$, $O_3$ and PM$_{10}$ were also significantly associated with asthma hospitalization in adults [5]. Although the evidence for the harmful effects of ambient air pollution on asthmatics are quite consistent, there are little data to support the role of air pollution in causing an increase in asthma prevalence. The early studies comparing the former East and West Germany clearly showed that asthma and bronchial hyperreactivity were far more common in the former West Germany than the more polluted East Germany [6]. Using the standardized ISAAC methodology, we have demonstrated that Chinese children from Hong Kong had a 3- to 4-fold higher prevalence of asthma than those children living in more polluted cities in mainland China such as Guangzhou or Chongqing [7]. From the data of these epidemiological studies, it appears unlikely that air pollution plays a major role in causing the increase in asthma prevalence in the past two decades.

With the process of urbanization in many countries around the world, the components of ambient air pollutants are changing along with the economic development. Traffic exhaust and power plants are the major sources of pollution in developed nations resulting in increasing level of ozone in the ambient air. Ozone is a highly reactive gas produced by photochemical reaction of oxides of nitrogen and hydrocarbons emitted from fuel combustion. A recent prospective study of 3535 schoolchildren recruited from southern California was conducted to investigate the long term effect of exposure to ozone [8]. These children were studied longitudinally for up to 5 years. For children recruited from communities with high ozone levels, the relative risk of developing asthma for those playing 3 or more team sports was 3.3, compared with those playing no sports. However, such effect was not found in areas of low ozone. Interestingly, exposure to other pollutants did not change the effect of team sports. Heavy exercise can possibly precipitate asthma attacks in previously undiagnosed children with asthma, but it cannot explain the result that the increased risk was only found in children with heavy exercise from the more polluted communities. In order to determine the role of traffic pollution in the development of asthma in young children, Brauer et al conducted a longitudinal study with a prospective birth cohort [9]. Over 3,000 children were recruited at birth and followed until 4 years of age. Air pollutants concentrations at the home address were calculated by a model combing air pollution measurements with a geographic information system. A number of respiratory outcomes including wheezing attack, and dry cough at night were associated with the levels of PM$_{2.5}$ and soot. However, no significant correlation was found between doctor-diagnosed asthma and the traffic-related pollutants. We have to interpret the data cautiously as the diagnosis of asthma in the first few years of life can be difficult. Long term follow up of the children until they reach school age is necessary to clearly determine the possible detrimental effect of exposure to traffic-related pollutants.

The current evidence of the detrimental effects of outdoor air pollution on children and adults with pre-existing pulmonary disease is fairly clear. Indoor air pollution has also been implicated in the development of asthma. In particular, the indoor use of open fire and gas burning have been found to be associated with asthma. A recent study from ISAAC phase 3 showed that the use of open fire cooking was significantly associated with asthma diagnosis and wheeze. However such findings were only significant in low-income countries [10]. Prospective intervention trials are needed to evaluate if reduction of such exposure may have beneficial effects. Putting all the available evidence together, it is clear that both outdoor and indoor air pollution have significant impact on childhood airway diseases especially those with preexisting abnormalities. There is an urgent need for greater efforts in reducing the current level of ambient air pollution as well as indoor air pollution in different regions of the world but there are no easy solutions to this global problem.

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VI - Technologies in Pediatric Pulmonology

RECENT ADVANCES IN LUNG IMAGING: WHERE WE ARE NOW

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Medical diagnostic imaging has evolved and rapidly improved, as a result of new developments in diagnostic digital imaging techniques.

Combined with technical advances in computer processing power, and high-resolution display monitors/workstations which have increased computing power and electronic data archive systems, diagnostic imaging departments have been transformed into digital environments.

Yet despite new technology, there remains a lack of dedicated equipment suitable for use in children.

PROJECTION RADIOGRAPHY

The development of digital imaging in plain film radiography is advantageous within paediatric imaging. First introduced to computed radiography (CR) and later in direct readout radiography (DR) systems (utilising flat-panel detector (FD) technology), this technology helped provide greater efficiency in converting incident X-ray energy into image signal.

FLUOROSCOPY

The introduction of digital fluoroscopy with its high-speed digitisation of the analog video signal has revolutionised real-time fluoroscopy that relied on the use of image intensifier/TV systems to display the diagnostic image.

COMPUTED TOMOGRAPHY (CT)

CT is a proven essential diagnostic imaging technique and is considered the most sensitive method for evaluating airway diseases in children.

Two CT imaging configurations exist: namely, multidetector CT (MDCT) with up to 320 detector rows and dual-source CT (DSCT) utilising MDCT technology. The increasing temporal and better spatial resolutions have extended the role of CT applications in young children to include cardiac imaging. Advantages of these systems include subsecond tube rotation times (down to 0.33 s). This increase in acquisition speed has the potential for reducing motion and respiratory artefacts and improving image quality. The overall reduction in examination acquisition time may also obviate the need for sedation in some children. The availability of small detector elements (0.5 mm) combined with thin-slice collimation provides isotropic resolution that allows image data to be manipulated/reformatted in any orthogonal plane and displayed as either 2- or 3-dimensional images that have the same spatial resolution as the base axial data set and with reduced partial volume artefact.

320-Row MDCT

The availability of a 320-slice MDCT allows for larger volume coverage of up to 16 cm in the z-axis coverage. The advantage of this is that this coverage is well within the clinical range of thoracic length in neonates and young children. Therefore, imaging of the entire chest can be accomplished in a single-volume cone-beam acquisition during one tube rotation of 0.35 s. This is much faster than either helical MDCT or DSCT acquisition.

Axial volumetric acquisitions have the potential of radiation dose saving. Due to the large nominal beam width used, the contribution of the penumbra effect is less prominent. Also unlike in helical scanning, over-ranging in the longitudinal axis is not applicable in this instance, as the exposed range corresponds exactly to the imaged range and therefore more effective usage of the radiation exposure for image formation. Axial volumetric acquisition can be applied to other clinical situations that include cardiac imaging in children, as when using prospective ECG-gating, the entire heart can be imaged within a single tube rotation.

Dual-Source CT

Second and third generation DSCT (Siemens Flash, and Force, Forchheim, Germany) are currently the latest in CT technology incorporating two X-ray tubes each with corresponding 64-row detector systems, (each contributing 128 slices by means of a z flying focal spot), mounted at an angular offset of 90° to each other.

Designed primarily for cardiac imaging, the two-tube detector system does not operate simultaneously, but in tandem, where data from the second detector system are collected a quarter of a rotation later following the first set of detectors. This allows gapless volume high-pitch scanning (up to 3.2 pitch), avoiding overlapping slices with reduced radiation dose.

Together with fast gantry rotation times and fast temporal for the first time imaging children with high heart rates is no longer a limiting factor, and is found to be invaluable in both pre- and post-surgical assessment of a wide variety of congenital cardiothoracic diseases even in younger children.

Dual-Energy Dual-Source CT

The availability of two X-ray tubes allows simultaneous acquisition of two data sets at different tube potentials (80 and 140kVP), during the same phase of contrast enhancement and excludes temporal changes and spatial misregistration. This technique takes advantage of differences between tissue and material composition and differences in their photon absorption characteristics. In particular, material with a high atomic number (like iodine) exhibit a different degree of attenuation between the two tube potentials. By applying specific post-processing algorithms to the acquired data, virtual unenhanced and virtual angiographic data sets can be generated, based on the three-material composition principle. e.g. within the abdomen materials analysed are soft tissue, fat and iodine, whilst in the chest, soft tissue, air and iodine are analysed. Application of the bone removal algorithm will display an angiographic data set without overlying bony structures, resulting in easier image interpretation. This eliminates the need for pre-i.v. contrast scans, as may be required if using a single tube device, for data subtraction purposes. Thus radiation doses are halved.

Patient Care

Due to the speed of present day CT machines, children over 3 years of age are usually compliant for their procedure, provided they are properly prepared through play therapy beforehand, using a mock-up toy of the machine to take the child and their parents through the scanning process. It is also a good opportunity to assess the child’s ability to respond to breathing instructions; otherwise, gentle respiration is encouraged. A range of suitable sedatives may be prescribed to younger children, which include the light-acting sedative chloral hydrate at a dose of 50 mg/kg, or the short-acting midazolam hydrochloride at 0.1 mg/kg body weight.

Some centres prefer the more quick-acting sedative Propofol but this must be administered in the presence of an anaesthesiologist. The use of general anaesthesia is reserved only for those non-compliant patients, or in cases where sedation had not been successful.

MAGNETIC RESONANCE IMAGING (MRI)

Apart from imaging of lung parenchyma and cortical bone, and in some cases of cardiovascular malformations and in trauma cases, MRI is the preferred cross-sectional imaging technique in children. This is due to the multitude of tissue contrasts inherent to this technique, and because there is no exposure to ionising radiation. Paediatric MRI is, in practice, somewhat different from the adult equivalent in that it requires particular attention to preparing the child, optimising the signal-to-noise ratio (SNR), handling motion artefacts and adjusting for differences in tissue contrast.

Further Reading and References

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Pediatric Pulmonology
Abstract

Lung Function: Is Lung Clearance Index the Clue To Early Disease?

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Early cystic fibrosis lung disease

While the lungs of patients with cystic fibrosis (CF) seem to be normal at birth, there is evidence of early infection and inflammation initiating the pathophysiological cascade that leads to the progressive destruction of the lungs over decades. The importance of detection and treatment of early lung disease is increasingly emphasised. Lung function assessed by means of forced expiratory manoeuvres allows for the measurement of FEV₁ (or FEV₁,₃₂ in younger children), which remains the most used functional parameter to assess lung disease in CF. However, two major issues have arose with these parameters. First, with improving CF care, most children have a normal FEV₁ until adolescence, despite clinical and radiological evidence of on-going lung disease. Accordingly, FEV₁ lacks the power to detect a treatment effect in these young patients with preserved lung function. Second, the feasibility of forced expiratory manoeuvres is not optimal in preschool children, and both the measurement technique and recorded parameters have to be adapted. These limitations prompted the search for other functional measurements with an improved ability to quantify early lung disease in children with CF.

What is the lung clearance index?

The lung clearance index (LCI) is calculated from a multiple breath washout maneuver. After a washing phase, during which a tracer gas (SF₆, He or Nitrogen) is inhaled to a steady-state concentration, the elimination, or ‘washout,’ of the tracer gas from the lungs is measured during tidal breathing. The lung clearance index (LCI) is the number of turnovers (volumes equivalent to the functional residual capacity (FRC)) that the patient had to breathe in and out to lower the tracer gas concentration to 1/40th of the starting value. A faster washout results in a lower LCI, and thus reflects more efficient intrapulmonary gas mixing[1].

The measurement requires some collaboration to obtain a regular tidal breathing pattern, which is easier to achieve in young children than a forced expiration. In infants, LCI can be measured either during sleep or after sedation. As LCI takes into account the FRC, it is nearly independent of age, gender and body size beyond the first months of life[1].

The measurement device consists of a bias flow to administer the tracer gas, a flow meter (ultrasonic or pneumotachograph) and a gas analyser (mass spectrometer or other)[1].

LCI as a research tool

While the measurement was described more than 50 years ago, interest in LCI was only recently regained by the CF community in search of new functional measurements sensitive enough to detect early lung disease. Cross-sectional observational studies in pre-school and school-aged children showed that LCI differentiated well between CF and non-diseased subjects and was more abnormal more frequently and at an earlier age than FEV₁ or spirometric indices of small airway disease (FEF₂₅₋₇₅ or FEF₂₅₋₇₅)[2]. LCI was more closely related to structural abnormalities on the CT scan of the lungs than the spirometric indices[3], and almost all of the children with an abnormal CT scan also had an abnormal LCI. Importantly, an abnormal LCI in pre-schoolers was predictive of spirometric abnormalities observed at school-age to some extent[4].

LCI as an endpoint for CF clinical trials

Several small interventional trials have used LCI as the endpoint. For example, a small number of patients was sufficient to demonstrate a significant effect of hypertonic saline[5] in school-age patients with CF and a preserved FEV₁, showing the superiority of LCI over spirometry as an endpoint in this patient group. More recently, an improvement in LCI was seen in patients who were carriers of the G551D mutation and were treated with ivacafator[6]. Thus, LCI is a possible surrogate endpoint for clinical trials.

The measurement protocols were recently standardised to ease multicentre trials. Commercial equipment is now available and has been validated against the ‘gold standard’ setup (mass spectrometry)[1].

LCI in infants and pre-schoolers

MBW measurements in infants are more challenging. As with other lung function tests, specific measuring protocols and devices are needed, and cooperation is not always achievable. Despite this, repeatable measurements have been obtained in infants and pre-school children. The standardisation of measurement protocols and validation of equipment for this age group is ongoing.

Infants with CF have a slightly elevated LCI compared with control subjects, and LCI is already abnormal at 3 months of age in a subset of patients[7]. In a cohort of screened newborns, the LCI at 3 months and at one year of age were correlated, as in most infants the abnormal LCI at 3 months remained abnormal at 12 months of age[7]. Infants infected with Pseudomonas aeruginosa had a higher LCI[8]. LCI has been successfully used as the endpoint in a single trial examining the effect of hypertonic saline in infants and pre-schoolers[9].

LCI as a clinical monitoring tool

Many issues need to be solved before LCI can be used as parameter for routine clinical monitoring of patients with CF. MBW measurements were shown to be feasible within the timeframe of a clinic, even in infants and pre-schoolers[10]. However, data on longitudinal changes in LCI are scarce. The magnitude of change that should be considered relevant is not known. There is no evidence that routine measurement of LCI could improve the treatment of patients with CF. However, as more therapies become available, an objective parameter able to detect early lung disease could help the clinician to select patients who are more likely to improve by additional treatments. In conclusion, LCI is a sensitive marker of early lung disease in patients with CF and seems to be a promising endpoint for clinical trials. Validation of measurement protocols and equipment has been achieved for school-age children and is on the way for infants and pre-school children. Future research will establish the value of LCI as a routine follow-up parameter in CF patients.

References


AEROSOL DELIVERY TO SMALL AIRWAYS: WHAT DO WE WANT TO DELIVER AND HOW?

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Overview—particle size and deposition

The small airways are generally defined as distal airways with an internal diameter of less than 2 mm. These last 7 of our 23 airway generations cover 95% of the total airway surface area. However because the small airways account for but a minute fraction of the airway resistance, the physiologic function of these small airways has been notoriously difficult to measure; thus small airways are sometimes called “the silent zone”. Nevertheless, the small airways are inflamed and narrowed in all stages of asthma and small airways disease is thought to figure prominently in difficult to control asthma, severe asthma, nocturnal asthma, etc.

Therapeutic aerosols

Aerosols usually consist of particles with various sizes, and often different shapes. Particles from a nebulizer solution are usually spherical but particles may have other shapes if the liquid is a suspension. In order to be able to compare particles from different sizes, shapes and densities, the mass median aerodynamic diameter (MMAD) is used. Particles with the same MMAD show the same aerodynamic behavior in the airway. Smaller particles with MMAD of 1–3 \( \mu \text{m} \) are more likely to reach peripheral airways than particles with an MMAD of 5 \( \mu \text{m} \) or higher. Aerosol are also described by the distribution of emitted sizes—the geometric standard deviation (GSD). By definition, a GSD <1.22 is considered a monodispersed aerosol. Most therapeutic aerosol are heterodispersed. In general, the GSD is much greater for aerosols produced by the typical Venturi jet nebulizer so that although the MMAD may be similar comparing the jet nebulizer with a similar vibrating mesh nebulizer with a smaller MMAD, the respirable mass of aerosol (or the fraction of the aerosol in the size range of 2–5 \( \mu \text{m} \) MMAD) is far greater with the mesh nebulizer. The location of deposition is also critically dependent on inspiratory flow. With a slower (30 L/min) and longer inspiration, a greater area can be reached with a larger particle size as with a short and fast inhalation of smaller particles. This is why attempts to deliver aerosol medication to a crying child are completely futile. One advantage of ultrafine particles is less oral deposition and subsequently, less swallowing of the drug.

Medication targeting

Beta-2 agonists are generally targeted to more proximal airway generations containing circumferential smooth muscle. The proximal airway can narrow by contraction of smooth muscle despite the presence of cartilage. Smooth muscle is present down to the respiratory bronchioli, but beyond generation 14, stretching and pulling are more important in maintaining airway patency. Therefore, the target areas for bronchodilators are the proximal airway generations. As a result of the Montreal protocol, chlorofluorocarbon propellants have been removed from pressurized metered dose inhalers (pMDI) and replaced with more environmentally friendly hydrofluoroalkane (HFA)134A. Some inhaled corticosteroids (ICS) will go into solution in HFA134A and, coupled with a redesigned metering valve, this permits the generation of an ultrafine particle with MMAD less than 1.5 \( \mu \text{m} \). There are three ICS with extra fine particle size: HFA beclometasone dipropionate (BDP) licensed in Europe and North America for children 5 years of age and older, ciclesonide, licensed for children 12 years of age and older, and flunisolide, licensed for 6 years and above. As well there is the fixed combination of BDP and flomoteron. Other ICS such as fluticasone remain in suspension in HFA134A and so the pMDI of these ICS has an MMAD no different from the CFC propellant inhaler. Smaller particle size may be of greater importance in young children because of smaller airways, higher breathing frequency, and smaller tidal volume. On the other hand, an adequate breath hold may be more important when using ultrafine particles to decrease medication loss on exhalation. Take for example of an ultrafine ICS pMDI, ciclesonide, a pro-drug that is converted in the airways into the active metabolite des-CIC. These particles with an MMAD size range of 1–3 \( \mu \text{m} \) will bypass the upper airway and have much greater small airways deposition when inhaled with appropriate flow, volume, and a breath hold. However, a recently published Cochrane review found six studies comparing ciclesonide with either budesonide or fluticasone in 3256 children (aged four to 17 years) with chronic asthma. After three months of treatment with ciclesonide compared to budesonide or fluticasone, no relevant differences could be found on asthma symptoms, exacerbations or side effects. Ciclesonide compared to a double dose of fluticasone was assessed in one study and no differences were found in asthma symptoms, use of rescue medication and adverse effects. However, children receiving ciclesonide experienced more asthma exacerbations than children in the fluticasone group. Follow-up time for the published studies was too short for the assessment of outcomes such as exacerbations and growth retardation.

References

S34 Abstract


EFFECTS OF SLEEP ON RESPIRATORY MUSCLE FUNCTION

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Introduction

Lung ventilation requires a highly coordinated contraction of thoracic and upper airway muscles throughout the respiratory cycle. Sleep induces important alterations in skeletal muscle contraction; this is especially true for REM sleep, which is characterized by an obligatory muscle atonia to prevent the subject from acting out his/her dreams. Sleep-related alterations in respiratory muscle contraction explains why many respiratory disorders get worse at night, especially during REM sleep.

Respiratory muscle activity

Upper airway muscles

For optimal lung ventilation to occur, a number of upper airway dilator and constrictor muscles must coordinate their respective phasic (inspiratory and/or expiratory) activities along with that of the thoracic respiratory muscles throughout the breathing cycle. The importance of this coordinated phasic activity is particularly manifest at the level of the pharynx; indeed, the collapsible nature of this muscular tube, necessary to fulfill other crucial functions such as vocalization and swallowing, carries the risk of airway closure. Furthermore, tonic activity of the pharyngeal dilators is also important to maintain the pharynx open, especially during inspiration, when intraluminal pressures are negative.

Thoracic muscles

The diaphragm is the main inspiratory muscle and, as such, is responsible for most inspiratory efforts at rest. Tonic contraction of intercostal muscles is important to affix the rib cage, which in turn prevents rib cage retractions in inspiration and preserves functional residual capacity at end-expiration. Accessory muscles of inspiration, such as the sternocleidomastoids, are active when larger inspiratory efforts are needed to prevent diaphragm fatigue. For any inspiratory contraction of the diaphragm, tonic contraction of abdominal muscles acts synergistically by allowing a greater increase in abdominal pressure, which in turn increases lower rib cage dimensions through the area of apposition of the diaphragm. With higher ventilatory demands, abdominal muscle expiratory phasic activity (i) increases expiratory flow and respiratory rate; (ii) increases tidal volume by decreasing end expiratory lung volume and (iii) acts synergistically with the diaphragm by driving it upwards and storing elastic energy in diaphragm muscle fibers for the next inspiration.

Effects of sleep on respiratory muscles

The “wakefulness stimulus” to breathing was reported some 50 years ago (1). While sleep onset is normally characterized by an immediate increase in PaCO₂ of 4–5 mmHg, the effect of sleep on respiratory muscle activity depends highly on sleep stages. In particular, the REM sleep-related inhibition of postural muscle activity further alters respiratory muscle contraction.

Sleep and upper airway muscles

Sleep has a major effect on pharyngeal dilator muscle activity. Indeed, the decrease in pharyngeal muscle tone during sleep is largely responsible for the normal increase in PaCO₂ with sleep onset. In addition, the REM sleep-related abolition of phasic inspiratory and tonic activity of the upper airway muscles promotes upper airway obstruction. Interestingly, recent studies in adult rats have unraveled that a muscarinic cholinergic pathway linked to G protein-coupled inwardly-rectifying potassium (GIRK) channels mediates REM sleep-related pharyngeal muscle inhibition (2). In addition, other potassium channels are responsible for pharyngeal muscle activity in non-REM sleep (3).

Sleep and thoracic wall muscles

The effects of sleep, especially REM sleep, upon a given thoracic respiratory muscle are highly dependent on the importance of non-respiratory (postural) activity of that muscle. The effects of sleep on the diaphragm, whose primary function is for respiration, are much slighth than on other respiratory muscles, such as the intercostal and abdominal muscles, whose non-respiratory function is largely at least as important as respiratory function. As with upper airway muscles, REM sleep induces total inhibition of muscular tone, as well as inhibition of phasic activity of intercostal and abdominal muscles. REM sleep-related inhibition of phasic activity of external intercostal muscles and other accessory inspiratory muscles leaves the diaphragm unsupported in conditions where greater inspiratory efforts are needed. Inhibition of intercostal muscle phasic inspiratory activity can even lead to inward paradoxical motion of the rib cage in REM sleep in early postnatal life (see below). In addition, REM sleep-related abolition of intercostal muscle tone is responsible for a decreased functional residual capacity.

Effects of REM sleep on respiration in early life

Consequences of the total loss of tonic activity in respiratory muscles with postural function are especially prominent in young infants during REM sleep. The increased work of breathing secondary to increased pharyngeal resistance imposes higher demands on the diaphragm. Simultaneously, loss of intercostal muscle tone leads to paradoxical inward inspiratory motion (i.e., an “expiratory” movement) of the highly-compliant cartilaginous rib cage in proportion to the intrathoracic negative pressure generated by the diaphragm. Such paradoxical inspiratory rib cage distortion can be observed in normal infants during REM sleep until, on average, 11 months of age (4). The high proportion of REM sleep in the first months of life renders these findings particularly relevant. Any added pathological condition, such as stiff lungs (e.g., with pneumonia), intrathoracic airway obstruction and hyperinflation (e.g., with acute viral bronchiolitis of infancy) or muscle fiber function compromise (e.g., with systemic hypotension, anemia, hypophosphatemia or acidosis), can precipitate respiratory failure in REM sleep. Obviously, the situation is worse in the newborn, especially in the setting of prematurity, given the extremely compliant rib cage, very limited respiratory muscle mass, small proportion of muscle fibers resistant to fatigue and the mechanical disadvantage of the diaphragm secondary to its perpendicular muscular fiber insertion on the ribs. This adds to the fact that REM sleep is very prominent in the newborn.

Effects of sleep in pathological respiratory conditions—a few examples

Ventilatory response to hypercapnia

Ventilatory response to hypercapnia includes increased activity of upper airway dilator muscles, as well as inspiratory and expiratory thoracic muscles. The net ventilatory effect depends on the relative and coordinated contribution of these various groups of muscles. During sleep, while the diaphragmatic ventilatory response is largely spared compared to wakefulness, a decreased ventilatory response to hypercapnia has been repeatedly reported in infants during REM sleep. This decreased ventilatory response has been largely ascribed to the absence of both tonic and phasic activity of (i) external intercostal muscles, which gives rise to an inspiratory inward motion of the highly compliant rib cage in response to marked negative intrathoracic pressures, and (ii) abdominal muscles, which limits
the increase in tidal volume, lengthens lung deflation time and prevents respiratory rate from increasing as well as deprives the diaphragm from storing elastic energy for the next inspiration (5). Again, all of these mechanisms may be especially relevant in the young infant with a high percentage of REM sleep and could explain his/her high propensity for respiratory muscle failure in the presence of hypercapnia.

Obstructive sleep-disordered breathing

As in adults, obstructive sleep-disordered breathing occurs when factors which promote upper airway obstruction (high pharyngeal wall compliance, intraluminal mass, high peripharyngeal pressure, maxillo-facial anatomic abnormality) predominates over factors which promote upper airway aperture (essentially upper airway dilator tonic and phasic inspiratory activity). Upper airway obstruction is worse in REM sleep, when pharyngeal muscle phasic inspiratory and tonic activity is inhibited. In addition, for reasons outlined above, inhibition of accessory muscles of inspiration and external intercostal muscles can aggravate the consequences of upper airway obstruction. Furthermore, we have reported a consistent abdominal muscle expiratory contraction in children with obstructive sleep-disordered breathing during non-REM sleep (6). As alluded above, abdominal muscle expiratory contraction can be synergistic to the diaphragm, by allowing the diaphragm to store elastic energy for the next inspiration. In addition, aside from promoting expiratory flow, abdominal muscle expiratory activity blunts upper airway obstruction at onset of inspiration by driving upper airway intraluminal pressure more positively at end-expiration. Lack of abdominal muscle expiratory contraction in REM sleep can thus be deleterious. Overall, REM-sleep related inhibition of pharyngeal dilator muscles, as well as of accessory inspiratory and abdominal muscles, explains that consequences of obstructive sleep-disordered breathing on lung ventilation are usually more important in REM sleep. Arousal is responsible for an immediate return of pharyngeal dilator muscle contraction, which brings an end to obstructive apnea. This surge in tonic and phasic activity with arousal is also true for all other respiratory muscles, which helps to restore optimal lung ventilation. Consequently, any condition blunting arousal, such as cigarette smoking during gestation for young infants, sleep deprivation or alcohol/sedative drug consumption in adolescents, can prolong obstructive apneas and lead to dangerous blood gas compromise.

Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (and other neuromuscular disorders) is another condition where ventilatory failure is observed at night, especially during REM sleep. Respiratory muscles, including thoracic pump muscles, as well as upper airway muscles, are all affected by the lack of dystrophin. The progressive decrease in maximal inspiratory and expiratory pressure, responsible for an increasingly severe restrictive lung function, is a hallmark of the disease. Smaller rib cage excursion with each respiration also leads to a considerable amount of information that may help to quantify the precise performance of the different inspiratory muscles, i.e. the diaphragm and the accessory inspiratory muscles, and the expiratory muscles. This review will provide a brief hierarchized summary of the different respiratory muscle tests that can be used in children.

II. Noninvasive tests respiratory muscle tests

Breathing pattern

The monitoring of breathing pattern with the recording of respiratory frequency (fr), tidal volume (Vt) and minute ventilation is easy and allows the calculation of the rapid shallow breathing index (fr/Vt). This index has been shown to be significantly higher in children requiring nocturnal noninvasive ventilation (NIV) as compared to those not requiring NIV. The analysis of the thoracoabdominal pattern of breathing by means of respiratory inductive plethysmography has been used to quantify thoracoabdominal asynchrony in young children with SMA.

Lung volumes

The association of a low VC with a reduced total lung capacity (TLC) is characteristic of inspiratory muscle weakness. RV, the volume that remains in the lungs at the end of a complete exhalation, is determined by the ability of the inspiratory muscles to compress the chest wall inward. Hence, inspiratory muscle weakness results in decreased RV. Measurement of VC is simple and valuable test. An at least 25% supine fall in VC has been shown to be associated with diaphragmatic weakness in patients with generalized neuromuscular disease. The regular monitoring of VC is of great value in patients at risk of rapidly progressive muscle weakness or paralysis. But it has to be known that a decrease in VC is not specific and that VC can be reduced by other factors than reduced muscle weakness. Maximal static pressures

The most widely applied tests of global inspiratory and expiratory muscle strength are the Pinax and maximal static expiratory pressure (Pemax) measured at the mouth. Conventionally, Pimax is measured from RV, which seems to be easier than from functional residual capacity (FRC). However, at RV, the measured Pimax is the sum of pressure developed by the
Abstract

Oesophageal and transdiaphragmatic pressures during a sniff maneuver

In normal subjects, sniff Pdi pressure change has a narrower normal range and a lower variability than the Pdi pressure change during the Pimax maneuver. In clinical practice, sniff Poes and sniff Pdi are the most accurate and reproducible volitional test available to assess global inspiratory and diaphragmatic strength in co-operative children over 6–8 years of age.

Gastric pressure during a maximal cough

The strength of the expiratory muscles can be easily measured by asking the patient to perform a maximal cough (Pgas cough). Again, the visualization of the Pgas cough trace on the computer screen is a simple and playful tool to motivate a child to perform a maximal maneuver.

Crying transdiaphragmatic pressure

Crying transdiaphragmatic pressure measurements allow assessment of diaphragm muscle strength during inspiratory crying efforts in awakened infants. Crying Pdi is ~ 60 cmH2O at 1 month postnatal age, and increases rapidly to ~ 120 cmH2O.

Respiratory muscle endurance

The diaphragmatic tension time index (TTdi) estimates the endurance of the diaphragm and is calculated during quiet breathing as TTdi = (Pdi.sniff Pdi) x Ti/Ttot, where Ti = mean Pdi during spontaneous breathing, sniff Pdi = Pdi during a maximal sniff, Ti = inspiratory time, and Ttot = total breath time. The same index can be calculated for the oesophageal tension time index (TTe) with the mean Pes and sniff Pes. This index was significantly higher in children with NMD requiring NIV as compared in children with NMD not requiring NIV.

IV. Conclusion

Respiratory muscle testing is particularly useful for children with NMD. Indeed, a precise respiratory muscle phenotyping may improve the understanding of the natural history of NMD and the evaluation of disease severity, it may assist and guide clinical management, and finally, it may help the identification and selection of optimal endpoints as well as the most informative patients for clinical trials. Minimally invasive measurements, by means of the recording of Pes and Pgas, may be of great value in young children.

References

HOME VENTILATION AND NEUROMUSCULAR DISORDERS

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Home mechanical ventilation has become the standard therapy for acute and chronic respiratory failure due to a number of underlying illnesses, including neuromuscular diseases. Over the last decade noninvasive ventilation (NIV) has been increasingly used for mechanical ventilation or ventilatory support for pediatric patients. Although the technique is more common today, data on this often heterogeneous group of patients are still very limited, and are usually derived from case series and not from randomized controlled studies. The advantages of NIV include the following: the equipment is easy to install; it is not invasive and involves less discomfort; a lower incidence of complications associated with the endotracheal tube was observed and the cost is low.

The goal of this lecture is to introduce the technique of home mechanical ventilation for patients with neuromuscular disorders

VII - Pulmonary Pearls

NEW ADVANCES IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS (PTB) IN CHILDREN

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Accurate diagnosis of pulmonary tuberculosis (PTB) in children is important to better define the epidemiology and burden of childhood TB, for timely use of optimal therapy and to enable effective treatment of drug resistant disease. Clinical scoring systems, radiological findings and tuberculin skin testing, traditional methods for diagnosis, are unreliable; the difficulty of diagnosis has been compounded by the HIV epidemic. Misdiagnosis and under diagnosis of PTB remains an important problem in children. There have been several recent advances in strategies to strengthen diagnosis in children. While microbiologic confirmation has not been the standard of care in children, the possibility of microbiologic diagnosis and detection of antimicrobial susceptibility has become increasingly important to accurately define the burden, to minimise pill burden, detect drug resistance and given the availability of rapid PCR tests for M tuberculosis. Recent advances have strengthened microbiologic diagnostic strategies in children. Improved specimen collection, particularly the use of sputum induction to obtain a good specimen for microbiologic testing, has been found to be feasible and effective even in infants. 1,2 In hospitalized children, a single induced sputum (IS) provides a similar culture yield to 3 gastric lavages. 1 Sputum induction, done as an ambulatory procedure in primary care settings, is effective, increasing the diagnostic yield for pulmonary TB (PTB) substantially in children. 2 A sequential second IS specimen is recommended, as this increases the yield from culture by approximately 15%. The yield from nasopharyngeal specimens from culture is lower than that from IS or from gastric lavage. 3,4 The availability of a PCR based molecular diagnostic test (Xpert MTB/RIF) has enabled rapid diagnosis of TB and simultaneous detection of resistance to rifampicin in children. Xpert testing of 2 induced sputum specimens detect approximately 75% of children with culture confirmed disease, almost 3 fold that of smear. 5,6 A Tanzanian study of older children, reported a similar sensitivity for Xpert on sputum specimens. A South African study reported that Xpert on 2 sequential NPAs was useful for microbiologic confirmation in hospitalised children. 7 Although NPAs provided a lower yield than IS specimens for culture, the sensitivity of 2 Xpert tests on NPAs was similar to that on two IS specimens. 8 A Zambian study found that Xpert on spontaneous sputum specimens in older children had a sensitivity of 90%; sensitivity in younger children on gastric lavage (GL) specimens was 69%. 9 Xpert on respiratory secretions was reported to be useful for diagnosis in children with suspected PTB presenting with mild disease at primary care health facilities. 10 Finally, Xpert on stool specimens may offer a promising strategy, especially for HIV-infected children. 11 The World Health Organisation has recommended that Xpert replace smear as the first line investigation in children living in areas of high HIV prevalence or where drug resistant TB is a concern. Rapid diagnosis of TB is desirable as young children or those with HIV infection may develop rapidly progressive or severe disease. However, a point of care rapid diagnostic test remains elusive. Urine lipoarabinomannan (LAM) has low sensitivity and specificity in children including HIV-infected children, making it unsuitable for diagnosis. 10

References


Pediatric Pulmonology
Multidrug-resistant tuberculosis (MDR-TB), where the tuberculosis is caused by Mycobacterium tuberculosis strains resistant to two of the most potent first line drugs Isoniazid and Rifampin, is today considered a major hurdle in the global efforts to control the disease. World Health Organization (WHO) estimated that about 630 000 (5.3%) of the world’s 12 million (range 11–13 million) prevalent cases of tuberculosis have MDR disease. It is also agreed that most cases of MDR-TB in the world remain undetected and untreated because of lack of access to laboratory diagnosis for drug resistance and to the expensive second-line treatment. (1)

No age, including children, is unaffected by the MDR-TB but little is known about the magnitude of this problem in children. There are inherent difficulties in isolation of bacilli per se, as also the resistant strains, as children mainly have paucibacillary and/or extrapulmonary disease wherein specimens for culture and drug susceptibility testing are often difficult to obtain even when the facilities for diagnosis exist. To improve the detection of MDR-TB among children for treatment and for surveillance purposes, investigation of all household childhood contacts of patients with MDR-TB is needed. Further more, children should also be included in drug resistance surveys when routine surveillance is not in place. In areas with constraints (which usually are also the communities where most MDR-TB exists) priority testing for individuals at risk for TB drug resistance should be done (See Box).

**Management of MDR TB**

**Resistance to anti tuberculosis drugs**

Resistance to anti tuberculosis drugs arises as a result of spontaneous mutations in the genome of M. tuberculosis which occur at predictable rates in patients with active tuberculosis subpopulations of resistant mycobacteria arise spontaneously and can emerge as the dominant strain in the presence of drug selection pressure - produced by irregular treatment and/or irrational therapy. Once created, drug resistant strains can be transmitted giving rise to drug resistant tuberculosis in individuals never previously exposed to anti tuberculosis drugs (Transmitted Resistance). Children with primary pauci-bacillary type of MDR disease are more likely to have transmitted resistance while those with multi-bacillary cavitary disease could have acquired resistance for reasons alluded to above.

**Clinical features and diagnosis**

The spectrum of disease caused by multidrug resistant bacilli is not any different from that caused by drug sensitive bacilli. Children and adolescents with drug resistant tuberculosis tend to have features of primary tuberculosis as hilar and/or mediastinal lymphadenopathy, segmental lesions or pleural involvement. The incidence of extra-pulmonary tuberculosis appears to be similar among drug sensitive and resistant infections. Thus, it may not be possible to differentiate between the drug sensitive and drug- resistant disease on the basis of clinical and radiological features alone. Though many studies reported that around one third to one half of patients had cavitary disease on chest X-ray and a very high proportion were smear/culture positive (44–94%).(3) This probably is due to delay in starting appropriate treatment till advanced stage of disease. Furthermore, the patients who acquire MDR-TB due to non-compliance with antituberculous therapy often have cavitary consolidations (50%) and generally demonstrate a postprimary radiographic pattern. The adult patients who developed primary MDR TB during an outbreak showed non-cavitary consolidations, pleural effusions, and a primary radiographic pattern (70%) (4).

Certain peculiarities of tuberculosis disease further tend to confound the diagnosis of drug resistance, if this is inferred solely from clinical and/or radiological failure to treatment. Persistent symptoms can be a poor proxy for activity. Intercurrent pneumonia can cause a radiological as well as clinical deterioration in patients with tuberculosis. The persistence of clinical symptoms like cough and sputum production can also be due to post tubercular sequel like bronchiectasis and bronchial hyper-reactivity. The resolution of radiological findings can be delayed for months after a successful therapy and chest skigrams can sometimes show progression in the absence of a bacillary failure. Tuberculomas of brain are known to increase in size and number despite successful therapy in a proportion of cases. About 15–20% of the patients with susceptible organisms continue to have lymph nodes of considerable size even after successful completion of therapy. In some cases these may fluctuate intermittently. Thus clinical definition has limitation in application.(4)

A high index of suspicion is therefore required to diagnose drug resistant tuberculosis early and the presence of risk factors as mentioned in the earlier section should be sought in every case, especially history of contact with a known case of multidrug resistant tuberculosis. In such cases the drug susceptibility tests should be ordered and results obtained at the earliest for starting appropriate treatment thus avoiding delay and its serious consequences. Since culture and DST can take long, rapid tests like line probe assays and Cartridge based Nucleic amplification tests (e.g. Xpert MTB Rif) may be used. Xpert MTB Rif is a promising technology that automates the process completely, requiring little input from laboratory workers and modest infrastructure thus making it more accessible to resource limited settings but is not cheap. The reported proportion of culture-confirmed cases among children with MDR-TB ranges from 25% to 100% (5–6). Xpert MTB Rif is able to pick up about 2/3 of the culture proven cases only. (7)

In many situations a presumptive diagnosis of DR-TB made on clinical symptoms or signs of TB and radiology, in combination with risk factors for drug resistance such as contact with a confirmed or presumed DR-TB source or the failure to respond to a regularly taken first-line regimen may be needed. Needless to say that still efforts should be made to confirm the bacillary diagnosis in all cases.

**Treatment regimen and duration**

The WHO has placed the drugs used in the treatment of MDR-TB into five groups. Group 1 drugs are considered first-line therapy, and the remainder are considered second-line therapy. Few of the second-line drugs are produced in pediatric formulations. The optimal dosing is unknown and that tablets must be broken or cut, potentially leading to inaccurate dosages and blood concentrations that are subtherapeutic or toxic. The pill burden can be vast an often needs to be spread over the course of the day to improve tolerability.(8–9)

Group 1 (First-line oral anti tuberculosis drugs—Ethambutol (E), Pyrazinamide(Z)—Being most potent and best tolerated anti tuberculosis drugs, these should be used but not counted in the total number of drugs being given. Group 2 includes injectable anti tuberculosis agents—(Kanamycin (KM), Amikacin (AMK)), Capreomycin (CM)). If the strain is susceptible, streptomycin should be used. Else Kanamycin or amikacin is the logical choice. Group 3 consists of Fluoroquinolones (FQ)—(Ciprofloxacin, Ofloxacin, Levofloxacin, Moxifloxacin, Gatifloxacin) - Newer generation FQs are better, the most potent available FQs in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin = ciprofloxacin. Group 4 is constituted by oral bacteriostatic second-line antituberculosis drugs—Ethionamide (Ethio), Prothionamide (Prothio), Cycloserine (CS),

**Pediatric Pulmonology**

**Abstract**

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Terizidone, \(\text{P}-\text{aminosalicylic acid (PAS)}\), Thioacetazone Group 4 drugs are added on the basis of estimated susceptibility, drug history, efficacy, adverse effects profile and cost. If only one of these agents is needed, ethionamide/prothionamide is often added because of its proven efficacy and low cost. If cost is not a constraint, PAS may be added first because the enteric-coated formulas are relatively well tolerated. If two agents are needed, cycloserine is commonly used in conjunction with ethionamide/prothionamide or PAS. Ethionamide or prothionamide should be used (if no inhA mutation is documented) because their metabolic pathways are similar and cross-resistance is total. Since the combination of ethionamide/prothionamide and PAS has a high incidence of gastrointestinal adverse effects, these two agents are commonly used together only when all three Group 4 agents are needed. Terizidone contains two molecules of cycloserine and can be used instead of cycloserine because its efficacy is assumed to be similar but has less side effects. The use of thioacetazone is limited by the development of rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death.

Group 5 (Clofazimine, Amoxicillin/Clavulanate, Clarithromycin, Linezolid) drugs are not recommended by WHO for routine use in MDR-TB treatment because of uncertain efficacy. When designing a regimen to treat children with MDR-TB, the target should be to use at least four drugs that are likely to have activity against the infecting organism. Because they are effective drugs with few adverse effects (8), any first-line drugs to which the organism has not been shown to be resistant should be used. Even when the organism is resistant to isoniazid, higher doses of isoniazid (15–20 mg/kg) have been shown to overcome resistance in children with MDR-TB. High-level resistance to isoniazid is usually caused by mutations in the katG gene, whereas low-level resistance is usually caused by mutations in the inhA promoter region. InhA mutations usually confer resistance to ethionamide. The same is true for cycloserine and terizidone, and only one of these two should be used. (8,9)

For children with cavitary or widespread disease with resistance to only rifampin and isoniazid, treatment is usually given for 18 months from the time of sampling of the first negative culture. Good outcomes have been reported in children treated with regimens of this duration, even in children with extensive disease. An injectable drug is given daily for the first 4 to 6 months. For children with limited, paucibacillary disease (e.g., isolated with extensive disease. An injectable drug is given daily for the first 4 to 6 months. For children with limited, paucibacillary disease (e.g., isolated

**Monitoring**

In children treated for MDR-TB, toxicity is common, occurring in up to 40% of cases (10). Significant adverse events mandating stopping or changing treatment are however less common. The adverse effects of the drugs used are summarized below:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Likely Offending Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nausea and vomiting</td>
<td>Ethio, PAS, F, E, Z, KM, OM, FQ, CS, AMK, CLV</td>
</tr>
<tr>
<td>2. Diarrhea</td>
<td>Ethio, PAS, KM, CM, FQ, AMK, CLV</td>
</tr>
<tr>
<td>3. Nephrotoxicity</td>
<td>S, Z, KM, CM</td>
</tr>
<tr>
<td>4. Hepatotoxicity</td>
<td>Z, H, E, Ethio, PAS</td>
</tr>
<tr>
<td>5. Hypokalemia</td>
<td>S, KM, AMK, CM</td>
</tr>
<tr>
<td>6. Hypothyroidism</td>
<td>Ethio, PAS, affect osteine uptake and organification</td>
</tr>
<tr>
<td>7. Depressed</td>
<td>S</td>
</tr>
<tr>
<td>8. Psychosis</td>
<td>F, FQ, CS, Ethio</td>
</tr>
<tr>
<td>9. Seizure</td>
<td>CS, CM</td>
</tr>
<tr>
<td>10. Osteonecrosis</td>
<td>S, KM, AMK, CM</td>
</tr>
<tr>
<td>11. Arthralgia</td>
<td>S, Z, Ethio, F, CS, dihydroartemisinines, OM</td>
</tr>
<tr>
<td>12. Rash</td>
<td>Usually due to Z, Ethio, but can be due to any medication</td>
</tr>
<tr>
<td>13. Peripheral Neuropathy</td>
<td>S, Z, Ethio, F, CS, aminoglycosides, OM</td>
</tr>
</tbody>
</table>

Sputum or Gastric lavage or any other appropriate body specimen smear and culture should be done monthly till smear and culture conversion (conversion is defined as two consecutive negative smear and culture taken 30 days apart). After conversion, smears should be done monthly and culture at least quarterly. For patients who remain smear and culture positive during treatment, Chest X-ray should be done six monthly or earlier if there is clinical worsening or surgery is being planned. RFT and electrolytes monitoring should be monthly till patient is on injectable drugs. LFT should be done 3–6 monthly and CBC 6–12 monthly. In addition, TSH should be monitored 6 monthly if patient is on ethionamide/prothionamide and/or PAS (11). The reported outcome of pediatrics cases is good if treated early and appropriately. (12)

While the management of MDR-TB is challenging and should only be attempted by experts and centers with experience, however, it is usually possible to achieve excellent outcomes in a wide range of settings. They should be treated with at least four drugs that are likely to be effective, and the child should be monitored carefully for adverse events and response to treatment.

**REFERENCES**


**GASTROESOPHAGEAL REFLUX AND THE LUNG**

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Gastroesophageal reflux

The Gastroesophageal reflux (GER) is defined as the regurgitation of gastric content into the esophagus. It is a condition that, to some extent, can be detected in everyone; however, if too frequent and too extensive it can be associated with various symptoms and even can cause severe pathological conditions. GER is normally prevented by the closed lower esophageal Pyloric Sphincter.
sphincter (LES) whose constriction or release should correlate with the peristaltic movement of the esophagus in the process of swallowing. Insufficient tone of the sphincter or anatomical alteration at the level of the diaphragm (as it is the case with hiatus hernia) can lead to insufficient function of the LES and return of the gastric content into the esophagus. If the reflux exits the upper esophagus and reaches the area of the hypopharynx, larynx or the upper airways, we speak about the extraesophageal reflux (EER). Gastroesophageal reflux disease (GERD) is a condition in which the reflux causes a significant pathological condition, such as irritation and inflammation of esophagus, irritation of larynx or upper airway area or even aspiration and damage to the lungs. GERD is a frequent condition affecting almost one third of the overall population [1]. The prevalence of GER in children is increasing. This has been partly related to increasing prevalence of obesity and poor eating habits of children in many areas of the world.

Gastroesophageal reflux and respiratory symptoms

GER has often been associated with respiratory symptoms. Several studies have put GER on a list of the main causes of chronic cough besides asthma and postnasal drip syndrome [2]. Interestingly, many patients with significant GERD associated respiratory symptoms may have a silent GER with no clear esophageal symptoms such as heartburn. The respiratory system can be affected at all levels. If the larynx is repeatedly exposed to the acid refluxate, a reflux associated laryngitis can develop affecting predominantly the posterior part of the larynx (laryngitis posterior) with coughing and hoarseness. Irritation of lymphatic tissue in the epipharyngeal area may lead to hyperplasia of adenoids and adjacent lymphatic tissue with occlusion of Eustachian tubes and development of otitis and hearing impairment. Enlargement of adenoids with subsequent focal infection can contribute to chronic coughing. Irritation of esophageal mucosa can trigger coughing mediated by the vagal reflex. Besides this reflex mechanism microaspirations associated with the EER are also a frequent cause of recurrent or chronic coughing. Acidification of tracheal and bronchial mucosa leads to inflammation, increased irritability of cough receptors and increased production of mucus. Even weakly acidic GER can trigger chronic cough; however, this has not been confirmed with an alkaline reflux [3]. If the aspiration is too frequent or too massive major damage to the lungs can gradually develop. Chronic EER associated bacterial bronchitis with subsequent development of bronchiectasis and destruction of pulmonary parenchyma is rare in children but can be a reason of major morbidity [4]. GERD has been involved in many patients with asthma. Irritation of esophagus and vagal reflexes can increase bronchial responsiveness. Microaspirations of acid content irritate the airways and induce an inflammatory response that can contribute to increased bronchial responsiveness to other stimuli and production of mucus [5]. Synergistic interactions between esophageal and airway sensory nerves have been implicated in the precipitation of asthma symptoms. On the other hand, pathophysiologic changes involved in asthma can contribute to GER. The mechanical influence of pulmonary hyperinflation can decrease tightness of the lower esophageal sphincter, and coughing or altered breathing patterns can alter the pressure gradients in the chest and abdomen. Some asthma medications can decrease the tone of the LES. Untreated GERD has been associated with severe asthma or with frequently exacerbating asthma. Diagnosis of GERD should also always be considered in all patients with difficult to treat or therapy resistant asthma. Chronic aspiration and recurrent irritation by acid gastric content has been associated with some diffuse parenchymal lung diseases and therefore GER should be also considered in patients diagnosed with diffuse alveolar damage and interstitial lung disease.

Diagnostic approach

In the diagnosis of GER(D) the patient’s history is a crucial initial step. It is not always easy to detect a clear association of respiratory symptoms and GER. Silent GER with no gastrointestinal symptoms is not rare and often patients do not feel or recognize any reflux related symptoms even though they suffer from significant respiratory problems. The diagnosis of GERD is always important to consider in patients with unexplained coughing or poorly controlled asthma as timely treatment can provide a benefit to the patient and reduce need of other medications. Clues in the patient’s history suggesting GERD are mainly coughing in a horizontal position or during activities associated with increased abdominal pressure, nocturnal coughing or worsening of asthma symptoms, respiratory symptoms after reflux prone situations such as eating large meals or drinking of carbonated drinks. Objective testing for GER includes detection of acid or non-acid content reverse propagation in the esophagus. Ultrasound detection, still often used in children, has been shown to be insufficiently reliable. Gastroesophageal scintigraphy can prove aspirations but does not provide sufficient information about the frequency and severity of reflux or its association with symptoms. Prolonged (24-hour) esophageal pH-monitoring has been considered the gold standard. A combination of pH and multiple channel esophageal impedance monitoring is more sensitive as it can also detect the non-acid reflux and can more reliably show the level reached by the refluxate within the esophagus [6]. Detection of the refluxate at the top of the probe (impedance or pH probe with distal and proximal sensor) is suggestive of the EER. Interpretation of the results must be carried out very carefully. It is always important to monitor all relevant symptoms together with the intraesophageal monitoring. As GER is rather prevalent in children it may occur at the same time as respiratory problems but with no causal relationship in either direction. However, as the GERD often just modifies the background inflammation and reactivity of the airways the absence of respiratory symptoms during monitoring does not exclude significant involvement of the GERD in respiratory problems. A barium esophagram is essential for detection of structural abnormalities, mainly diaphragmatic hernia. In patients indicated to bronchoscopy for chronic cough or uncontrolled asthma it is possible to analyze lipid laden macrophages (LLM) in bronchoalveolar lavage (BAL). An increased proportion of macrophages containing lipids (LLM index) has been found in patients with GER [7]. The original enthusiasm for this method has been suppressed by studies finding the LLM also in GER unrelated chronic lung inflammation where apparently endogenous lipids from tissues damaged by inflammation were ingested by the macrophages. Detection of pepsin in BAL is potentially more reliable for confirming the EER with aspirations than measuring LLMs [8]. A significant problem in diagnosing GER and GER-related disease in some settings is the availability of modern diagnostic methods such as 24-hour pH monitoring or esophageal impedance. This may often be the case in regions with limited access to health care resources. A therapeutic test with proton pump inhibitors (PPI), usually administered for a period of three months, can be used if no objective test is available. Resolution or significant improvement of symptoms is suggestive of GER involvement in the respiratory symptoms.

Management of the gastroesophageal reflux disease

First step in the management of the GERD must always be adjustment of diet, reduction of weight if needed and introducing some modifications of a lifestyle. Irritating food, acid and carbonated drinks should be avoided. Eating and drinking should be terminated at least three hours before going to bed. Sleeping in an elevated position may be helpful. Pharmacological treatment is currently mainly based on proton pump inhibitors as they have been shown to be superior to the H2 blockers. However, PPIs are not sufficiently effective in infants and there is still a lack of good placebo controlled studies in older children. Nevertheless, in patients treated by PPIs respiratory symptoms improved in several studies. In documented GER the initial treatment usually lasts three to six months, along with the evaluation of the effect on the symptoms. After this period of time the need for further treatment should be determined by follow-up pH monitoring and evaluation of clinical effect. If the effect was sufficient but reflux persists, ongoing long term therapy may be necessary. As long term administration of PPI has been shown to be associated with a higher risk for respiratory infections, the indication should always be based on a good evaluation of the diagnosis [9]. The need for continuing therapy must be regularly reevaluated. Therapy should only be continued in patients with a documented positive diagnostic effect.

In patients with severe therapy resistant GERD clearly associated with risk of damage to the respiratory tract, surgery remains the ultimate step. Nissen
fundoplication is the preferred method that helps to seal the area of esophagogastric junction and mechanically prevents the recurrence of the reflux [10].

Conclusion

Gastroesophageal reflux is a pathological condition closely related to the respiratory system. GER should be considered in the diagnostic process of many respiratory symptoms, mainly severe asthma, chronic cough, chronic bronchitis and some interstitial lung diseases. Treatment options are still limited and any long term administration of anti-reflux therapy needs a good reason and properly documented effect.


DIAGNOSTIC AND THERAPEUTIC FLEXIBLE BRONCHOSCOPY IN RESOURCE LIMITED ENVIRONMENT

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In 2010, nearly 0.4 million under five children died due to pneumonia alone. Not only is the mortality due to respiratory infections high they also contribute greatly to the outpatient attendance (20–40% of all outpatients) as well as in-patients (12–35%). Prevalence of asthma in school going children varies between 4%–20% in different parts of India. The areas with high prevalence of Human immunodeficiency virus (HIV) also have added burden of associated pulmonary illnesses. Drug sensitive and drug resistant pulmonary tuberculosis further adds to the respiratory burden.(1) Major efforts are made to manage these illnesses with simple tools at the peripheral most levels as closed to the community as possible. Developing nations have the challenge to provide service to a disproportionately high number of sick children in a resource constrained environment. Given the limited health spending in these situations, the public health approach dictates that the resources are more directed towards the leading causes which can be managed by low cost technologies. This perhaps is one of the reasons for the poorer development of skills and equipment or sophisticated tools like flexible bronchoscopy. Globally, the availability of small sized flexible bronchoscope—appropriate for use in children—have made it an important tool for managing respiratory cases since 1980s. This came about largely through the efforts of paediatric respiratory physicians originally trained in rigid bronchoscopy who have gained flexible bronchoscopy experience with adult thoracic physician colleagues. It is only in recent past that increasing numbers of paediatric respiratory physicians have been trained solely with flexible instruments. However, in the absence of well developed and designed training in pediatric respiratory medicine in many resource constrained areas, no such progress has been made. It is not surprising that nations like India have less than 20 centers providing bronchoscopy services for a huge childhood population while the services are practically non-existent in the neighbouring Bangladesh, Nepal, Bhutan and Myanmar (Personal communication).

We share here with the details of available equipment, services, methodology and yield of the procedure in the resource constrained settings. Opening of global markets have ensured that wide variety of different brands and sizes of instruments ranging from 1.8 mm to 4.9 mm are available in these countries. Video bronchoscopes as well as regular bronchoscopes attached to camera technology providing high quality monitor enhanced viewing while performing the procedures are available.

Biopsy forceps and cytology brushes are available for most bronchoscopes with channel of size 1.2 mm. In addition urological ureteric instruments like Dormia are also available for use with bronchoscopes. However bronchoscopes with a diameter of 3.5 mm or greater have a combined suction and biopsy port.

Bronchoscopes of 3.5 or 3.6 mm diameter are most versatile as they can be used for neonates, children and adults. The suction ports are adequate for most BAL and suctioning procedures though the small size of their working channel often necessitates clearance and/or withdrawal of the bronchoscope when secretions are tenacious or copious. Biopsy is limited to very small and superficial mucosal or prominent tissues through these bronchoscopes. Placement of a biopsy forceps through this port results in reduced suction capacity and tip control during a biopsy procedure. Bronchoscope with 4.7 mm outer diameter can only be used in children over 6 years of age but they have the advantage of enhanced view, suctioning and biopsy capacity.

The use of these 1.8–2.4 mm diameter bronchoscopes is limited because of their relative fragility. They are however useful in Intensive Care Units (ICU) and Neonatal ICU areas to check for endotracheal tube patency and position and in the diagnosis of lower airway lesions without the need for removal of the endotracheal tube, general anaesthesia or enhanced sedation.

Methodology

In most developed countries, both general and local anaesthetic techniques are available, though gaseous general anaesthetic techniques are used in almost all centres. This is perhaps because of a preference to have an experienced anaesthetist present to assist in airway management particularly when difficult airway lesions are present. Unlike these in resource constrained areas, cost factors and limited access to operating theatres has resulted in preference for sedation and local anaesthesia. All the 4 major centers in Delhi use conscious sedation with Pentazocine/midazolam and local anaesthesia and flexible FOB is almost never done under general anaesthesia.

Indications for bronchoscopy

Diagnostic

Common indications for paediatric flexible bronchoscopy are noisy breathing or stridor, dysphonia, persistent moist cough, haemoptysis, persisting chest signs such as crackles in a localised area, radiographic infiltrates including persistent atelectasis, recurrent infiltrates, recurrent pneumonia or interstitial disorders.

Flexible bronchoscopy can define abnormal anatomical features such as laryngomalacia, tracheomalacia, bronchomalacia, airway stenoses, as it
Flexible bronchoscopy is quite useful in cases with airway obstruction due to extraneous compressions as well as endobronchial granulations due to non-infectious or infectious causes. Bronchial dilatation procedures for strictures or stenoses can be performed through paediatric instruments using cardiac catheter balloons but are not limited. Flexible bronchoscopy though few centers are using this method provides a dynamic, visual assessment of the airways. It can also help identify H type fistula, hypoplasia, complete rings, foreign bodies, obstruction due to extraneous compressions as well as endobronchial granulations due to non-infectious or infectious causes.

Broncho-alveolar lavage (BAL) is often performed for the bacterial diagnosis of infections in immune-competent as well as the immunocompromised child. While the cytological analysis is useful to a much lesser extent but can be diagnostic in presence of alveolar bleed and hemosiderosis. BAL derived bacteriological isolation in tuberculosis is useful though more information is often received from direct visualization which may pick up other suggestive findings like caseation, widening of the primary or secondary carina, etc. Transbronchial lung biopsy and mucosal biopsy can be performed through paediatric flexible instruments (larger than 3.5 mm) using the same techniques as for adults but is not preferred due to small tissue sample size, risk of pneumothorax and bleeding. An audit was done for the yield of flexible bronchoscopy in our setting for about 1800 procedures and the results are detailed below:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diagnostic %</th>
<th>Contributory %</th>
<th>Non Contributory %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Radiological Opacity /Pneumonia (n=930)</td>
<td>33</td>
<td>13.3</td>
<td>56.7</td>
</tr>
<tr>
<td>Suspected Foreign Body Aspiration (n=441)</td>
<td>91</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis Complications (n=196)</td>
<td>34</td>
<td>7.5</td>
<td>58.5</td>
</tr>
<tr>
<td>Evaluation Of Upper Airway (including H-TEF) (n=165)</td>
<td>96.5</td>
<td>-</td>
<td>3.5</td>
</tr>
<tr>
<td>Non-Resolving Pneumonia In Immune-compromised Children (Including HIV) (n=41)</td>
<td>17</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>Acute Atelectasis (n=37)</td>
<td>30</td>
<td>16</td>
<td>54</td>
</tr>
<tr>
<td>Interstitial Lung Disease (ILD) (n=13)</td>
<td>30</td>
<td>7</td>
<td>63</td>
</tr>
</tbody>
</table>

Yield of Flexible Bronchoscopy in various indications

Therapeutic
Flexible bronchoscopy is quite useful in cases with airway obstruction due to mucous plugs etc which cannot be cleared by more routine suctioning and lavage methods. In cases with atelectasis the flexible bronchoscopy can not only be therapeutic but can also be diagnostic of alternate etiologies like congenital airway anomalies, hypoplasia, endobronchial granulation tissue and foreign body in cases with unresolved atelectasis. (6)

Interventional
The role of flexible bronchoscopy in removal of large foreign bodies is very limited. Flexible bronchoscopy though few centers are using this method commonly. However great caution is required with its use in this situation as the size of the foreign body may be underestimated and objects may be substantially larger than expected and therefore get stuck at the glottis. (7) Bronchial dilatation procedures for strictures or stenoses can be performed through paediatric instruments using cardiac catheter balloons but are not frequently used.

The use of the flexible bronchoscope has progressively increased to cover the visual diagnosis of the upper and lower airways lesions as well as interventional, therapeutic and supportive work such as bronchoalveolar lavage (BAL) for cytological, virological, bacteriological data; bronchoscopic intubation for anaesthetists; removal of distal foreign bodies, and limited selective segmental or lobar bronchographic procedures.

In conclusion, Flexible bronchoscopy is evolving into a useful and important tool for the diagnosis, management and research of paediatric respiratory diseases. There is a need for training guidelines for trainers to ensure competency and enhanced safe use in children living in resource constrained situations.

References

PEDiatrics IS MAGICAL
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What is this workshop?
This workshop will not make you a magician but will give you an appreciation of what magic is and how you can use it in your practice. You will learn principles of setting patterns, misdirection, performing simple sleights, and performance psychology. At the end of this workshop, you will have learned several effects that you can immediately put to use in your practice and you will have tools and resources for learning a great deal more on your path to becoming an amateur magician.

Magicians often talk about magical effects rather than magic tricks. The intention is to produce a moment of wonder and suspended belief rather than to fool somebody. A trick is a gimmick, a puzzle to be solved. Much more important is how the effect is presented. In this workshop I teach age appropriate, close up magic for children. This is magic that can be done for an individual child with minimal technical effort on the part of the magician.

What is magic?
Magic is a form of entertainment that relies on communicating and connecting with your audience; it be a single child or larger audience. Magic suspends belief to create joy and wonder. The most effective magicians understand their audience, believe in their own magic, practice their presentation and are themselves enchanted and fascinated by magic. People watch magic to be entertained and amazed. Magicians watch magic to appreciate the artistry of other magicians.

How is magic like medicine?
Much of what we as doctors do is mysterious and often wonderful in the eyes of our patients. We wear special coats; have mystical instruments that we use to look deep within the body and we prescribe magical potions that can miraculously cure. The best physicians are confident, competent and communicate well with their patients. So it is with the magician who loves and practices his or her craft communicates directly to their audience and brings them into their world of magic.

Like physicians, magicians have their own societies; primarily the International Brotherhood of Magicians (IBM) and The Society of American Magicians (SAM). Magicians also have their local organizations.
or “rings”. Magicians also have their own journals like The Linking Ring, Genii and MUM.

As in medicine, there are specialists within magic. Some magicians prefer to do close-up work, and others do street magic, stage magic, walk around or restaurant magic, or children’s shows (with their own specialty journals). Some magicians specialize in the type of magic they do such as card tricks, rope magic, coins, mentalism (mind reading), even rubber band magic. Also similar to medicine, there is a code of ethics for practicing magicians. If you attend this lecture you will be required to agree to abide by the joint code of ethics by IBM and SAM:

1. Oppose the willful exposure to the public of any principles of the Art of Magic, or the methods employed in any magic effect or illusion.
2. Display ethical behavior in the presentation of magic to the public and in our conduct as magicians, including not interfering with or jeopardizing the performance of another magician either through personal intervention or by placing any legitimate performer in a predicament while that person is before an audience.
3. Recognize and respect for rights of the creators, inventors, authors, and owners of magic concepts, presentations, effects and literature, and their rights to have exclusive use of, or to grant permission for the use by others of such creations.
4. Discourage false or misleading statements in the advertising of effects, and literature, merchandise or actions pertaining to the magical arts.
5. Discourage advertisement in magic publications for any magical apparatus, effect, literature or other materials for which the advertiser does not have commercial rights.
6. Promote the humane treatment and care of livestock used in magical performances.

It is natural to combine magic and medicine, particularly if you are a pediatrician. Most children and their parents love magic, and giving them a taste of magic at each visit makes the visit more fun, it can enhance your reputation, and opens great opportunities for communicating. Magic can put a child’s mind at ease. By teaching children simple magic tricks, they are empowered. I have also had the pleasure to see some of my patients go on to become proficient amateur magicians.

It is important that you don’t turn clinic visits into magic shows but rather do no more than 1 or 2 effects at a visit leaving the children and their parents wanting more. This will also leave you with something new to show at the next clinic visit. I prefer to present these effects as a surprise with no build up, sometime during the exam. For kids who know this, it keeps everybody much more attentive waiting for something cool to happen.

Finally, it is important to never give away the secret of a magical effect. When you do this the mystery vanishes and you have cheated not only the spectator and yourself but you have cheated future magicians who use that effect. I will show you some simple tricks that are OK to teach to children and to your own track record, but you have cheated exclusive use of, or to grant permission for the use by others of such creations.

Writing grants is time-consuming and often frustrating. Reviewing grants is even more frustrating, because many submissions have given themselves exactly no chance as a result of making basic errors. This presentation will not ensure your grant gets funded, but is intended to prevent you killing any chances before you start.

**Getting started, part 1:** The first essential is to have an idea that excites you. If you are not keen on the idea, no-one else will be. The only two questions of any importance about any research project are: what for? and: so what? The answers must be clear. Also be clear as to whether you are trying to determine mechanisms of disease or treatment benefit; this sounds an obvious point, but the methods and challenges will likely be quite different. Thus for example, a difference in the levels of a biomarker may be statistically significant, and give clues to basic mechanisms, but be clinically useless because of overlap between the occasions, a point that is all too often neglected. The criteria for a clinically useful biomarker are very different and much more stringent.

Assuming you have passed this hurdle, the next question to determine is whether you are testing a focussed hypothesis or conducting a fishing expedition. The latter is more frowned upon by grant-giving bodies, but if you have to go that route then acknowledge it as a hypothesis generating exercise, and preferably include validation as part of the work. So for example if you propose to develop a prognostic scoring system, then include a second, validation cohort.

Grant writing is significantly different from writing a manuscript. Manuscript writing involves a very critical and cautious approach to data; grant writing needs to optimistic and confident about what you WILL discover, without going over the top. In particular, many charitable grant giving bodies who rely heavily on public donations need to see positives to sell their activities to the public. This is of course a fine line, between cautious doubt and brashness.

It is also worth thinking through the practicalities of the methods. Useful questions are shown in the text box. It is always worth thinking through the ideal experiment (which usually can never be done) and the inevitable compromises that have to be made. Ask yourself: What ethically and practically can I measure? What are the best tools? Does the act of measurement alter what I am measuring? What is the shortfall between what I can measure and what I would like to measure? Does it matter? Finally, if this is a re-submission, pay attention to previous feedback. You may disagree, but you may very likely get the revised version refereed by the same people, and if you have paid no attention to their suggestions, this is not going to endear you too them. Rebuttal is fine if it is done in a courteous and sound manner, ignoring them like the idle wind passing by is not.

**Getting started, part 2:** These days the paperwork and the logistics are increasingly time-consuming, so leave plenty of time. Most institutions will want to ensure costs are correct; and it is no good going back cap in hand for more money after the grant is awarded, because none will be forthcoming. Ethical review, and in many Institutions, independent scientific review are mandatory, and again take time. You will make no friends with a rushed application, and thrusting an obviously under-prepared scientific review are mandatory, and again take time. You will make no friends with a rushed application, and thrusting an obviously under-prepared document for signature from the Head of Department is not a way to make friends. Most grants are collaborative; get the collaborators right. Be realistic about your own track record; if your biggest ever grant is 5,000, if you go for 10 million, you’ll need someone else. Get professional statistical advice, also where appropriate experts including Health economics and qualitative researchers if your project is suitable. Patient involvement is increasingly crucial, and do not neglect this. Many funding bodies attach huge importance to the lay abstract, so work on this too; so many investigators ignore this, concluding they will be more frustrated, because many submissions have given themselves exactly no chance as a result of making basic errors. This presentation will not ensure your grant gets funded, but is intended to prevent you killing any chances before you start.

**The Basics of Writing** It sounds obvious but is not; you MUST read the instructions and follow them to the letter. The background must demonstrate why your study is logical and important, and cover previous work, especially systematic reviews and meta-analyses; if one has not been performed you may need to do this first. The project must be realistic, and you must show that your group has the right track record to do the job. An
absolute must is pilot data; to show that what you are offering is feasible. Lack of pilot data is an absolute guarantee of failure! The hypotheses, aims and objectives must be clearly stated at the end of background and must be a logical development from the background. They have to be attainable, and really need to have the ‘wow’ factor!
The methods section is crucial. Recruitment is always a problem, investigators are notoriously over-optimistic. Do the numbers add up? I will recruit 157 patients with Type 4 Hermansky-Pudlak syndrome (or some other rare syndrome) will fail because there are not enough such patients in the world! Demonstrate you are likely to recruit: e.g. ‘in the last 12 months, we had 50 admissions to our intensive care unit with severe pneumonia who would have been eligible for the study, so our target of 100 patients in three years is realistic’. Has the group got a track record in the proposed methodology—grant giving bodies will rarely want to reinvent hot water, and will expect you to collaborate with known experts in sophisticated techniques. The statistical section is crucial, and must be done by a professional statistician—amateur attempts deceive no-one. There MUST be a power calculation and an analysis plan. If the study is a randomised controlled trial, it must be registered on a suitable website.

Last steps: There is a temptation to collapse exhausted after writing the main body of the grant and not give due attention to the ‘bits’. The abstract is first port of call for the reviewer—make sure it grips the attention. Get lay people to read the lay summary to make sure it is intelligible. Check the costings are realistic, and neither asking for stuff that is irrelevant to the grant (a new coffee machine for the Professor) nor leaving you with a hopeless shortfall when it comes to do the work. Think whether there should be a health economics or qualitative component to the work. Do make sure all boxes have been filled in!

Finally, really punch out the implications: saying ‘these findings will have important clinical implications for X’ is a translation of: ‘I’d like to believe these are important, but I know they are not really in any clear way’ and this will fool no-one. If you cannot spell out in detail the implications loud and clear, you are Toast! It comes down to being able to answer the ‘so what’ and ‘what for’ questions.

Conclusions: Grants take longer to write than you think, and should be collaborative, especially if they are big ones! Keep trying, remember everyone has had grants bounced but persistence will be rewarded. Sooner or later you will land the big one—and then your problems REALLY start, because you have to do the work.

II. ORAL COMMUNICATIONS FROM YOUNG INVESTIGATORS

#150 - SIGNIFICANT INFLAMMATION IS NOT PRESENT IN THE BRONCHIAL MUCOSA OF VERY YOUNG CHILDREN AT RISK FOR DEVELOPING ASTHMA.

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AIM: In our previous work we have shown the presence of remodelling of the bronchial mucosa in young children at risk for developing asthma. The aim of the current study was to compare the presence of inflammatory cells in the sub-epithelial part of bronchial mucosa in very young children at risk for developing asthma and controls. The cell counts were also correlated with the basement membrane thickness in both groups.

METHODS: Fifteen children under 4 years of age (range 3–38 months) undergoing flexible bronchoscopy for various clinical reasons were included in this cross-sectional study. Children were divided into 2 groups according to the selected criteria of Asthma Predictive Index (API): risk-group and control group. From each patient at least one endobronchial biopsy was taken. Using the methods of indirect immunohistochemistry we analysed the presence of neutrophilic (NL) and eosinophilic (EL) leukocytes in the subepithelial part of bronchial mucosa. For NL analysis we obtained 7 representative samples from children in the risk group and 8 representative samples from controls. For EL analysis we obtained 4 representative samples from each group.

RESULTS: We did not find significant differences in the neutrophilic and eosinophilic leukocyte counts between the groups. The average count of NL in the risk group was 43.81 cells/mm² compared to 15.79 cells/mm² in controls (P = 0.96). For EL, we found less EL in the risk group (18.32 cells/mm²) compared to controls (25.99 cells/mm²) but the difference was not statistically significant (P = 0.89). In both parameters and both groups we observed substantial inter-individual variability. We found neither positive nor negative correlation of NL or EL count and BM thickness in risk-group and controls (for NL count r = 0.17, P = 0.36 and r = 0.07, P = 0.62 and for EL count r = 0.98, P = 0.08 and r = 0.68, P = 0.18, respectively for both groups).

CONCLUSION: Based on the results of this study we suggest that neutrophilic or eosinophilic inflammation might not be associated with early initiation of bronchial remodelling in children predisposed to asthma.

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#178 - CD48: AN INDEPENDENT BIOMARKER FOR ASTHMA

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Background: Asthma, a heterogeneous inflammatory airway disorder is multifactorial but involves a strong genetic component. Despite ongoing research, the molecular mechanisms controlling asthma are still elusive. Highly inbred populations with high incidence of asthma and allergic disorders, like the Jews of Cochin, makes an ideal population for etiological studies. CD48 is a member of the CD2 subfamily of immunoglobulin-like receptors, present as membrane bound on hematopoietic cells and as a soluble (sCD48) form. Recently, CD48 was found to be involved in allergic eosinophilic airway inflammation and shown to be a potential target for the suppression of asthma in mice.

Aim: To establish the prevalence of asthma and atopy in a unique population of Cochin Jews and to evaluate the expression of CD48 as a possible biomarker for asthma.
Patients and methods: Included in the study were individuals of a genetically homogenous population of the Israeli Cuchin Jews. Patients completed an asthma and allergy questionnaire, performed spirometry, methacholine challenge test, a common allergen skin prick test, a complete blood count, and measured IgE levels. In randomly selected patients an ELISA was performed to assess levels of plasma sCD48.

Results: 678 individuals participated in the study with a mean age 34.6 ± 19.9 years (range 4–88), 317 (47%) were male, 290 (43%) had evidence of an allergic disease and 165 (24.3%) were diagnosed with asthma of which 121 (78%) was allergic asthma. Levels of sCD48 were significantly elevated in asthmatic vs. non allergic non asthmatic individuals (1234.18 ± 317.62 Pg/ml (n = 44) vs. 979.89 ± 127.49 Pg/ml (n = 22), P < 0.001). Objective parameters predicting asthma were elevated IgE levels (OR 3.41, CI 2.28–5.08, P < 0.001), eosinophilia (OR 3.82, CI 2.53–5.77, P < 0.001) positive skin prick tests (OR 2.76, CI 1.91–3.98, P < 0.001) and sCD48 above 1000 Pg/ml (OR 4.67, CI 1.54–13.92, P < 0.05). There was no correlation between sCD48 levels, total eosinophil count and IgE levels (R2 = 0.04, R2 = 0.017, respectively).

Conclusion: There is a high prevalence of atopic diseases and asthma in the unique population of the Israeli Cuchin Jews. Elevated sCD48 in this population confered an increased risk towards asthma not correlated to classical laboratory risk factors for asthma. sCD48 is possibly an independent biomarker for asthma and may become a future potential therapeutic target.

#101 - NATURALLY ACQUIRED PRIMARY INFECTION BY PNEUMOCYSTIS INDUCES AIRWAY EPITHELIAL AND PERI-VASCULAR LUNG PATHOLOGY IN IMMUNOCOMPETENT YOUNG RATS.

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Pneumocystis is a slow-replicating respiratory fungus well-recognized as a cause of severe pneumonia in immunocompromised patients. However, it is now clear that the vast majority of normal healthy infants develop an asymptomatic Pneumocystis primary infection that typically peaks between 2 and 5 months of age and goes undiagnosed. Immunocompetent animal models reveal Pneumocystis-induced strong immune responses that include activation of mucus secretion-related genes and inflammatory lung pathology. We developed an immunocompetent rat model to characterize and follow the course of mucus-related and inflammatory changes associated to the primary Pneumocystis infection using histological morphometry. Twelve timed-pregnant Sprague-Dawley rats were placed inside an HEPA-filtered isolator and given tylosin in the drinking water to prevent bacterial infections. Colonies adding up 30 pups were co-housed at birth for 48 hr with tylosin-treated rats with steroid-induced-Pneumocystis pneumonia, and additional colonies summing 30 pups were started on Trimethoprim-Sulfamethoxazole (TMP/SMZ) for Pneumocystis prevention (controls). All rats were kept in the isolator until sacrifice. Ten rats per group were sacrificed under anesthesia with ketamine-xylazine on days 46, 60, and 75 of age, respectively. Five of them were exanguinated and their lungs removed and frozen at −80°C until Pneumocystis RT-PCR analyses, while the other 5 were sacrificed by vascular perfusion of 3% formalin via inferior vena cava at a pressure of 25 H2O cm. Their lungs were removed from the thorax after 24 hr to avoid collapse, immersed in formalin for additional 24 hr, paraffin embedded, and longitudinally oriented sections examined using Image ProPlus microscopy software. Pneumocystis remained suppressed in control rats, while detected in all rats at 46, 60, and 75 days in the primary infection group. Mean epithelium thickness measured using H&E stain were 16.9, 18.2, and 17 μm in the primary infection group versus 15.2, 14.0, and 12.6 μm in controls (P < 0.001); the % area of epithelium occupied by mucus measured using alcin blue stain remained constant at 0.5% in controls increasing to 1.6%, 9.5%, and 8.3% in the primary infection group (P < 0.001); peribronchial reticular fiber thickness measured using Gordon & Sweet stain changed from 13.8, 11.7, and 9.9 μm in controls to 12.5, 17.1, and 17.9 μm in the infected pups (P < 0.01); Peribronchial infiltrates increased 3-fold by day 45 (P < 0.05) and 4-fold by days 60 and 75 (P < 0.01) in the infected animals, and perivascular infiltrates were constant 3-fold higher in the Pneumocystis primary infection rats (P < 0.001). The primary infection by Pneumocystis in immunocompetent newborn rats induces measurable airway and perivascular lung changes that persist at 75 days of age. Pneumocystis is highly prevalent in infants. Therefore further research to understand a potential role in respiratory disease of infancy is warranted.

#172 - SAFETY OF INTRAPLEURAL ALTEPLASE IN CHILDREN WITH PLEURAL EFFUSION.

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Background: Pneumonia is one of the most important health concerns in children and often requires hospitalization. Parapneumonic effusion accompanies pneumonia in 2% to 12% of cases. In complicated cases requires thoracostomy or intrapleural fibrinolysis. According to current knowledge, recommended dose of intrapleural alteplase (recombinant tissue plasminogen activator, t-PA) is 0.1 mg per kilogram of body weight with a maximum of 3 mg and not exceeding 9 doses. Aim: The aim of this study was to evaluate the safety of intrapleural alteplase administration in children with pneumonia complicated with pleural effusion. Material and methods: Children hospitalized due to community-acquired pneumonia (CAP) with complicated parapneumonic effusion (confirmed by chest X-ray and ultrasound) were eligible for the study. Patients qualified to pleural drainage were given intrapleural fibrinolytics in case of respiratory distress, empyema, flocculated or growing effusion. Seven children (4 boys and 3 girls, aged 22–196 months) were included in the study. After intrapleural alteplase administration patients were strictly monitored.
monitored for adverse events, such as chest pain, hemorrhage, hypersensitivity reaction or fever related to the drug administration. Also, due to observed increase in the number of platelets, repeated blood counts were performed and patients were observed for embolic complications. All the patients were also followed-up in respect of long-term complications related to the treatment.

Children were given doses of alteplase ranging between 0.09 and 0.2 mg/kg (median 0.13 mg/kg) and total number of doses ranging between 4 and 24 (median 10). Four patients obtained more than 9 doses and in 5 of 7 patients alteplase dose was higher than 0.1 mg per kilogram.

Results: We found no adverse reactions following alteplase administration, even in patients who were given more than 9 doses and/or more than 0.1 mg of t-PA per kilogram of body weight. Previously reported increase in the number of platelets was seen in every child who was administered t-PA, although there was no correlation between the total number of doses, dose per kilogram or total dose of alteplase and the increase in the total number of platelets. Importantly, in 2 patients the drainage was stoppered due to high thickness of effusion, what was related rather to too short fibrinolytic therapy than to increase in the number of platelets and those patients required additional doses of alteplase after initial improvement. No long-term adverse events of the therapy were reported.

Conclusions: To conclude, intrapleural administration of alteplase is safe treatment in children with complicated parapneumonic effusion. The length of fibrinolytic treatment may be longer than currently recommended, taken into consideration that higher number of doses did not exert any bad influence. Moreover, doses higher than 0.1 mg/kg proved to be safe in this study.

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**#97 - THE CASE OF LATE ONSET CONGENITAL CENTRAL HYPOVENTILATION SYNDROME CAUSED BY NOVEL MUTATION IN PHOX2B GENE**

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Congenital central hypventilation syndrome (CCHS) is a rare disorder of respiratory control with inadequate ventilatory response to hypercapnia during sleep or during both sleep and awake state. It is associated with other autonomous nervous system dysfunctions such as Hirschsprung disease and tumors of neural crest origin. The disease can present as classical form, in neonatal period or as milder, late onset form from infancy to adulthood. CCHS results in 90% cases from polyalanine repeat expansion mutations in paired-like homeobox 2B (PHOX2B) gene, but in 8–10% of cases the other type mutation: missense, nonsense or frameshift mutation is present. We present a case of a 3 year old, previously healthy girl that presented with fever associated with nasal secretion and cough. She was diagnosed with bilateral pneumonia and antibiotic treatment was initiated right away. Her condition worsened as she developed signs of right-side cardiac decompensation with tachycardia and pulmonary hypertension. Periodic breathing pattern was noted with hypercapnia up to 118 mmHg and hypoxemia of 55 mmHg in arterial blood during sleep. After her infection was under control and cardiac function has normalized, moderate hypercapnia and mild hypoxemia during sleep were still present. Polysomnography revealed the presence of hypoventilation with normal apnea index (AI 2.5) and markedly elevated apnea-hypopnea index (AHI 30.2). Chest and head CT excluded the presence of intracranial AV malformations, brain tumors and intracardial or intrapulmonary shunt. Clinical data suggested the presence of late onset CCHS and the analysis of PHOX2B gene showed the presence of novel, missense mutation c.374T>A, p.I125N. Mother was shown to have the same, de novo mutation in PHOX2B gene, but with much milder phenotype. Noninvasive mechanical ventilation by nasal mask was initiated in this girl during 2 hr at night. She is doing well and has no signs of pulmonary hypertension. Late onset forms of CCHS can present at any time of life. It should be suspected in a child with signs of abnormal breathing resulting in hypercapnia during night. Genetic testing of both parents can help establish the mode of inheritance and mutation penetrance.

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**#93 - LUNG UNITS IN CYSTIC FIBROSIS STUDIES WITH MICROCT**

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Background

MicroComputerized Tomography (μCT) allows high-resolution three-dimensional morphometry of the human pulmonary acinus. This technique has already proven successful in elucidating the small-airway disease in COPD (1). In CF, CT is used to monitor progression of CF lung disease and small airways disease is assessed by functional tests. However, the structural correlate of CF small airways (<2 mm in diameter) disease has not yet been established.

Purpose

To study the site and nature of lung injury in CF explant lungs with μCT and determine structural correlates of lesions seen on clinical CT.

Methods

Explant lung of CF patients (n = 6) and control lungs (non-used donor lungs; n = 5) collected at transplantation were inflated and frozen at total lung...
capacity. In frosted state cores were isolated, fixed and used for μCT scanning (Skyscan 1172®).
Pre-transplant CTs were identified as mainly hyperinflation (n = 2), mainly destruction (n = 2) or mixed changes (n = 2). We compared the number per milliliter (ml), minimal diameter and cross-sectional area of CF terminal bronchioles with those of healthy controls using OsiriX® imaging software.

Results
On μCT a significant reduction in the number (2.9 vs. 5.6/ml; P < 0.001), diameter (212 vs. 363 μm; P <0.001) and cross-sectional area (92 vs. 177 μm²; P <0.001) of CF versus healthy terminal bronchioles was found (unpaired t-test).
“Hyperinflated lungs” had a lower density than “destructed” and “mixed lungs” (217 vs. 302 g/L). They showed narrowing (mean diameter 90 μm) and collapse of terminal bronchioles with preservation of alveolar ducts (fig 1A).
“Destructed lungs” showed multiple bronchiectases and important loss of terminal bronchioles (mean 2.5/ml) with disappearance of distal alveoli possibly due to fibrosis (fig 1B).
Conclusions
μCT demonstrates heterogeneous CF small-airway disease. Narrowing as well as disappearance of terminal bronchioles are found.

Reflections and concrete proposals for action stimulated by the research:
- Early CF lung histology reports described collapse and fibrotic lesions (2). Ongoing research in our center will compare μCT terminal bronchiolar collapse and fibrotic lesions with histologic changes in the explant core.
- Microbiome analysis of the cores will try to establish a correlation between infectious pathogens and small-airway lung lesions seen on μCT.

References
(1) Mc Donough et al. NEJM 2011
(2) Spencer et al. Pathology of the lung 1985

Figure 1. MicroCT showing terminal bronchiole A) collapse B) disappearance

#135 - ADHERENCE TO THE BRITISH THORACIC SOCIETY GUIDELINES IN MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN.

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Introduction: Childhood pneumonia is a common reason for hospital presentation. The British Thoracic Society (BTS) published the guidelines for the management of community-acquired pneumonia (CAP) in children in 2002 (updated in 2011). A recent national audit showed poor adherence to these guidelines. The aim of our work was to determine the adherence to the guidelines in a tertiary care hospital.

Methods: A retrospective data was collected on all children admitted to the University Hospital of North Staffordshire with a diagnosis of pneumonia, lower respiratory tract infection or consolidation between August 2012 and August 2013.

Results: 120 admissions were recorded and 48 case records were randomly selected for analysis. The median age was 2.25 years [range: 0.1–13 years]. Adherence to the main recommendations of the BTS guidelines are summarised below under four headings:
Severity of illness: 36/48 (75%) children satisfied at least one admission criterion listed in the the BTS guideline. The commonest reasons for admission were oxygen requirement and increased work of breathing. 6/48 (13%) required admission to intensive care.
Investigations: All patients had pulse oximetry recorded and all patients had a chest radiograph. Blood cultures and nasopharyngeal aspirates were reserved for sick or septic children admitted to general paediatric ward. Microbiological investigations were sent in 25 children and were positive in 11 (44%). All children admitted to Paediatric Intensive care had blood cultures and bronco-alveolar lavage done as part of their microbiological investigation.
Antibiotic management: 30/48 (62.5%) of children received IV co-amoxiclav with only 2/48 (4%) of under-5 year-olds receiving amoxicillin and 2/16 (13%) of over-5s receiving a macrolide antibiotic as recommended in the BTS guideline. Co-amoxiclav was also the most commonly prescribed oral antibiotic at discharge: 37/48 (77%).

General management: One child on the ward had physiotherapy whilst all admitted in intensive care received physiotherapy. 20/48 (42%) received out-patient follow-up. Only 7 of these met the criteria for follow-up (six of them being discharged from intensive care and the other one with pneumonia complicated with pleural effusion).

Conclusions: This audit found poor adherence to the the BTS CAP guideline, particularly with respect to antibiotics use, chest x-rays and out-patient follow up. We intend to improve adherence by increasing awareness of the BTS guidelines amongst doctors at our hospital and then re-audit this topic in 12 months time. Increasing adherence to the BTS guidelines would improve care and reduce the cost associated with unnecessary investigations, treatment and follow-up.

#96 - IDENTIFICATION OF DISTINCT CILIARY BEAT PATTERN ABNORMALITIES BY HIGH-SPEED VIDEO MICROSCOPY IN PRIMARY CYSTIC DYSKINESIA.

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Introduction
Primary Ciliary Dyskinesia (PCD) is a rare, genetically heterogenous disorder characterized by recurrent respiratory tract infections due to abnormal ciliary motility, which progresses bronchiectasis and leads to a destructive lung disease. The current standard of PCD diagnostics includes high-speed videomicroscopy analysis (HVMA) of ciliary beat pattern and frequency as first-line diagnostic test, followed by ultrastructural analysis using transmission electron microscopy (TEM) and immunofluorescence microscopy (IF) or genetics. Recent molecular studies have widely expanded the spectrum of HVMA findings associated with PCD posing an increasing challenge to investigators. In this study we have correlated HVMA findings with TEM-, IF-, and molecular genetic findings in order to identify typical patterns for distinct PCD variants.

Methods
We analysed 1478 videos from nasal brush biopsies of 65 PCD individuals and 10 disease control persons. Image recording and processing was performed using SAVA. HVMA findings were correlated with TEM, IF, and genetic findings that have been assembled as part of other projects or routine diagnostic work-up.

Results
Respiratory cilia from individuals with outer dynein arm defects showed minimal residual movements with a minority of cilia being completely immotile. Cilia from individuals with combined inner and outer dynein arm defects were almost invariably immotile. Defects of the central pair apparatus resulted in a rigid and uncoordinated beat pattern. Combined inner dynein arm and microtubular disorganization defects resulted in a hyperkinetic, very stiff and vibratory ciliary beating pattern. Nextin link defects showed an almost regular beat pattern with only a slightly reduced beating amplitude.

Conclusions
This study improves clinical PCD diagnostics by classifying different PCD subtypes using HVMA as the first line diagnostic tool and facilitates the subsequent diagnostics.

#74 - EARLY LIFE RHINOVIRUS (RV) INFECTION IS ASSOCIATED WITH STEROID-RESISTANT AIRWAY SECRETION OF THYMIC-STROMAL-LYMPHOPOIETIN AND TH2 CYTOKINES

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Background: Thymic-stromal-lymphopoietin (TSLP) is a recently identified epithelial-derived cytokine responsible for priming the differentiation of naïve Th0 cells into Th2 cells. Rhinovirus (RV) has been shown to increase TSLP levels in airway epithelial cells, suggesting that TSLP may be the missing link between antiviral and Th2 pro-asthmatic immune responses in the airway. Since RV infections in early life are a risk factor for persistence of asthma beyond childhood, we postulated that naturally occurring RV infections in young children are associated with elevated airway TSLP levels and enhanced airway Th2 responses, which together may facilitate the establishment of the asthmatic condition during early childhood. We also examined the effect of inhaled corticosteroids (ICS) in RV-induced TSLP/Th2 airway immune responses given that ICS is the backbone of pediatric asthma treatment and a potential therapy for viral-induced wheezing.

Methods: Nasal airway secretions were obtained from children (<3 y/o) during acute respiratory illnesses using standard nasal lavage technique. Samples were analyzed with viral multiplex PCR to identify RV and other common respiratory viruses and then were analyzed for protein levels of TSLP, IL-1β, IL-12p70, IFN-γ, TNF-α, IL-4, IL-5, IL-13, eotaxin-1, TARC, MDC, IL-17, and IL-8 using a multiplex immunoassay. Multivariate regression models were built to study the link between RV infection and TSLP/Th2 levels adjusted by clinical variables including demographics and ongoing use of ICS (P < 0.05)

Results: A total of 125 subjects (mean age 11 ± 7 months) were included in this study. 71 subjects had RV and 54 subjects had negative viral PCR testing. Subjects with RV had higher nasal TSLP levels compared to those with no identifiable virus (mean ± SE 5.5 ± 0.9 pg/ml vs. 16.7 ± 1.2 pg/ml; P < 0.001) (Fig A). These increased nasal TSLP levels correlated positively with a Th2 biased nasal airway response in children with RV infection,
#23 - SEROTYPE DISTRIBUTION AND DRUG RESISTANCE OF STREPTOCOCCUS PNEUMONIAE ISOLATED FROM CHILDREN WITH COMMUNITY ACQUIRED PNEUMONIA IN JAPAN.

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Purpose: To reveal the impact of the heptavalent pneumococcal vaccine (PCV7) and newly approved oral antibiotic (tositufloxacin) for children on serotype and drug resistance of Streptococcus Pneumoniae (Sp) isolated from blood and sputum samples of children admitted in hospitals with community acquired pneumonia (CAP) in Japan.

Methods: PCV7 and oral tosufloxacin (TFLX) were newly approved for children in Japan in February 2010 and August 2009, respectively. The study periods were between April 2008 to March 2009 and April 2012 to March 2013. Children living in Chiba city, Japan, aged under 16 years admitted with CAP in 5 major tertiary hospitals were enrolled in this study, and patient backgrounds were collected. Patients with positive blood culture or cultured sputum (smears Geckler's group 4 or 5) dominant for microorganisms such as Sp, Haemophilus influenzae (Hi), Moraxella catarralis (Mc) were diagnosed with bacterial pneumonia. Antimicrobial susceptibility of Sp was tested according to CLSI guideline M100-S23. 

For Statistical analysis, the Fisher's exact test was used to compare between-group differences in patient characteristics and the proportion of PCV7 serotypes in patients with a diagnosis of Sp pneumonia. A logistic regression model adjusted by potential confounders was used to estimate the odds ratio for the PCV7 vaccine effect in relation to the risk of Sp pneumonia.

Results: In this study, 486 and 495 patients under 16 years old were enrolled for the PCV7 vaccine effect in relation to the risk of Sp pneumonia.

Although MIC 50 (µg/ml) of penicillin declined from 0.5 to 0.25, the MIC 50 (µg/ml) of TFLX increased from ≤ 0.12 to 0.25 from 2008 to 2012, respectively. 

Conclusions: The prevalence of Sp pneumonia in Chiba city showed a significant reduction post 2 years of PCV7 vaccination. Decline in PCV7 serotypes lead to improvement in penicillin sensitivity. Japan is the only country in the world with oral quinolone approved for children. Considering the worsening of TFLX resistance, we should be careful for the use of broad-spectrum antimicrobial agents for children in outpatient clinics.

#25 - COMPARATIVE STUDY OF RADIOLOGICAL FINDINGS IN PULMONARY PARAGONIMIASIS AND TUBERCULOSIS IN A SOUTHERN NIGERIAN FISHING COMMUNITY

Author:
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Introduction: Paragonimiasis is one of the re-emerging public health diseases. most of the presenting symptoms of pulmonary paragonimiasis are similar to that of tuberculosis (TB). Clinical and radiological differentiation between pulmonary paragonimiasis and tuberculosis can be difficult

Aim: To identify the chest radiological features that could be consistently used to differentiate between pulmonary TB and paragonimiasis in children in the resource limited environment of south-south nigeri.

Subjects and methods: Two hundred forty children selected by stratified random sampling from two schools in the community were screened for pulmonary paragonimiasis and pulmonary tuberculosis. An administrative questionnaire was used with each subject to identify their sociodemographic characteristic and symptoms related to the respiratory system. A thorough respiratory system examination was performed on each subject. Each subject had two slides prepared from their sputum, one slide was examined under light microscopy at 10× and 40× magnification for paragonimus ova, while the other slide was stained with Ziehl Neillson stain and examined at 100× magnification for mycobacterium tuberculosis. The chest radiographs of subjects who were sputa positive for paragonimus ova and mycobacterium tuberculosis were taken in full inspiration. The radiographs were read by two radiologists independently.

Results: A total of 204 children were examined; 91 (44.6%) were males while 113 (55.6%) were females. Ten (4.9%) of the subjects were sputum positive for paragonimus ova while four (1.96%) were sputum positive for paragonimus ova and mycobacterium tuberculosis were full inspiration. The signs and symptoms of both diseases were similar. Radiologically, subcutaneous wasting was an important differentiating feature between both diseases (P = 0.002).

Conclusion: Paragonimiasis and tuberculosis, exist in the same locality. The clinical features of both conditions are similar hence differentiation on clinical grounds is difficult. Radiological evidence of subcutaneous wasting is therefore an important differentiating feature of both conditions.

#57 - ADHERENCE TO TREATMENT IN CHILDREN WITH PRIMARY CILIARY DYSKINESIA (PCD): IDENTIFYING ATTITUDES AND PERCEIVED BARRIERS TO PRESCRIBED TREATMENT

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Pediatric Pulmonology
Introduction: Primary Ciliary Dyskinesia (PCD) is a rare, chronic lung and upper airway disease caused by ineffective beating of the motile cilia. The cornerstones of the treatment are physiotherapy to improve mucociliary clearance and antibiotics to treat infections. Patients performing treatment, report less symptoms (McManus et al. 2003). A high treatment burden is related to a decline of health related quality of life in patients with PCD (Pifferi et al. 2010). Patients often feel frustrated through mistrust in medical care and a lack of knowledge surrounding PCD (Whalley & McManus 2006). Research about attitudes and barriers to treatment in PCD has not yet been reported.

Aim: This study aims to investigate and identify attitudes and barriers related to treatment adherence in children with PCD and their parents.

Methods: Children with PCD (<18 years, n = 31) treated at the University Hospital Leuven and their parents, were asked to participate by mail. A questionnaire consisting of demographic information and treatment related questions, a list of 18 barriers and 10 statements of attitudinal patterns (Dziuban et al. 2010) was included, along with the informed consent. Adolescents (14–18 years, n = 9) were asked to fill out the questionnaire themselves, after parental consent.

Results: Seven adolescents and 25 parents participated. Physiotherapy was prescribed to all patients, nebulizers to 80%, nose spray to 72%, antibiotics to 60%, puff to 60%, ear drops to 29%, and nose can to 30%. The most commonly reported barriers to treatment were “too busy” (parents 60%; adolescents 57%), “forgetting” (parents 48%; adolescents 71%), “family issues” (parents 36%; adolescents 42%), “wanting to be normal” (parents 28%; adolescents 57%) and “it takes too much time” (parents 28%; adolescents 57%). For adolescents, attitudes influencing non-adherence include “My PCD team does not understand how though it is to follow my treatments” (57.1%), “Even though I want to follow my treatments, sometimes I just forget” (71.4%). “I have trouble sticking to my treatments because they make me feel worse” (85.7%) and “Having to follow the PCD treatments means less freedom in my life” (42.9%). For parents, this last one is most often reported as an attitude towards treatment (76%).

Conclusion: A variety of reasons were described for non-adherence to treatment for PCD, which seem especially related to time management and a loss of freedom because of treatment. Adolescents report different attitudes to treatment compared to parents. For adolescents these attitudes predominately relate to feeling misunderstood and feeling restricted by the PCD treatment. The identified barriers and attitudes to treatment adherence pose a real challenge to PCD care teams in their day to day care for children with PCD.

III. ABSTRACTS

1. Bronchial Asthma and Other Chronic Obstructive Pulmonary Diseases

#24 - THE ASSOCIATIONS OF POOR ASTHMA CONTROL WITH LIFESTYLE HABITS, STRESS LEVELS AND QUALITY OF LIFE IN SINGAPOREAN ADOLESCENT PATIENTS

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#27 - EFFECT OF STEP UP THERAPY ON BRONCHIAL HYPERRESPONSIVENESS IN CHILDREN WITH POORLY CONTROLLED ASTHMA ON INHALED CORTICOSTEROID (ICS) MONOTHERAPY.

Author:

Thomas B. (Paediatric Respiratory Medicine, KK Women’s and Children’s Hospital - Singapore, Singapore)

Introduction: The effect of asthma step-up therapy on the degree of bronchial hyperresponsiveness (BHR) in children is not well understood. Aim: The aim of this pilot study was to determine the effect of three different step-up therapies (high dose ICS, ICS + LABA [Long Acting beta-agonist] and ICS + LTRA [Leukotriene-receptor antagonist]) on the degree of BHR,
in children with uncontrolled or partially controlled asthma, on low-medium dose (<400μg) BDP [Beclomethasone dipropionate] equivalent) ICS monotherapy.

Methods: In this open-label parallel group study, children (aged 6–18 years) with uncontrolled or partially controlled asthma on <400μg BDP, after a 4-week run-in period on 100μg Fluticasone (Flovent 100 Accuhaler, GlaxoSmithKline) twice daily, were assigned to one of the three step-up therapies: 200μg of Fluticasone twice daily [ICS step-up], 100μg of fluticasone plus 50μg of salmeterol (Sere tide 50/100 Accuhaler, GlaxoSmithKline) twice daily [LABA step-up], or 100μg of fluticasone twice daily plus montelukast (Singulair, MSD) 5 mg (for children 15 years) or 10 mg (for >15 years) [LTRA step-up]. Comprehensive assessment of asthma control (clinical assessment, spirometry, FeNO, asthma symptom diary, Paediatric Asthma Quality of Life Questionnaire [PAQLQ] and Asthma Control Test [ACT]) and BHR (using Mannitol dry powder challenge test [MCT], Aridol®). Fluticasone plus 50μg salmeterol (Sere tide 50 mg Fluticasone [Flixotide 100 Accuhaler, GlaxoSmithKline] twice daily [LABA step-up], or 100μg of flutzicasone twice daily plus montelukast (Singulair, MSD) 5 mg (for children 15 years) or 10 mg (for >15 years) [LTRA step-up] were used; n = 11 in each of the three step-up therapy groups. There was no significant difference in ACT score, PAQLQ score, FeNO, FEV1, FVC, FEF25-75 and the proportion of asthma symptom-free days between the three groups, before and after step-up therapy. The difference in the degree of BHR within the three treatment groups before and after step-up therapy was not statistically significant. The proportion of children in whom the MCT test changed from positive to negative was 42.8% in the ICS step-up, 25% in the LABA step-up and 10% in the LTRA step-up group. Improvement in BHR (defined as either a change of MCT or P% from positive to negative or an increase in PD15, after step-up therapy) was noted in 85.7% in the ICS step-up, 37.5% in the LABA step-up and 10% in the LTRA step-up group. Between groups comparison showed significantly higher improvement in BHR in the ICS step-up group compared to that in the LTRA (P = 0.0012) and the LABA (P = 0.0256) step-up groups.

Conclusions: Asthma step-up therapies resulted in an improvement in BHR, with the best response seen in the ICS step-up group. The effect size of the change in BHR in response to step-up therapy noted in this study may help plan future randomised placebo controlled cross over trials, comparing objectively the effect of asthma step-up therapies on the degree of BHR in children. Evidence from such studies may guide the choice of step-up therapy in asthmatic children.

**#30 - TRIGGERING THE SUCCINATE RECEPTOR GPR91 ON SMOOTH MUSCLE CELLS ENHANCES ARTERY REMODELING IN PULMONARY HYPERTENSION**

Author: Yang L. (Department of Cardiothoracic Surgery, Nanjing Children's Hospital Affiliated of Nanjing Medical University, Center of Children with Congenital Heart Disease of Jiangsu Province, Nanjing Children's Hospital Affiliated of Nanjing Medical University, Center of Children with Congenital Heart Disease of Jiangsu Province - Nanjing, China)

Background Pulmonary arterial hypertension (PAH) is associated with structural changes in the pulmonary vasculature characterized by the proliferation of pulmonary artery smooth muscle cells (PASMCs). The renin-angiotensin-aldosterone system (RAAS) plays a key role in this progress, but the underlying mechanism is unclear. GPR91 is a G-Protein-Receptor that may have an important role in this process. Therefore, we investigated whether RAAS was modulated by GPR91 in the rat models of PAH.

Methods and Results GPR91-RAAS signaling was investigated in 2 rat models of PAH induced by monocrotaline in pulmonaryocemotized (MCT + PE) rats and hypoxia. PASMC could express GPR91 and in PAH models, there were significant increased expressions of GPR91 and RAAS in lung and these changes were more pronounced in MCT + PE model. In 2 models, activation of GPR91 by the selective agonist succinate, further increased RAAS expression, and thus further aggravated pulmonary arterial pressure, pulmonary vascular remodeling, RV hypertrophy. In vitro studies confirmed that succinate stimulated proliferation of PASMCs and this effect was inhibited by Losartan.

Conclusion Our results suggested that GPR91 was involved in activating RAAS, thus leading to the PASMCs proliferation in vivo and in vitro. Inhibition of GPR91-RAAS signaling via captopril prevented development and progression of PAH induced by the GPR91 agonist, Succinate in PAH rats. Targeting GPR91 might be a potential treatment for PAH.

**#31 - EFFECT OF THE SUCCINATE RECEPTOR GPR91 ON PRESSURE OVERLOAD-INDUCED RIGHT VENTRICULAR HYPERTROPHY**

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Background-Cardiac hypertrophy leads to decompensated heart function, heart failure, and sudden death in patients with congenital heart disease. The PI3K/Akt pathway plays an essential role in this process, but its precise being activated mechanism was unclear. GPR91 is a G-Protein-Receptor that regulates the PI3K/Akt pathway. Therefore, we investigated whether PI3K/Akt was modulated by GPR91 in cardiac hypertrophy.

Methods and Results-We studied GPR91-PI3K/Akt signaling in pulmonary artery banding model. GPR91 was located in cardiomyocytes. The expressions of GPR91 and p-Akt were significantly increased in RV models. Activation of GPR91 in vivo by succinate increased p-Akt expression which in turns aggravated RV hemodynamics and RV hypertrophy. In vitro studies also revealed the similar data. All these effects were reversed by the antagonist of PI3K, wortmannin, in vivo and in vitro. Conclusions-Our results suggested that the GPR91 was involved in activating PI3K/Akt, thus leading to the hypertrophy. Inhibition of GPR91-PI3K/Akt signaling via wortmannin prevented development and progression of hypertrophy induced by the activation of GPR91.

**#32 - IMPAIRMENT AND RISK IN ASTHMA CONTROL IN CHILDREN ARE RELATED TO MATERNAL QUALITY OF LIFE**

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S52 Abstract

The aim of this study was to investigate the relationship between asthma control (impairment and risk) in children and their mothers’ quality of life (MQoL).

Three hundred ninety-four 0–14 years-old children with asthma were evaluated in 22 primary care pediatric practices in Spain. Impairment was evaluated through a combination of symptom frequency, nighttime awakenings, interference with normal activity, beta-agonist use and spirometry, and asthma was classified as well controlled, not-well controlled and poorly controlled, according to the National Asthma Education and Prevention Program. Risk of loss of control was classified as high or low according to history of hospitalization, adverse effects of medication, recent exacerbation and frequent exacerbations. MQoL was measured by means of the validated IFABI-R questionnaire, which quantify the impact of pediatric asthma on three domains of caregivers’ quality of life: functional, emotional and socio-occupational. Higher IFABI-R scores mean poorer quality of life.

Multiple regression models were built with each dimension of MQoL acting as dependent variables. The effects on them of impairment and risk were adjusted by education level, social class and family functioning, and measured as percent change in IFABI-R score. Additional regression models were built to evaluate the effect on MQoL of each single item that conform evaluations of impairment and risk.

There was a lineal relationship between asthma control in children and MQoL, affecting the three dimensions. Compared with well controlled, not well controlled asthma increased IFABI-R scores in 18.6% (95% confidence interval 8.1–30.2%) in the functional domain, 9.6% (0.2–19.8%) in the emotional domain, and 9.2% (1.4–17.5%) in the socio-occupational domain. The impact was even greater in poorly controlled asthma: 25.2% (9.0–43.8%), 20.8% (5.5–38.3%) and 15.1% (3.1–28.7%), respectively.

None of the individual items that form the evaluation of the impairment in asthma control were associated with MQoL. On the other hand, a high risk of loss of control was independently associated with MQoL, measured as percent change in IFABI-R score. Additional regression models were built to evaluate the effect on MQoL of each single item that conform evaluations of impairment and risk.

Introduction: A review was conducted in children with frequent attendances for acute asthma at Children’s Emergency Department KK Women’s and Children’s Hospital in 2002. The clinical audit revealed that children with problematic asthma were seldom referred for regular management. An initiative was developed to identify children with high acute care needs and recruit them to an integrated program for appropriate management. The objectives of our program were to reduce urgent care needs, control symptoms and improve the quality of life of these children.

The strategies used were:
1. Standardized care: Early initiation of anti-inflammatory or controller therapy, and the use of inhaled Beta agonist via a holding chamber for all patients;
2. Every patient was given an individualized written asthma action plan (WAAP);
3. Intensive education by asthma resource nurses and 4. To encourage adherence, the program also provided 50% subsidy for the non-subsidized drugs in the hospital formulary.

This program was piloted in August 2002 and had since completed 10 years.

Study objective: A critical review of the asthma outcome after the introduction of the integrated asthma program.

Methods: Retrospective analysis was conducted on the clinical database of the children recruited.

Results: A total of 4158 patients 63% male and 37% female, was recruited to this program.

Asthma Control: Eighty percent of the children had needed acute care needs in the past 3 months before enrolment. Less than 30% had needed urgent care with optimization of controller therapy. About 70% of children had achieved symptom control by 6 months of therapy. More than 70% no longer report exercise limitation and did not missed any school days. All these improvement were statistically significant.

Controller: More than 70% of the problematic asthma was controlled with the use of a single agent low dose inhaled corticosteroids (ICS). Only 25% had needed to step up to moderate dose ICS or combination of long acting beta agonist (LABA) with ICS and/or Montelukast.

Discussion: The results showed that the integrated program was able to achieve the objectives to reduce acute care needs, improved asthma control and quality of life. Intensive patient/caregiver education, the introduction of inhaled bronchodilator via holding chamber and the use of WAAP throughout the hospital including at the CE, had proven to be useful strategies which had contributed significantly to the success of the program. The results also indicated that majority of the problematic asthma were not difficult to treat. Establishing a strong partnership with community doctors to create awareness of early therapy would improve asthma care in the community and potentially could reduce the "problematic asthma" patient load by up to 70%, thus allowing limited resources to be better distributed to the truly difficult asthma.

S33 - THE IMPACT OF AN INTEGRATED ASTHMA PROGRAM IN A CHILDREN’S HOSPITAL IN SINGAPORE

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Pediatric Pulmonology

#34 - PERSISTENT BRONCHIAL HYPERRESPONSIVENESS IN CHILDREN WITH MODERATE PERSISTENT ASTHMA

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Background: Available evidence suggests that bronchial hypersensitivity (BHR) and the resultant mechanical forces may have a potential role in the development of airway remodeling in patients with asthma (1). It has been argued that prevention of bronchoconstriction and normalising the BHR should be an important aim of the asthma management (2). Aim: To study the degree of BHR in children with moderate persistent asthma (MPA), on British Thoracic Society (BTS) asthma treatment steps 2 or 3. Methods: Comprehensive assessment of asthma control was done on children with MPA on BTS treatment steps 2 or 3, on follow up under the Singapore National Asthma Program. Subjects also had assessment of their degree of BHR, using Mannitol dry powder challenge test [MCT], Aridol®, Pharmaxis, Australia).
Results: Table 1 Demographic and clinical details

<table>
<thead>
<tr>
<th>Age (year)*</th>
<th>BTS treatment step 1 (n=27)</th>
<th>BTS treatment step 1 (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (8-13)</td>
<td>20 (12-29)</td>
<td>20 (12-29)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male1: Female1 13:10 (53.0)</td>
<td>Male19: Female11 (63.7)</td>
</tr>
<tr>
<td>Race</td>
<td>Chinese: 19 (69.3), Malay: 11 (40.8), Indian: 4 (14.8), Eurasian: 1 (3.3)</td>
<td>Chinese: 10 (33.3), Malay: 12 (40.8), Indian: 5 (16.7), Eurasian: 3 (10.0)</td>
</tr>
<tr>
<td>BMI*</td>
<td>0.7 (1.5-2.23)</td>
<td>0.9 (1.5-2.42)</td>
</tr>
<tr>
<td>Age (year) at diagnosis*</td>
<td>4 (2-7)</td>
<td>4.5 (2-7)</td>
</tr>
</tbody>
</table>

Eczema

FeNO (ppb)* | <25 (15-25) | >25 (12.5-25) |
FEV1 (%) | 82 (74-86.6) | 81 (78-87.4) |
FVC (%) | 89 (87-93.5) | 94 (87-93.5) |
FEF25-75 (%) | 88 (86-83.5) | 86 (86-83.5) |
Asthma control criteria | Controlled (75%) | Partially controlled (70%) |
MCT† Positive | 10 (33.3) | 10 (33.3) |
BHR Grade | Mild=6, moderate=3, severe=1 |
BHR to HDM† | Positive=15 (55.5), Negative=12 (44.5) | Positive=15 (55.5), Negative=12 (44.5) |
BHR to SPT | Positive=10 (33.3), Negative=20 (66.7) | Positive=10 (33.3), Negative=20 (66.7) |
BMI-Body Mass Index, SPT-Skin Prick Test, HDM-House Dust Mite. Data expressed as *Median (IQR) and †n (%)

Table 2: Measures of asthma control and BHR

#48 - AIRWAY RESISTANCE BY IMPULS OSCILLOMETRY PREDICTS ASTHMA EXACERBATIONS IN YOUNG CHILDREN

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Background: It is difficult to predict asthma exacerbations in young children with episodic asthma. In a retrospective analysis of an asthma study (Zielen et al. “Predicting short term response to anti-inflammatory therapy in young children with asthma”, Curr Med Res Opin. 2010) we identified predictors of asthma exacerbations and related it to the parameters forced expiratory volume (FEV1), respiratory resistance (Rrs) by impulse oscillometry (IOS), and bronchial hyperresponsiveness (BHR) to methacholine testing. Method: Sixty-nine patients (4-7 years) with episodic asthma corresponding with the characteristics in the above-mentioned study were included. We defined an asthma exacerbation as an increased use of Salbutamol during cough periods (>2 puffs/week, >2 puffs/2 weeks). Pulmonary function and BHR were measured in symptom free intervals. To define the sensitivity and specificity to detect an asthma exacerbation, a receiver-operating characteristic (ROC) curve was plotted, and the accuracy was measured by the area under the ROC curve (AUC). A logistic regression model was used to predict the probability of an exacerbation.

Results: Mean results in the total group were: FEV1 106.6% ± 14.3, Rrs 0.76 kPa.s.L-1 ± 0.19, and PD20FEV1 methacholine 0.34 mg ± 0.55. The following cut-off values showed the best combination of sensitivity and specificity to predict an asthma exacerbation: FEV1 103.2% (AUC 0.62), Rrs 0.76 kPa.s.L-1 ± 0.19 (AUC 0.80), and PD20FEV1 methacholine 0.13 mg (AUC 0.61). In the logistic regression analysis a combination of all parameter predicted the individual risk of an asthma exacerbation with an accuracy of 86%.

Conclusion: Simple pulmonary function parameters predicted the probability of asthma exacerbations in young children to a large extent. The airway resistance Rrs was superior to FEV1 and methacholine testing. In recent studies bronchodilator response using IOS distinguished asthmatics from non-asthmatics as FEV1 did not and small-airway IOS measurements significantly indicated children with uncontrolled asthma. The current data suggests that peripheral airway obstruction is even present in symptom free periods and that these children exacerbate during infections.

#60 - ROLE OF MITOCHONDRIAL BIOGENESIS IN ASTHOMATIC AIRWAY SMOOTH MUSCLE FIBRILATION: FOREVER YOUNG

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4. Fayon M. (Pediatric Pneumology, CIC 005, Chu Bordeaux - Bordeaux, France)

Background: Increased bronchial smooth muscle mass is one of the key structural features of severe asthma. In adults, asthmatic airway smooth muscle cells (ASMC) demonstrate greater mitochondrial biogenesis associated with an increase in ASM C proliferation rate vs non-asthmatic ASM C. However, to the best of our knowledge, there is no evidence that such a difference between asthmatic and non-asthmatic ASM C occurs in pre-school children. Aims: The primary aim of the study was to compare asthmatic and non-asthmatic ASM C proliferation and mitochondrial biogenesis in adults and pre-school children. The secondary aim was to assess the effect of factors released by the epithelium upon stimulation by environmental factors such as house dust mite and rhinovirus, on ASM C proliferation. Methods: We cultured ASM C and bronchial epithelial cells (BEC) obtained by endobronchial biopsy from children and adults with severe asthma undergoing bronchial endoscopy for other reasons. We then studied ASM C proliferation (cell counting and CFSE dye assay) in 10% fetal bovine serum (FBS), 0% FBS and after the addition of the BEC culture supernatant. Results: Mean results in the total group were: FEV1 106.6% ± 14.3, Rrs 0.76 kPa.s.L-1 ± 0.19, and PD20FEV1 methacholine 0.34 mg ± 0.55. The following cut-off values showed the best combination of sensitivity and specificity to predict an asthma exacerbation: FEV1 103.2% (AUC 0.62), Rrs 0.76 kPa.s.L-1 ± 0.19 (AUC 0.80), and PD20FEV1 methacholine 0.13 mg (AUC 0.61). The logistic regression analysis a combination of all parameter predicted the individual risk of an asthma exacerbation with an accuracy of 86%.

Conclusion: Simple pulmonary function parameters predicted the probability of asthma exacerbations in young children to a large extent. The airway resistance Rrs was superior to FEV1 and methacholine testing. In recent studies bronchodilator response using IOS distinguished asthmatics from non-asthmatics as FEV1 did not and small-airway IOS measurements significantly indicated children with uncontrolled asthma. The current data suggests that peripheral airway obstruction is even present in symptom free periods and that these children exacerbate during infections.

Pediatric Pulmonology
associated with an increase in mitochondrial mass and biogenesis. ASMC proliferation is increased after a viral infection or an allergen exposure.

#64 - MEASUREMENT OF EXPIRED VOLUME FOR VARIOUS EXPIRATORY FLOW LEVEL DURING FORCED EXPIRATORY MANEUVERS IN CHILDREN: TO ANALYZE PARTIAL FLOW-VOLUME LOOPS?

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Because preschool children hardly manage to achieve prolonged expiratory maneuvers usual parameters (FEV1, FEV1/FVC, maximal expiratory flow) cannot be used to analyze flow-volume loops in this age group. Measuring the expired volume at different steps of level expiratory flow could be another way to analyze flow-volume loops in this age group. The aim of our study was to determine if expired volume (Vexp) obtained at various level of expiratory flow during a forced expiratory maneuver decreases in obstructive children.

Methods: In a first retrospective study, we measured Vexp obtained when expiratory flow reaches 90%, 60% and 30% of the theoretical peak expiratory flow (Vexp90, Vexp 60 and Vexp 30) in obstructive and non-obstructive preschool-aged children. We then prospectively measured Vexp90, Vexp 60 and Vexp 30 on partial flow-volume obtained in obstructive and non-obstructive preschool children whose bronchial obstruction was also assessed by resistance measurement.

Results: In the retrospective study, Vexp 30, Vexp60 and Vexp90 were significantly lower in the obstructive group (n = 26) than in the non-obstructive group (n = 32). Furthermore, in the obstructive group, Vexp 30, Vexp60, Vexp90 significantly increased after inhalation of salbutamol. In the prospective study, all of the 55 preschool children managed easily to perform partial expiratory maneuvers. Vexp 90 and Vexp60 were significantly lower in the obstructive group (n = 7) than in the non-obstructive group (n = 48) (P < 0.05).

Conclusion: Airway obstruction evaluation is very important in asthma management of the preschool children: it is predictive of the severity of asthma and predictive of lung function in adulthood. We will compare the Vexp in healthy and asthmatic preschool children in a largest study to obtain reference values.

Keywords: MEFV curves, preschool children, asthma, expiratory volumes

#66 - THE STATE OF NON-SPECIFIC RESISTANCE FACTORS IN SMALL AIRWAYS DISEASES OF BRONCHIAL TUBES IN CHILDREN

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Objective: To study the dependence of the state of phagocytic activity of granulocytes on the stage of the pathological process in asthma (BA), chronic bronchiolitis obliterans(BO) and bronchopulmonary dysplasia (BPD).

Materials and Methods: 112 children with BA and 139 patients with BO and 103 with BPD were observed in age from 1 year to 15 years. Studies were conducted in the period of exacerbation and remission. In all patients the study was carried out phagocytic activity of neutrophils through the spontaneous and stimulated nitroblue tetrazolium reduction test (NBT)

Results of the study: In all cases aggravation observed increase of phagocytic activity of neutrophils in the spontaneous (BA-10, 1 ± 0.37, BO-8, 04 ± 0.26, BPD-10.0 ± 1.12) and a stimulated (BA-31, 6 ± 0.57; BO-30, 3 ± 0.10; BPD – 30.9 ± 0.43) test. In the case of BO phagocytic activity of neutrophils was slightly reduced in comparison with BA and BPD. In remission indicators of these continue to grow (BA-11, 26 ± 1.3, BO-9.97 ± 0.25; BPD-10.1 ± 1.1) and (BA-37, 5 ± 1.5; BO-39 ± 0.9, BPD-40, 0 ± 0.5) in all groups

Conclusion. Thus, the phagocytic activity of granulocytes not suffer in BA, BO and BPD. However, indicators of NST are on the lower limit of normal at BO. Probably slight inhibition of phagocytosis associated with the presence of viral infection in the presence of infectious factors in the genesis of disease and, consequently, the growing process of endogenous intoxication.

#78 - AGE AND BODY SIZE EFFECT ON THE SYSTEMIC EXPOSURE TO DRY POWDER INHALED BECLOMETASONE/FORMOTEROL

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Purpose of the study: Guidelines for treatment of childhood asthma recommend prescription of inhaled anti-asthmatic drugs at half the nominal dose as for adults in order to reduce the risk of systemic side effects. However, the influence of age and body size on the blood concentrations of inhaled drugs is not fully elucidated. We aimed to compare the systemic exposure to the active ingredients of a fixed combination of beclometasone dipropionate (BDP) and formoterol after dry powder inhaler (DPI) administration in children, adolescents and adults.

Methods: The pharmacokinetic profiles of formoterol and beclometasone-17-monopropionate (B17MP; active metabolite of BDP) were evaluated over 8 hours from two independent studies comprising children (6–11yrs, n = 27), adolescents (12–17yrs, n = 28) and adults (≥18yrs, n = 30) receiving a single, fixed dose of BDP/formoterol (children: 200 µg/24 µg, adolescents and adults: 400 µg/24 µg) via DPI.

Results: The systemic exposure (AUC0-t) for children vs. adults was almost doubled for formoterol (despite the same nominal delivered dose) and similar for B17MP (despite the BDP dose being halved in children). In adolescents the AUC for formoterol and B17MP were approximately one third higher than in adults for both compounds. After normalization for the BDP/formoterol dose in the three populations the systemic exposure and peak concentration (Cmax) correlated inversely with age and body surface area of the patients (r ≤ -0.53; P < 0.0001).

Conclusion: The systemic exposure to the active ingredients of BDP/formoterol administered as DPI correlates inversely with age and body size suggesting that dry powder dosage regimens should be adjusted for age and body size to avoid high systemic drug levels in children.

Reflections stimulated by the research: Contrasting the present findings, previous similar investigations demonstrated that when using a pMDI with a spacer the systemic exposure for the same nominal dose in children was...
similar to that in adults. This suggests that drug delivery by inhalation via pMDI plus spacer is lower in children as compared to adults resulting in similar exposure due to the lower body size of the paediatric population. Therefore guideline recommendations of a reduced dosage regimen in children could be appropriate for DPI administration only.


#80 - PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENT OF PRESSURISED Metered-dosE INHALED BECLOMETASONE/FORMOTEROL IN ADOLESCENT ASTHMA

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Purpose of the study: Asthmatic adolescents are generally recommended to be dosed like adults. However, this population is unique in many ways and limited pharmacokinetic (PK) and pharmacodynamic (PD) data are available on fixed combinations of inhaled-corticosteroids/long acting β2-agonists (ICS/LABA). In addition the influence of age on the systemic exposure of drugs administered via pMDI with or without valved holding chamber is still not fully elucidated. The aim of the study was to investigate the PK/PD profile of a fixed dose combination of ICS/LABA pMDI in asthmatic adolescents with or without valved holding chamber in comparison to a free combination of licenced pMDI products. A comparison of adolescent and adult asthmatics was also conducted.

Methods: Open label, randomized, three-way crossover study, on 30 asthmatic adolescents receiving a single dose of the fixed combination of beclomethasone dipropionate (BDP)/formoterol pMDI 100/6 μg per actuation (Foster®) with or without AeroChamber PlusTM or a free combination of BDP 100 μg pMDI (Qvar) plus formoterol 6 μg pMDI (Atimos). An open, parallel arm of 30 asthmatic adults receiving Foster® was added as a control. All patients received a total single dose of BDP and formoterol of 400 μg and 24 μg, respectively. Assessments were performed over 8 hours.

Results: In adolescents, Foster® with or without AeroChamberPlusTM was equivalent to Qvar® - Atimos® or Foster® alone in terms of systemic exposure (AUC0-t) to beclometasone-17-monopropionate (B17MP, active metabolite of BDP) and formoterol; 90% confidence intervals (CIs) for the geometric means ratio fixed/free were all within the 0.80–1.25 range interval. After treatment with Foster® the systemic exposure to B17MP and formoterol was also comparable between adolescents and adults (90% CIs within 0.78–1.17). The PD profile was equivalent between all treatments in terms of plasma potassium, plasma glucose, pulse rate and forced expiratory volume in one-second.

Conclusions: In adolescents the PK and PD of Foster® with or without AeroChamberPlusTM, is comparable to that of a free combination of licensed single entity pMDIs, which have established safety and efficacy profiles. The findings in adolescents adults were comparable.

Reflections stimulated by the research: These results support the indication for use of ICS/LABA pMDIs in adolescents at the same dosage as in adults.

#82 - BRONCHODILATING EFFECTS OF EXTRAfine BECLOMETASONE DIpropionate AND FORMOTEROL FUMARATE VIA PRESSURIZED METERED DOSE INHALER IN ASTHMATIC CHILDREN

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Introduction: In asthmatic children older than 5 years, the GINA guidelines 2012 update recommend to add inhaled long-acting β2- agonists (LABA) when the disease is not adequately controlled with inhaled corticosteroids (ICS) alone. Controlled studies have shown that fixed combination therapies are as effective as giving each drug separately and may increase patients’ compliance. A paediatric extrafine fixed combination of beclomethasone dipropionate (BDP) and formoterol fumarate (FF) via pressurized metered dose inhaler (pMDI) containing 50 μg of BDP and 6 μg of FF per actuation (CHF1535) was developed by Chiesi Farmaceutici S.p.A. (Parma, Italy).

Methods: in a phase-2, double blind, randomised, active- and placebo-controlled, 5-period cross-over study, the bronchodilator effect of a single administration of CHF1535 (2 actuations, total dose BDP 100 μg and FF 12 μg) was compared to that of a free combination of licensed extrafine BDP pMDI 50 μg (2 actuations, total dose 100 μg) plus FF 6 μg pMDI (2 actuations, total dose 12 μg) in 56 asthmatic children aged ≥5 and < 12 years. The primary objective was to demonstrate the non-inferiority of CHF1535 vs the free combination in terms of forced expiratory volume during the first second (FEV1) AUC corrected by time over 12 hours following the morning dose (AUC0–12h) (primary efficacy variable). Secondary objective was to explore the dose-related efficacy of different doses of CHF1535 (BDP 50 μg/FF 6 μg, BDP 100 μg/FF 12 μg and BDP 200 μg/FF 24 μg) in terms of FEV1 AUC0–12h. All treatments were administered with AeroChamber Plus spacer device. Safety was assessed through monitoring of adverse events (AEs), ECG and vital signs.

Results: the non-inferiority of CHF1535 100/12 μg compared to the free combination of BDP 100 μg + FF 12 μg in terms of FEV1 AUC0–12h was demonstrated (adjusted mean difference (95% CI): −0.004 L (−0.050, 0.041) as the lower confidence limit of the 95% CI of the adjusted mean difference was - greater than the non-inferiority limit set at −0.1 L. All treatment groups showed an increase from pre-dose in mean FEV1 at each time-point over the period to 12 hours post-dose. A trend towards a dose-related efficacy response, (FEV1 AUC0–12h) was shown. The comparisons of each CHF1535 dose vs placebo were: 0.037 L (P = 0.160), 0.119 L (P < 0.001) and 0.094 (P < 0.001) for CHF1535 50/6, CHF1535 100/12, CHF1535 200/24, respectively. No serious AEs were reported during the study and no safety signals were found in terms of ECG and vital signs. Conclusion: CHF1535 100/12 μg was non-inferior to the free combination of BDP + FF at the same dose in terms of lung function over the 12-hour post-dose period and a trend towards a dose-related efficacy response was seen. All treatments were safe and well tolerated.

Reflections stimulated by the research: according to the above results, the 100/12 μg dose was selected for the pivotal phase-3 studies of CHF1535 clinical development.

Pediatric Pulmonology
#83 - FACTORS ASSOCIATED WITH EXERCISE-INDUCED BRONCHOCONSTRICTION IN CHILDREN: ASSESSMENT OF GASTRO-OESOPHAGEAL REFLUX.

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Background. Knowledge on pathophysiology of exercise-induced bronchoconstriction (EIB) is still debated. Studying gastro-oesophageal reflux (GOR) in children with reported exercise-induced respiratory symptoms could help in our understanding of EIB. Aims. To assess clinical, functional, inflammatory data and gastrointestinal acidity during EIB in children. Methods. In 27 asthmatic and 18 non-asthmatic children (aged 5.9–17.1 yr; 30 males) we assessed exercise-induced respiratory and chronic gastrointestinal symptoms, blood samples for IgE and eosinophil count, exhaled nitric oxide (FeNO), baseline spirometry; then started a 24-h GE pH monitoring (GE pH24). All children underwent treadmill-exercise testing during GE pH24. Spirometry was repeated 1, 5, 10, 15 and 20 minutes after exercise as well as FeNO (5° and 20'). Spirometry was assessed 20 min following exercise after inhalation of salbutamol. EIB was defined as a post-exercise fall in FEV1 of at least 10% from baseline. The reflux index (IR) was calculated as the percentage of time with a pH below 4.0, either for the all 24-hours and 6 min-intervals before, during and after the exercise test. Pathological GOR was defined when IR raised over 4.0% of the GE pH24. Results. Subjects with EIB (n = 11) had lower baseline lung function and higher bronchial response to salbutamol but no different frequency of pathological GOR. IgE levels, eosinophil-blood count and FeNO than subjects without EIB (n = 34). Reported exercise-induced respiratory symptoms and chronic gastrointestinal symptoms were also similar between children with EIB and those without EIB, though most subjects with EIB had a previous diagnosis of asthma (10/11) as compared with those without EIB (17/34); P = 0.04. In the whole population, the fall in FEV1 was found correlated with low age-related variables, low baseline FEV1 and FEF25-75%, high bronchial response to salbutamol and low 6-min post-exercise IR (e.g. with FEV1: r = 0.47, P = 0.001, with DFEV1: r = −0.34, P = 0.021, with IR: r = 0.53, P < 0.001).

Conclusion. From our results, EIB is mainly associated to measurements of bronchial patency and reactivity. EIB does not seem influenced by reported symptoms, measurements of atopic inflammation, pathological GOR or changes in gastro-oesophageal acidity after exercise. Selection of subjects by asthma phenotypes could better explore the relationship between EIB and GOR.

Pediatric Pulmonology

#85 - KETAMINE VERSUS AMINOPHYLLINE FOR STATUS ASTHMATIC IN CHILDREN: A RANDOMIZED, CONTROLLED TRIAL

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Objective: To evaluate efficacy and safety of ketamine as compared to aminophylline in children with moderate to severe acute exacerbation of asthma who respond poorly to standard therapy. Methods: It was a randomized controlled trial. Children of 1 to 12 years of age with acute moderate to severe exacerbation of asthma having Pediatric Respiratory Assessment Measure (PRAM) score ≥5 at 2 hours of standard therapy (salmeterol and ipratropium bromide nebulization, steroids, and magnesium sulphate) were included in the study with appropriate consent and ethics committee approval. Enrolled patients were randomized to intravenous (IV) ketamine (0.5 mg/kg bolus followed by continuous infusion of 0.6 mg/kg/hr) OR IV aminophylline (5 mg/kg bolus followed by continuous infusion of 0.9 mg/kg/hr) for 3 hours. Patients and treating team were not blinded to intervention but person assessing outcome was blinded to intervention. Primary outcome measure was change in PRAM score. Secondary outcome measures included adverse effects, change in pO2 and pCO2, change in Peak Expiratory Flow Rate (PEFR), need for mechanical ventilation, and duration of hospital stay. Statistical analysis was done as appropriate using SPSS version 16.

Results: A total of 48 subjects, 24 each in ketamine and aminophylline group, were enrolled in the trial. Age (median [IQR], 42 [22.0-72.0]) versus 60 [24.2-72.0] months; P = 0.468), PRAM score (7.71 ± 1.68 versus 8.04 ± 1.55; mean difference 0.33; 95% CI –1.27, 0.61; P = 0.478), and other baseline demographic and clinical parameters were similar between the groups. Change in PRAM score from enrollment to at three hours of intervention was similar in both the groups with a change of 4.00 ± 1.25 and 4.17 ± 1.68 (mean difference 0.16; 95% CI –1.02, 0.69; P = 0.699) in ketamine and aminophylline group respectively. At three hours of intervention PRAM score was similar between the groups (3.79 ± 1.84 versus 3.88 ± 1.92; mean difference 0.08; 95% CI –1.18, 1.01; P = 0.879) and it decreased significantly from enrollment in both the groups (P = 0.000 for both group) (Figure 1). There were no adverse effects in both the groups except for one episode of small vomiting in one patient from ketamine group. The changes in pO2, pCO2 and PEFR, and duration of hospital stay were similar between groups. No patient required mechanical ventilation. Conclusion: Ketamine and aminophylline were equally effective for improvement in PRAM score in children with moderate to severe acute exacerbation who respond poorly to standard therapy without any significant adverse effects. Reflections and concrete proposals for action: In children with moderate to severe acute exacerbation who responds poorly to standard therapy either IV ketamine or IV aminophylline may be used depending on availability of drug and experience of users with drug.

Trial is registered at Clinical Trials Registry-India: CTRI/2013/09/004000.

#89 - BRONCHIAL REACTIVITY, INFLAMMATORY AND ALLERGIC PARAMETERS, AND VITAMIN D LEVEL IN CHILDREN WITH MILD ASTHMA

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Objectives: To assess the correlation between Vitamin D levels and airway hyper-reactivity (AHR), fractional exhaled No (FeNO), high sensitivity-CRP (hs-CRP), and allergic parameters in non-obese children aged 6–18 years with mild asthma not receiving anti-inflammatory treatment.

Methods: Each patient underwent evaluation including spirometry, methacholine challenge test (MCT), FeNO, serum vitamin D level, total IgE level, peripheral blood eosinophil count, and hs-CRP level. Primary end points: The correlation between vitamin D level and AHR as assessed by MCT. Secondary end points: The correlation between vitamin D level and FeNO, systemic markers of inflammation and allergy.

Results: Seventy-one asthmatic children (25 female; 35%), age 12.46±3.61 years were included. Their median vitamin D level was 23 ng/ml (range: 6–48.5; mean 23.02 ng/ml) (range: 0–13.9), and median FeNO 26.5 ppb (range: 3.6–285).

There was no correlation between vitamin D level and the response to MCT, FeNO, hs-CRP levels, IgE, eosinophil count, and the frequency of allergic rhinitis or atopic dermatitis.

Conclusions: In our group of asthmatic children, there was no correlation between vitamin D levels and the degree of airway reactivity, airway inflammation, and allergy. Cause and effect relationship between vitamin D, asthma, and allergy should be further studied and intervention double blind placebo controlled clinical trials assessing the effect of vitamin D administration on asthma and allergy are needed.

#100 - RECOGNITION OF RESPIRATORY SOUNDS IN CHILDREN

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Aims: To investigate parental ability to recognise wheeze in children.

Methods: Scenes of children breathing were captured on video. These children demonstrated audible wheeze, stridor, snoring, transmitted noises and normal breathing. The video clips were then validated by a group of qualified pediatricians. Videos with a kappa value of ≥0.8 were selected. The video clips were then shown to parents of children with and without asthma. Parents were asked to label the sound in each clip and to determine the location from which it originated.

Results: A total of 12 video clips were successfully selected and validated to be shown to the parents. Two hundred participants were enrolled to participate. Only 38.5% of respondents were able to correctly label wheeze. Respondents were better at locating the origin of wheeze. The commonest Bahasa Malaysia word by parents to describe wheeze was “susah nafas”. The commonest English words used by parents to describe wheeze was “wheeze” and “asthma”. Having a child with asthma, higher education level and worse asthma severity in the child did not result in more accurate labeling.

Conclusion: Parents were better at locating respiratory sounds than labeling them. Most parents use vague words to describe respiratory noises. Hence history taking should be modified to asking parents where the origin of these abnormal respiratory sounds is.

#105 - DUAL-CENTRE RANDOMISED TRIAL ON TAILORED ASTHMA THERAPY BASED ON EXHALED NITRIC OXIDE (FENO) VS ROUTINE CLINICAL CARE

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A Cochrane review that examined the efficacy of using FeNO to tailor the dose of inhaled corticosteroid (ICS) showed that FeNO cannot be routinely recommended for clinical practice at this stage and remains uncertain. However all the 6 studies used a single FeNO cut-off. In this RCT we determined if asthma monitoring using FeNO (using 2 different cut-offs dependent on atopy) is better than control (symptoms and FEV1) in preventing asthma exacerbations in children on inhaled corticosteroids.

Methods: Over 12-months, children underwent spirometry, FeNO, QOL and asthma/cough diary during every visit. The study was a dual centre randomised controlled trial. Treatment for asthma was adjusted according to pre-determined criteria taking into account atopy status and dependent on allocation group (FeNO or control).

Results: 63 children from Hong Kong and Brisbane were randomised (FeNO = 31, controls = 32) and 55 (86%) completed the study. Over 12-months, significantly fewer children in the FeNO group (6 of 27) had an asthma exacerbation compared to controls (15 of 28), P = 0.021; number to treat for benefit over 12-months was 4 (95%CI 1.2–9.4). However, there was no difference between groups any of the secondary outcomes (quality of life, symptoms, FEV1). Also, the final daily inhaled ICS dose was significantly (P = 0.037) higher in the FeNO group (median 400 µg/m, IQR 250–600) compared to the controls (200, IQR100–400).

Conclusion: Taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations at the expense of increased ICS use. However, the strategy is unlikely beneficial for improving asthma control. A larger study is required to confirm or refute our findings.

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#108 - LCI IS RESPONSIVE TO TREATMENT IN PRIMARY CILIARY DYSKINESIA

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Background: Primary Ciliary Dyskinesia (PCD) is a rare genetic disorder, characterized by chronic airway infection and an increased incidence of sinus inversus and male infertility. The treatment of the chronic airway infection is not evidence based but often derived from evidence based treatment schedules for cystic fibrosis. With the perspective of upcoming PCD clinical trials, the need for reliable outcome parameters is obvious.

Pediatric Pulmonology
Candidate outcome measures in PCD are chest CT score (Maglione et al, Ped Pulmonol 2011) and lung clearance index (Green et al, Thorax 2011, Irving et al, AJRCCM 2013), a measure of gas mixing efficiency. As in CF, both might be more sensitive than FEV1 to detect early disease.

Aim of the study: To investigate whether lung clearance index (LCI) is responsive to treatment in patients with PCD.

Methods: We included children and adolescents with PCD and a pulmonary exacerbation that was treated with intravenous (iv) antibiotics and measured LCI (N2 multiple breath washout using EComedics set-up) and FEV1 before and after treatment.

Results: So far, 4 patients were treated with iv antibiotics for a mean duration of 5.8 days because of a respiratory exacerbation. Mean LCI z-score decreased from 6.3 (range 2.05–10.73) to 4.4 (range –0.04 to 9.42, p 0.06), LCI z-score improved in each individual. Mean FEV1 z-score improved from –2.6 (range –5.52 to –0.01) to –1.6 (range –3.18 to 0.65, p 0.038). The mean improvement was 1.9 z-scores for LCI, and 1 z-score for FEV1.

Conclusion: Preliminary data demonstrate that in subjects with PCD, treated with iv antibiotics for a pulmonary exacerbation, both FEV1 and LCI seem sensitive to intervention than FEV1. More research is needed to clarify the role of LCI versus FEV1 measurements in the follow-up of patients with PCD.

Conclusion: Both LCI and FEV1 are responsive to treatment and might therefore be used as outcome parameter in clinical trials for PCD treatment.

#111 - STUDY OF V/Q SCAN IN CHILDREN WITH BRONCHIOLITIS OBLITERANS

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Bronchiolitis obliterans (BO) is a chronic airflow obstruction syndrome associated with inflammatory lesions of the small airways. Biopsy is limited in clinic, so far the diagnosis is based on clinic presentations. Pulmonary perfusion/ventilation scan (V/Q) can reveal pulmonary airway ventilation function (PAVF) and blood perfusion (pBP) that is supposed to be helpful for diagnosis and assessment. Objective: To explore the clinical significance of V/Q for children with BO. Methods: V/Q was performed for total of 30 children with BO during February 2005 to April 2011. Analysis of relations of V/Q with clinical presentations was performed. Result: Of all 30 children received V/Q tests, 26 (86.7%) children presented impaired ventilation function and blood perfusion, in whom the kids with moderate or severe degree accounted for 92.3%. including impaired pulmonary ventilation in 8 kids (30.8%), impaired pulmonary blood perfusion in 3 (11.5%), 15 (57.7%) presenting matched impairment of PAVF and pBP. Only 4 (13.3%) kids were intact in both ventilation function and pulmonary blood perfusion. All 5 kids deteriorated in follow up who presented bilateral severe impairment of V/Q, while 9 kids develop favorable outcome who presented mild to moderate impairment in 5 and intact in 2. Conclusion: V/Q correlated with the clinical presentations, is helpful for diagnosis, evaluation and prediction of outcome for children with BO.

#112 - THE DIFFERENCE OF REACTIVITY IN CONTROL TREATMENT BETWEEN ASTHMATIC CHILDREN AND THE ANALYSIS OF ITS RELATED FACTORS

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Pediatric Pulmonology

Objective: To dynamically observe and assess children’s asthma control level, so as to determine the difference between children’s reactivity to treatment, and to analyse the characteristics of change of pulmonary function indicators and fractional nitric oxide concentration in exhaled breath (FeNO) in children who had different reactivity to treatment. Methods: A total of 52 asthmatic children who had started regular control treatment and been on a regular follow-up were enrolled, all the patients were on the assessment of asthma control, pulmonary function testing and FeNO measurement every three months. The indicators of pulmonary function testing contained FEV1%, PEF%, FEV1/FVC, MMEF%. The level of treatment of asthma control medicine, daily dose and course of treatment were recorded, and the average daily dose of each medicine in the 9 months was calculated. Results: At the end of the nine months’ follow-up, all the patients were divided into two groups, there were 30 cases in stable group and 22 cases in unstable group. There was no significant difference between the two groups in FEV1% or PEF% of the four times of follow-up, in the stable group of the third, sixth and ninth month follow-up time were significantly higher than those in the unstable group (P < 0.05), the MMEF% of patients in the stable group of the third and ninth month follow-up time were significantly higher than those in the unstable group (P < 0.05), FeNO concentrations of patients in the stable group of the baseline and the third month followup time were significantly higher than those in the unstable group (P < 0.05). There was no significant difference between the two groups in the average rate of change of FeNO or pulmonary function testing indications (P > 0.05). The daily dose of fluticasone, salmeterol and montelukast of each patient in the stable group was significantly lower than those in the unstable group (P < 0.05). Conclusion: The FeNO, FEV1/FVC and MMEF% were higher in the stable group than those in the unstable group. The daily dose of fluticasone, salmeterol and montelukast of each patient in the stable group was significantly lower than those in the unstable group.

#117 - QUALITY OF LIFE AMONG PARENTS AS A DETERMINING FACTOR IN CONTROLLING ASTHMA IN CHILDREN

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Objective: Determine whether the quality of life of the caregivers and the family functioning influence the control of asthma in children.

Methods: An observational, longitudinal study at twenty-two primary healthcare centers in Spain, with children between 4 and 14 years of ages who had active asthma and whose main caregiver (father or mother) had sufficient skills in the Spanish language. During the initial visit, the child was assessed: (1) asthma-related quality of life of the parents, measured by the IFABI-R instrument, developed and validated in Spanish. This tool measures the impact of asthma on a 1–4 scale, in which the higher the score, the greater the deterioration of the quality of life. (2) The family functioning was assessed using the “family Appgar” instrument, with a 1–3 score; the higher the score, the better the family functioning. At the second visit, sixteen weeks later, the degree of the child’s asthma control was determined following the NAEPP-3 classification for asthma severity.

The influence of family variables on the later control was analyzed using a logistic regression model, with asthma control at the second visit as the dependent variable. Co-variables were added, including age, sex, degree of asthma control at the first visit, risk factors for impairment of asthma control (hospitalization or recurring crisis in the past 12 months, recent crisis), treatment modifications at the first visit (increase or decrease in the treatment steps), years since diagnosis, sensitivity to inhalants, educational level of the parents, social class of the parents, time elapsed between the first and second visit, and whether the assessment of the quality of life and the family functioning was made by the father or the mother. The results were presented as odds ratio (OR) and their 95% confidence interval (95%CI) of having the asthma controlled. Another logistic model was created, limited to children with daily pharmacological treatment and adding therapeutic adherence (Morisky-Green test) as another co-variable.

Results: 471 children and their caregivers were recruited; the data from 396 children (84.0%) were analyzed with full data for all variables. The family functioning had no association with the control of asthma. However, the quality of life of the parents was strongly associated with asthma control. In the adjusted model, an increase in IFABI-R (worse quality of life) was associated with a lesser probability of having good control 16 weeks later (OR = 0.60, 95% CI = 0.38-0.93, P = 0.022). This association was maintained in the restricted model, only with children who received pharmacological treatment (OR = 0.56, 95% CI = 0.34-0.90, P = 0.045).

Conclusions: The quality of life among parents is a determining factor in the probability of achieving good control of asthma in the medium term. Assessing the quality of life of the caregivers could be important in deciding the therapeutic management of the disease.

#119 - RELATIONSHIP OF FRACTIONAL EXHALED NITRIC OXIDE AND CLINICAL ASTHMA CONTROL ASSESSMENT TOOLS IN CHILDREN

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Background: Fractional Exhaled Nitric Oxide (FeNO) is a marker of eosinophilic inflammation and has a potential role in monitoring airway inflammation in asthmatic patients; however its relationship with clinical asthma control assessment tools has not been established.

Objective: To measure the association between FeNO levels and clinical evaluation of asthma control.

Methods: Patients aged 7–15 years with persistent asthma were enrolled. Clinical asthma control was evaluated using Asthma Control Test (ACT) questionnaires and Global Initiative for Asthma (GINA)-defined criteria. FeNO measurement was done using NIOX MINO® device. Association of FeNO to clinical asthma control status was controlled for Skin Prick Test (SPT) using binary logistic regression. The cut-off point for FeNO was determined using Receiver Operating Characteristics (ROC) curve.

Results: Sixty-two children were included. A weak agreement was found between ACT and GINA-defined asthma control (66.2%, k = 0.313, P = 0.007). FeNO was significantly associated with both ACT and GINA-defined asthma control status when controlled for SPT (OR = 1.032, 95% CI 1.002, 1.063 and OR = 1.030, 95% CI 1.003, 1.059). For both ACT and GINA-defined asthma status, the best cut-off point for FeNO was at 32 ppb giving area under the curve (AUC) of 0.673 (95% CI 0.532, 0.815) and 0.684 (95% CI 0.551, 0.812) respectively. When level > 32 ppb defined high value, the sensitivity and specificity in predicting ACT and GINA-defined uncontrolled asthma were 76.5% (95% CI 50.1%, 93.0%), 57.8% (95% CI 42.2%, 72.3%) and 66.7% (95% CI 47.2%, 82.7%), 62.5% (95% CI 43.7%, 78.9%) respectively.

Conclusions: Our data suggests that FeNO level > 32 ppb supports the clinical evidence of uncontrolled asthma as defined by ACT and GINA.

#126 - CONFIRMATORY FACTORIAL ANALYSIS OF THE SCALE OF OVERLOAD OF THE CAREGIVER OF ZARIT, IN THE PARENTS/CAREGIVERS OF PEDIATRIC ASTHMATIC PATIENTS

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Introduction: In spite that there are many tools to measure the level of overload in parents / caregivers, few studies have validated them to be used in the context of pediatric asthma.

Methodology: It was performed a cross-sectional analytical study and of validation of scale. We assessed the overload degree of parents/caregivers of asthmatic children using the Zarit Scale (ZS). We performed a confirmatory factor analysis to verify the factor structure of the ZS, and assessed its construct validity and internal consistency. Logistic regression models were adjusted to identify factors associated with an severe overload level in parents and/or caregivers of asthmatic children.

Results: Of the total of parents and/or caregivers, 26 (10.0%) were considered to be experiencing a severe overload. The factor structure described for ZS fits adequately when it is used to measure the level of overload experienced by parents/caregivers with asthmatic children (X² = 59.47; gl. = 19; P < 0.001; CFI = 0.93; TLI = 0.90; RMSEA = 0.09). The age of caregiver (OR 1.07; IC 95% 1.00-1.15; P = 0.04), free marital union of parents/caregivers (OR 3.96; IC 95% 1.27-12.35; P = 0.02), and the mother as the only type of caregiver (OR 8.87; IC 95% 1.13-69.61; P = 0.04) were identified as independent predictors of a severe overload.

Conclusions: The ZS is an appropriate instrument to determine the level of overload experienced by parents and/or caregivers of asthmatic children. The age of the caregiver, free material union of parents/caregivers, and mother as the only type of caregiver are independent predictors of a severe overload level.

#128 - THE THIRD NATIONWIDE SURVEY OF CHILDHOOD ASTHMA IN URBAN AREA OF CHINA

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Background: This national wide study was conducted to investigate the prevalence of childhood asthma in urban areas of large cities in China, and to find the characteristics of attacks, the diagnosis and treatment status, and provide scientific data for improving the prevention and management of asthma in children.

Methods: This national-wide, cross-sectional survey was organized by the National Cooperative Group on Childhood Asthma, and conducted in 43 cities all over the country, including 27 capital cities of provinces or autonomous regions, 4 municipalities, from September 2009 to August 2010. Children born from July 1st 1995 to June 30th 2010 were enrolled in the survey, consisting of children who had been living in the surveyed cities and those born outside the city but had lived in the cities for over 6 months. Schools, kindergartens and communities in each city were selected by phase stratified random cluster sampling. Standardized preliminary questionnaire was used for screening out possible patients in the survey. Diagnosis of asthma was confirmed by enquired of history, together with review of previous record and tests, physical examination in suspected asthmatic children.

Results: 463,982 children were investigated for the survey. Asthma was diagnosed in 13,992 children, 12,634 children with classical asthma (90.3%) and 1358 children with cough variant asthma (9.7%). 4387 cases (31.4%) from the bronchial asthma. The principle of the remodeling consists in together with the inflammation, various structural changes known as remodeling constantly appear in the bronchial walls of patients suffering from the bronchial asthma. The principle of the remodeling consists in changes of properties of the bronchial epithelium including hyperplasia of its goblet cells, thickening of the basement membrane predominantly in the area of its reticular lamina, differentiation and activation of myofibroblasts and proliferation of smooth muscle, multiplication of submucosal glands, deposition of extracellular proteins to the lamina propria mucosa and changes of vascularization. While these morphological changes in bronchial walls of patients with asthma have been thoroughly described, predominantly in the adults, fewer papers exist about the bronchial remodeling in small children and even lesser about the changes in laboratory animals.

We decided to analyze structural changes of intrapulmonary airways in rats of Brown Norway (BN) strain, which are especially responsive to sensitization by allergens and tend to develop the state that clinically and morphologically highly resembles the human bronchial asthma when stimulated with appropriate allergen challenges.

Young and adult BN rats were sensitized by repeated intraperitoneal injections of ovalbumin (OA). During following 2 weeks, the rats regularly inhaled OA. Two control groups of each age were housed simultaneously. The first of them was injected and inhaled by saline (S), the second group was untreated (C). At the end of the experiment, the animals were sacrificed, their lungs were processed for the light microscopy. We concentrated to the airway morphometric parameters, occurrence of eosinophilic granulocytes in the airway walls and number of epithelial secretory cells together with a glycoconjuge quality of their secretion.

The airway walls of the OA group were showing marks of remodeling in both young and adult animals. The total wall areas of all intrapulmonary airways were significantly increased compared to groups S and C. The thickening of inner wall areas was more pronounced in adult rats; outer wall areas were more increased in the young group. There were some significant signs of the muscular hypertrophy or hyperplasia only in young challenged animals. The number of eosinophilic granulocytes was predominantly increased in airway walls of OA young rats. Secretory cells were more multiplicated in airway epithelium of OA adult animals. Proportions of neutral and acidic glycoconjuges in their secretion were shifted towards the acidic ones in adult rats.

The study confirmed the bronchial sensitivity of BN rats and different reactivity of adult and young individuals. The remodeling changes were ascertained in all layers of the airway wall; more in the epithelium and connective tissue than in the muscle. A morphological base for further experiments was constituted.

#137 - ASSOCIATION BETWEEN BODY MASS INDEX AND THE LEVEL OF ASTHMA CONTROL IN A LATINO POPULATION OF ASTHMATIC SCHOOL CHILDREN

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Background: Many observational studies have shown association between Body Mass Index (BMI), particularly in obese children, asthma control level and the degree of quality of life. However this association remains uncertain particularly in Latino children because results of the studies have resulted inconsistent.
Objective: The aim of the study was to determine whether there is any association between the Body Mass Index (BMI) and the Asthma Control level in a group of asthmatic school children.

Materials and Methods: Cross sectional study. 106 children with asthma were evaluated in the Outpatient asthmatic Program at Hospital Militar Central in Bogotá, Colombia. a thrid level institution, during the second semester of 2012. Logistic regression models were developed to determine odds ratios unadjusted and adjusted to identify whether the body mass index is associated with the Level of Asthma Control.

Results: Of 106 children evaluated 62 (58.5%) were boys and 44 (41.5%) girls. 77 (72.6%) had normal weight, 20(18.9%) were overweight and 9 (8.5%) were obese. With regard to treatment, 59 (55.7%) were receiving controller medications and 47 (44.3%) were untreated. Of the subjects with use of controllers, 45 (76.2%) used inhaled steroids; alone or in combination, and 14 (23.7%) anti-leukotriene monotherapy. Of those who used inhaled steroids, 27 (60%) received low or medium dose, 16 (35.5%) low or moderate combined with anti-leukotriene and 2 (4.4%) inhaled steroid plus long action beta2 agonist. Adherence to inhaled medication was good, in 77 (72.6%) and 65.1% of children were controlled. The bivariate analysis showed that exposure to the controller medication was associated with better control (P = 0.003), lower likelihood of hospitalization for asthma crisis 0.25 (95% CI: 0.175-0.356, P = 0.000) and better asthma control (P = 0.045). Multivariate analysis did not show any association between BMI and asthma control. In the subgroup of more severe children exposed to controller medication there was an independent association between quality of life and level of disease control OR 2.22 (95% CI: 1.03–4.80, P = 0.04).

Conclusions: For this Latino population of asthmatic children was no found any association between obesity and level of control of the disease. Variables such as gender, age, level of maternal education, exposure to smoking, inhaled medication adherence were not associated either. The study also concluded that it is possible to achieve a good controller medication adherence, good level of asthma control and reduction in the number of crisis per year when the child is followed regularly in a Program of Asthma Care.

#145 - ECONOMIC EVALUATION OF TWO THERAPEUTIC STRATEGIES FOR TREATING PEDIATRIC MILD PERSISTENT ASTHMA IN A LOW- TO MIDDLE-INCOME COUNTRY

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Rationale. Despite the many benefits that have been demonstrated by the continuous administration of inhaled corticosteroids (ICS), a new strategy for control of recurrent wheezing and mild-to-moderate asthma is emerging, consisting of using intermittent or as-needed ICS treatment in conjunction with short-acting beta2 agonists (SABA) in response to symptoms. However, no previous studies have reported both the clinical consequences and the costs attributed to these two therapeutic strategies.

Methods. A Markov-type model was developed in order to estimate costs and health outcomes of a simulated cohort of patients less than 18 years of age with persistent asthma treated over a 12-month period. Effectiveness parameters were obtained from a systematic review of the literature. Cost data were obtained from official databases provided by the Colombian Ministry of Health and Social Protection. The study took the perspective of national healthcare in Colombia. The main outcome was the variable “quality-adjusted life-years” (QALY). Results. For the base-case analysis, the model showed that compared to intermittent ICS, daily therapy with ICS had lower costs ($437.02 vs. 585.03 and US$704.62 vs. 749.81 average cost per patient over 12 months for school-age children and preschoolers, respectively), and the greatest gain in QALYS (0.9629 vs. 0.9392 QALYS and 0.9238 vs. 0.9130 QALYS on average per patient over 12 months for school-age children and preschoolers, respectively), resulting in daily therapy being considered dominant. Conclusions. The present analysis shows that in Colombia, a low- to middle-income country (LMIC) country, compared to intermittent therapy, daily therapy with ICS for treating pediatric patients with recurrent wheezing and mild persistent asthma is a dominant strategy (more cost effective), because it showed a greater gain in QALYS with lower total treatment costs. This dominance of daily over intermittent therapy was more marked for school-age children than for preschoolers.

#146 - FACTORS ASSOCIATED TO REHOSPITALIZATION FOR ASTHMA IN CHILDREN LIVING IN A LOW-TO MIDDLE-INCOME COUNTRY.

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Introduction: Although hospital admissions for pediatric asthma constitute a significant problem in high-income countries, they are an even greater health problem in low-and-middle income countries (LMIC). However, previous studies that aimed to identify predictors of hospital admission for asthmatic children have mainly been conducted in high-income countries, and these findings might not be applicable to LMIC.

Methods. In a prospective cohort study, we aimed to identify predictors of hospital admission for asthma, including measures of parental knowledge about asthma and maternal depression level, in a population of children aged 1–18 years living in urban Bogota, Colombia hospitalized for acute asthma symptoms, over a 6-month period. Results: Out of the total of 101 included patients, 37 (36.6%) had at least one hospital admission for asthma during the year following admission. After controlling for the age of the patients, dog ownership in the previous 12 months, asthma severity variables in the previous 6 months, maternal allergic rhinitis, level of maternal education, and measures of parental knowledge about asthma and maternal depression level, we found that maternal smoking (IRR, 3.12; 95% confidence interval [95%CI], 1.12–8.68; P=0.029) was the only independent predictor of hospital admissions due to asthma exacerbations in the year following admission to the study. Conclusions: In a population of asthmatic Latino children admitted to hospital for an asthma exacerbation, approximately one-third of the patients had at least one hospital admission for asthma during the year following admission, and maternal smoking was the only independent predictor of these hospitalizations.

#153 - DECISION SUPPORT SYSTEM IN EARLY IDENTIFICATION OF CHRONIC DISEASES OF SMALL BRONCHIAL TUBES AT CHILDREN

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Diseases of respiratory organs dominate in structure of incidence of the children’s population. Diagnostics of the chronic diseases of small bronchial tubes (CDSBT) is a complex challenge. It concerns the bronchial asthma (BA), the bronchopulmonary dysplasia (BLD), bronchiolitis obliterans (Bzoobl.).
Research objectives: evaluate the quality of official CDSBT diagnostics in children using expert knowledge-based decision support system Materials and Methods: CDSBT diagnostics in small city of Sosnovy Bor in 2012 is analysed. The analysis of primary medical records allowed us to estimate the informativeness of disease symptoms. Decision support system for CDSBT diagnostics was developed on the basis of questionnaire about most informative symptoms. The studied pediatric area contains 850 children (49% girls, 51% boys) including 150 children with BA, 100 with BLD and 50 with BO. 

Results and discussion: Official data concerns only one form of CDSBT, bronchial asthma, which is 1.05% in the whole city and 0.8% in the analysed city area. Actual prevalence of BA is 3.72%. Officially there is no information about the prevalence of BLD and BO. At the same time the true incidence study results using the questionnaire and subsequent survey of 1,500 children show prevalence of BLD and BO respectively 0.13% and 0.37% in Russia North-West region. This indicates the low quality of diagnosis in primary CDSBT observation. 

The proposed decision support system for CDSBT diagnostics gives significantly higher percentage than the official statistics at the pediatric section: BA 10.7%, BO 0.35%, BLD 0.23%. 

Conclusions: official prevalence of CDSBT is underestimated at least in small Russian cities weak IT infrastructure. The proposed decision support system can help to adjust official statistics to the actual one, identifying rare and specific pathologies such as BLD and BO. 

#158 - BODY HEIGHT AND BODY MASS INDEX OF MALE CHILDREN WITH ASTHMA ON LONG-TERM TREATMENT WITH INHALED CORTICOSTEROIDS IN PANCEVO SERBIA 

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INTRODUCTION: Asthma is the most common chronic disease in childhood with a tendency to increase morbidity and inhaled corticosteroids (ICS) are the most effective anti-inflammatory therapy in patients with asthma and they are recommended in all protocols. 

OBJECTIVE: Considering the controversial data of the impact of inhaled corticosteroids (ICS) on growth and body weight in children with asthma, the goal of this work is to determine the growth and nutritional status of male children with asthma on long-term therapy of ICS. 

METHODOLOGY: The study included 150 male children aged 7 to 18, with partly controlled and uncontrolled asthma, which are in one year received ICS from 6 to 10 months. The control group consisted of 122 healthy males of the same age. Children are grouped by age into three groups: 7–10, 11–14 and 15–18 years. Growth and body mass index (BMI) of these children we followed four years. For reference values we took the standard deviation (SD) for these ages by WHO in 2007. Children with body height and BMI SD -3 we considered low and malnourished at -2 SD lower and less nourished, the +2 SD higher and overweight, SD +3 and higher is obese, and the SD of -1 to +1 normal high and normal weight. 

RESULTS: The results showed that 49.3% of children with asthma with ICS Th, and 49.2% of healthy children had height within the SD1. Statistically significant slowing of growth was observed at age 7, 8, 13 and 15 year in children where the ICS is a Th P < 0.05, t-test confirmed. Normal weight children with asthma with ICS Th was 57.3%, a healthy 65.6%. Overweight children with asthma were: 18.7%, 16.4% healthy, obese children with asthma, 10.7%, healthy 9.8%, with no statistical significance. Malnourished children were in a small percentage, 2% with asthma, a healthy 4.1% without statistical significance. Poorly nourished children with asthma was 11.3%, a healthy 4.1%, and this difference was statistically significant, P < 0.05, confirmed χ² test. Four-year analysis of height and BMI showed that children in both groups, the majority of normal stature and normal body weight. This study did not determine the effect of ICS Th on the growth of children with asthma, because the 18th year of the difference in height was 0.3 cm in favor of healthy children and of no significance. Transient slowing of growth can partly explain the delay puberty in children with asthma, but also partially affected by long-term ICS Th at a time of intense growth. Increased percentage of overweight and obese children can be explained by the increasing use of fast food and less physical activity. Poor nutritional status of children with asthma can be partially explained by the disease. 

Conclusion: Continuous use of ICS did not significantly affect the growth and nutritional status in children with asthma. We can say that the ICS for now safe drugs in the treatment of asthma in children. 

#159 - A NATIONAL SURVEY OF PREOPERATIVE TREATMENT OF ASTHMATIC CHILDREN IN ISRAEL. COMPARISON OF PEDIATRIC PULMONOLOGISTS TO ANESTHESIOLOGISTS 

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Background: No consensus guidelines exist for the respiratory treatment of asthmatic children who are referred for elective anesthesia and surgery. Our previous study demonstrated a large variability regarding preoperative management of asthmatic children among all the pediatric pulmonologists (PP) in Israel (CIPPXII-Valencia 2013). The aim of this study was to investigate the practice of pediatric anesthesiologists and to find out whether they differ from PP using a national survey. 

Methods: A mail survey of preoperative management of children with asthma was conducted. All certified pediatric pulmonologists and pediatric anesthesiologists in Israel were contacted and were asked to answer questions regarding their approach to 6 case scenarios, two multiple choice questions and 11 prestructured questions that included a variety of clinical situations of children at different ages covering a wide spectrum of chronic asthma treatments from the well to the poorly controlled preschool and school aged child. Results were tabulated and analyzed for all responders combined and for each group separately. Variation in practices between responders was evaluated using the R project version 3.02. 

Results: Forty-eight pediatric pulmonologists (PP) (response rate = 100%) and a sample of 17 pediatric anesthesiologists (PA) responded. Compared to the PP, the PA showed a much lower variability regarding the 4 clinical scenarios of school aged child. Concerning the well-controlled school-aged asthmatic child with no prophylactic treatment; 25% of the PA did not recommend any treatment (versus 2% for PP); 56% recommend short-acting beta agonists (SABA) alone (PP = 25%) and 19% recommend a combination of SABA and inhaled corticosteroids (PP = 49%). None of the PA suggested adding oral corticosteroids to the treatment regimen (PP = 13%) (P = 0.008 for all options). In addition, PA rely on pulmonary function tests significantly less and tends to down-grade treatment regimens compared to PP. 

Pediatric Pulmonology
Abstract

S63

169 - THE EFFECTS OF INHALED B2 AGONISTS AND ANTI-CHOLINERGIC THERAPY ON RESPIRATORY AND AUTONOMIC FUNCTION IN PATIENTS WITH FAMILIAL DYSAUTONOMIA

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Background: Familial dysautonomia (FD) is a rare genetic disease characterized by autonomic instability, wide variation of blood pressure and severe respiratory obstructive and restrictive disease. Many FD patients are treated empirically with inhaled bronchodilators that target receptors of the autonomic system. However, the use of these drugs in the FD population has not been studied, and it is not known whether such drugs are safe and effective.

Aim: The aim of the study is to evaluate the effects of bronchodilators (anti-cholinergic ipratropium bromide and beta-2-agonist albuterol) on FD patients and to compare the potency of these agents. The second aim is to evaluate the cardiovascular effects of these two drugs.

Methods: we conducted a randomized, double-blind, placebo-controlled, crossover study. All patients were diagnosed with FD. The study included three sessions for each patient. In each session we recorded 5 minutes of continuous ECG and blood pressure. Spirometry and Impulse oscillometry (IOS) measurements were obtained. One of the three drugs was then administered via inhalation: albuterol, ipratropium bromide or placebo (sodium chloride 0.9%), after 30 minutes cardiovascular data and pulmonary function were obtained as previously detailed.

Results: 10 patients were enrolled. Mean age was 29 ± 11.8 (16–55) years. Both Albuterol and Ipratropium were effective in improving pulmonary function. Pre and Post Albuterol inhalation showed significant improvement in FEV1 (47.2% ± 17.5% vs. 51.6% ± 16.8% respectively, P < 0.001), and with MEP25-75 (34.1% ± 21.4 vs. 37.2% ± 18, P < 0.05). Ipratropium demonstrated improvement in Pre and Post FEV1 that was statistically insignificant (47.7% ± 12.9 vs. 51.1% ± 15.3 respectively, P = 0.08). However, when compared ipratropium with placebo, the increment of FEV1 in percentage was statistically significant (8.5%/vs 0.2% respectively, P < 0.05). IOS results: Pre and Post inhalation of Albuterol demonstrated reduction in R5Hz (4.67 ± 2.5 vs. 3.64 ± 2.1 respectively, P < 0.02), R20Hz (3.51 ± 1.9 vs. 2.83 ± 1.59 respectively, P < 0.02). Ipratropium bromide showed statistically significant improvement Pre and Post inhalation with R5Hz (3.67 ± 2.2 vs. 3.06 ± 1.6 respectively, P < 0.05) and AX (6.5 ± 6.4 vs. 3.46 ± 5 respectively, P < 0.02). Increment of more than 12% in FEV1 was documented in 5/10 patients post Albuterol and in 3/10 patients post ipratropium. No cardiovascular side effects or ECG abnormalities were observed during and after inhalation of both drugs. Blood pressure recording showed the characteristic variability but no extremely high measurements that required medication therapy.

Conclusions: Although autonomic dysfunction is a cardinal feature of the disease, leading to the expectation that medication targeting the autonomic system will not have the expected effect; both drugs were effective in FD patients. No major cardiovascular side effects were observed and both drugs were proven safe for FD patients.

174 - IMPACT OF THE PEDIATRIC REGULATION ON RESEARCH IN THE FIELD OF PEDIATRIC ASTHMA

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Introduction: The Paediatric Regulation No 1901/2006 entered into force in all EU member states on 26 January 2007, with the aim to improve the development of medicinal products, to address the lack of age appropriate formulations and to provide information on efficacy, safety and dosing for the paediatric population. The Regulation requires applications for marketing authorizations to be accompanied by either a product-specific waiver or a paediatric investigation plan (PIP), to be agreed by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

Aim of the study was to collect information on ongoing/planned development of medicinal products approved by the EMA in the condition of asthma in paediatric population.

Method: A retrospective search on already published opinions and decisions on PIPs in the condition asthma using a publicly available database of the EMA has been performed.

Results: Until December 2013 eighteen decision on PIPs in the condition asthma have been published by the EMA. Subsets of the paediatric population concerned by paediatric development are mainly related (10 PIPs) to children aged from 5 years to less than 18 years, in 6 PIPs to children 6–18 years and only in 2 PIPs younger children were planned to be included in the clinical development (from 6 months of age in 1 PIP and from 1 year in another one). Mode of medicinal products administration for asthma treatment were mainly subcutaneous/ intravenous or inhalation use (8 and 7 PIPs respectively), sublingual/oral use was limited to 3 PIPs. Until time of analysis (December 2013) 3 PIPs were planned to be completed. Completion of clinical trials for ongoing developments is expected within 1 to 16 years (mean value 9 years; median value 11years).

Conclusions: This is a first analysis of the impact of the Paediatric Regulation on development of medicinal products for treatment of asthma in paediatric population. Majority of PIPs are related to children aged 5 or 6 years and older. Prefer mode of medicinal products administration is inhalation or subcutaneous/ intravenous use. Results of clinical trials will be known in approximately 10 years time.

Pediatric Pulmonology
Abstract

#177 - THE IMPACT OF WRITTEN ASTHMA ACTION PLAN COUPLED WITH A PRESCRIPTION (WAAP-P) ON ASTHMA OUTCOMES

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Background: Control of asthma is the main goal for asthma therapy. Many strategies to control asthma symptoms and reduce unassessed health care utilization exist, including (1) the provision of a written asthma action plan, (2) actively monitoring asthma symptoms and (3) patient education and regular medical review. In children, the specific, independent effect of WAAP-P, divided in three control zones identified by symptoms (optional peak flow values) and symbolised by traffic lights, in improving outcomes remains unclear. The objective of this study was to evaluate the utility of a written asthma action plan with a prescription (WAAP-P) on asthma control in a pediatric tertiary care center.

Methods: We conducted an observational analysis of asthmatic children with a WAAP-P and without WAAP-P (verbal counselling). Patients were a random sample of asthma patients aged 3–17 years with no other pulmonary diseases and followed in the Asthma Clinic of the Centre Hospitalier Universitaire de Sherbrooke. Asthma control parameters were those defined by Canadian Asthma Guidelines. We collected information about their use systemic corticosteroids, the number of hospitalizations, emergency room visits and disruption of pulmonary function tests. Outcomes were compared using Chi-square test and Fisher’s exact test (where appropriate). A 0.05 was considered to be statistically significant.

Results: There were no differences in gender and asthma severity among subjects without WAAP-P (n = 80) and with WAAP-P (n = 77). Subjects with WAAP-Ps were older (median 11, range 8–13) compared to those without WAAP-P (median 6, range 6–11, P = 0.001). In the WAAP-P group the rate of hospitalizations was 2.6% versus 6.3% for the control group (P = 0.443). With regard to the Emergency Department, visits the rate was 13% for the WAAP_P Group versus 13.8% for the control group (P = 0.883). With respect to systemic corticosteroids and pulmonary function tests, the results were not statistically significant (P = 0.597 and P = 0.576 respectively).

Conclusions: Compared to medical management alone, the use of a written asthma action plan did not significantly affect asthma control. Further studies with a sufficiently powered randomized controlled trial is needed to revaluate the utility of this universally recommended intervention.

2. Allergic Bronchopulmonary Disorders excluding Bronchial Asthma

#141 - THE RELATIONSHIP OF SERUM INTERCELLULAR ADHESION MOLECULE-1 AND INTERLEUKIN-17A IN CHILDREN WITH ACUTE MYCOPLASMA PNEUMONIAE PNEUMONIA AND WHEEZE

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Pediatric Pulmonology

Abstract: OBJECTIVE To examine serum soluble intercellular adhesion molecule (sICAM-1) and Interleukin-17A (IL-17A) in acute mycoplasma pneumoniae pneumonia (MMP) and investigate if there is any relation between these inflammatory mediators and the occurrence of wheezing. METHODS We studied 93 patients who admitted with pneumonia. These patients were divided into three groups: MMP with wheeze (n = 25) and without wheeze (n = 38), and the patients without the evidence of MP infection (n = 30). Age-matched controls (n = 20) were also studied. The serum concentrations of sICAM-1 and IL-17A were measured using ELISA kits in patient groups and controls. Total serum IgE levels were determined using immunocytometry.

RESULTS The patients with MMP had significantly higher serum sICAM-1 than those without evidence of MP infection and controls. In the presence of MMP, sICAM-1 concentrations were significantly higher in the patients with wheeze than those without wheeze (P < 0.05). Serum IL-17 levels were higher in pneumonia patients with or without MP infection than those in control group. In the presence of MMP, serum IL-17 concentrations were higher in the patients with wheeze than those without wheeze (P < 0.05). Total serum IgE(TIgE) levels were significantly higher in the MMP patients with wheeze than those without wheeze. A positive correlation was observed between serum sICAM-1 and log10 transformed TIgE(r = 0.261, P < 0.01).

CONCLUSIONS sICAM-1 may play a role in the mechanism of wheezing in children with MMP.

3. Bronchopulmonary and Pleural Infections (including Tuberculosis)

#5 - IS LOWER RESPIRATORY TRACT INFECTION WITH ADENOVIRUS MORE DETRIMENTAL THAN OTHER VIRAL INFECTION IN EARLY CHILDHOOD?

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Background: Adenovirus is suspected to be more virulent than other viral infections when causing lower respiratory tract infection (LRTI). Our aim was to describe the clinical characteristics, hospital admissions and ongoing respiratory morbidity of adenoviral LRTI in early childhood.

Methods: A retrospective review of children aged < 2 years clinically diagnosed with LRTI and evidence of adenovirus infection on nasopharyngeal aspirate who were admitted to KidzFirst Hospital between August 2007 to July 2008 & August 2009 to July 2011. Demographic, clinical, radiological data and outcomes from index admission till 31 December 2012 were recorded.

Results: Two hundred and thirteen children were admitted with a median age of 8.5 months with 92% being Maori or Pacifica. Median length of admission was 2 days (range 1–30) with 79% from areas of high deprivation. Children under 6 months were more likely to have longer admission of ≥3 days (OR 2.4, P = 0.01), require oxygen (OR 2.9, P = 0.004) and for > 24 hours (OR 3.2, p ≥24 hours or ICU) between adenovirus alone versus co-infection with other virus (P = 0.099) or S.pneumoniae carriage (P = 0.11).

In the first year following admission, 74 children (55%) were admitted and 68 (32%) presented to the emergency department with respiratory illness and 31 children (15%) were seen in respiratory clinic.
Conclusion: Admissions for adenoviral LRTI were more common in Maori and Pacifica, those from deprived areas and were more severe in young children. Literature suggests that co-infection of any viruses and/or bacteria causes more severe disease. However, our data demonstrates adenovirus alone or in combination was equally problematic with ongoing morbidity. This suggests all infants with adenoviral infection may need follow up to improve long term outcomes.

#17 - HAEMOGLOBIN OXYGEN SATURATION LEVELS AS DETERMINANT OF OUTCOME IN HOSPITALIZED CHILDREN WITH PNEUMONIA IN ILORIN, NORTH CENTRAL NIGERIA

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Background/Objectives: Pneumonia remains a major contributor to morbidity and mortality in Sub-Saharan Africa and hypoxaemia is a significant complication associated with an increased risk of death. The study aims to define the relationship between haemoglobin oxygen saturation (SpO2) levels and parameters of outcome, duration of supplemental oxygen and duration of hospitalisation amongst children with pneumonia.

Method: A descriptive cross sectional study was carried out amongst 200 children aged between 2 and 59 months with pneumonia seen at the University of Ilorin Teaching Hospital, Nigeria over one year. The diagnosis of pneumonia was based on clinical findings. Chest radiographs were taken and SpO2 level was determined using a pulse oximeter and the various recordings compared with clinical presentation and relevant outcome parameters. Data was analysed with SPSS 20.

Results: The male: female ratio was 1.5:1. Thirty-two of the patients had lobar pneumonia while the rest had bronchopneumonia. Eighty-three (41.5%) of the children had hypoxaemia and their mean SpO2 was 81.3(8.1) percent. Ninety-three complications were recorded in 73 (36.5%) children; 52 (27.5%) had one complication while 21 (10.5%) children had more than one complication. Heart failure was the single most common complication recorded. A significantly higher proportion of the subjects with pneumonia-associated complications had hypoxaemia compared to the corresponding proportion in those without hypoxaemia, P = 0.001. The proportion of subjects with complications increased with increasing severity of hypoxaemia, P = 0.001. Seventeen (8.5%) fatalities occurred. The mean (SD) SpO2 level of 78.3(10.9) percent in the fatal cases was significantly lower than the corresponding value of 91.5(7.8) percent recorded in the survivors, P = 0.001. Among the survivors, children with hypoxaemia had a longer mean (SD) duration of hospitalization of 6.9(6.4) days compared to those without hypoxaemia of 4.9(2.7) days, P = 0.001. The mean duration of hospitalization in children with lobar pneumonia was significantly longer than the corresponding value for those with bronchopneumonia, P = 0.001. Also, children with hypoxaemia spent a longer duration receiving supplemental oxygen compared to those without hypoxaemia (P = 0.001). The mean duration of oxygen therapy in children with pneumonia increased significantly as the SpO2 level decreased, P = 0.001.

Conclusion: Hypoxaemia with increasing severity significantly predicts a longer duration of hospitalization, duration on supplemental oxygen and poorer outcome in children with pneumonia. Thus, it would be essential for health facilities to have capacity for monitoring oxygen saturation as a guide to oxygen therapy and aggressive management.

Abstract S65

#18 - ELEVATED TRANSCUTANEOUS CARBOXYHEMOGLOBIN AS A PREDICTOR OF A LATE COMPLICATION OF STAPHYLOCOCCAL PNEUMONIA IN A CHILD

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Background: Carbon monoxide (CO) may be produced endogenously during inflammatory conditions. Carboxyhemoglobin can now be measured transcutaneously (SpCO%). During measurements of SpCO% in children with pulmonary problems, a significant case was a 12 year old female with Influenza B, methicillin sensitive Staphylococcus aureus pneumonia and sepsis, shock, and acute renal failure. Monitoring continued from hospitalization through follow-up.

Methods: The Rainbow-SET Rad-57 Pulse CO-Oximeter (Masimo Inc., Irvine, CA) was used to measure SpCO%. The Institutional Review Board approved exploratory measuring and waived the need for informed consent. No treatment decisions were made based on SpCO%.

Results: During 3 weeks of ICU care, SpCO% was 0%, then rose to 14 at 34 days, and declined to 0% after 2 months. Productive cough resolved, and spirometry and physical endurance improved despite rising SpCO% of 6% then 15% at 6 and 7 months after admission. At 7.5 months, productive cough, right sided chest pain, and dyspnea recurred. Chest radiograph showed a right pneumothorax and air and liquid filled cysts. Right upper lobe pneumatoceles, bronchopleural fistulae and right visceral and parietal pleura were resected. SpCO% fell to 6% and remained stable over the next year during which she experienced no acute illnesses and continued to improve in clinical status and spirometry.

Conclusions: This report describes a late effect of severe pneumonia that was preceded by a progressive rise in SpCO% despite ongoing clinical improvement. This suggests that SpCO% may be an easily attainable predictive measure of ongoing, subclinical inflammation.

Abstract S65

#51 - SENSITIVITY OF A NOVEL SKIN TEST WITH RECOMBINANT PROTEIN ESAT6-CFP10 IN NEW CASES OF TUBERCULOSIS IN CHILDREN AND ADOLESCENTS.

Author:

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Background. Tuberculin skin test (TST) is simple and relatively inexpensive. The main disadvantage of TST is the occurrence of false-positive responses due to cross-reactivity to antigens in PPD that are shared by environmental mycobacterial species as well as by BCG vaccine strains. The Russian company has developed a preparation known as Diaskintest (DST), which represents two Mycobacterium tuberculosis-specific recombinant proteins CFP10-ESAT6, which are absent in all M. bovis BCG substrains and in most of non-tuberculcos mycobacteria. The preparation is manufactured by the pharmaceutical company, according GMP conditions. It is for skin testing, 0.2 mcg/0.1 ml (in the same way as the Mantoux test).

Objective. To determine sensitivity of DST in new cases (children and adolescents) of tuberculosis (TB) in 2012 in Moscow

Methods. 511 children and adolescents were identified with TB in Moscow in 2012. They received the Mantoux test with 2 TU PPD-L and DST 0.2 mg/0.1 ml intradermally and induration responses measured. Any size induration was considered positive DST reaction, positive Mantoux reaction was >10 mm. Order of the Ministry of Health of Russia allowed to use DST in children with positive Mantoux test. All children with positive DST reactions were performed chest X-ray, including computer tomography (if necessary) - it was possible to diagnose light forms of intrathoracic lymph nodes TB.

Pediatric Pulmonology
Results. Both tests were positive in 493/511 cases (96.5%; 95%CI 94.5–
97.8%), even in both patients with HIV. Mantoux - positive and DST-
negative reactions were in 13/511 (2.5%) - in child with BCG-ostitis (the
isolated strain was identified as M.bovis BCG) and in the cases when the
processes are in the reverse stage of development, which may indicate loss
of activity (TB changes were detected in the calcification phase). Both tests
were negative in 5/511(1.0%) -in children with household sputum positive
TB contacts in neonatal period, when immune response has not been
developed yet and in patient after immunosuppressive therapy. No one had
Mantoux- negative and DST- positive reactions.
Conclusion: DST is highly sensitive in new cases of tuberculosis in children
and adolescents.

#63 - EVOLUTIONARY FEATURES OF ACUTE RESPIRATORY
INFECTIONS ASSOCIATED WITH MIXED HERPES INFECTIONS
IN CHILDREN

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Acute respiratory infection associated with persistent herpes infections, can
facilitate the diminishing of the body activity, inducing severe disturbances
of body immune response. According to OMS evaluation, the herpes
infections are the most widespread infections on the planet, the mortality
caused by these infections is on the second place (15.8%), in the group of
viral infections, after influenza (38.8%). World statistics data shows that
33% of children up to 5 years present antibodies against HVS-1, being an
indirect indicator of immune deficit. The incidence with CMV infections is
between 50-64% in children.

Purpose: The study of evolutionary, immunological features, in the patients
with severe respiratory infections associated with mixed herpes infections.

Objectives:

1. The appreciation IgG, IgM anti CMV, HVS type 1,2 in blood serum.
2. The study of cellular and humoral immunological status.

Materials and methods:

1. In the study group were included 100 children with acute respiratory
infections, severe evolution.
2. The diagnosis of herpes infection was noted by PCR and immunoenzym-
matic methods.
3. The humoral immunity was appreciated by Mancini method.
4. The cellular immunity was assessed with specific monoclon.
5. The statistical interpretation of anamnesis and epidemiological data was
used.

Results:

1. The anamnesis data have revealed the following aspects:
   92% of mothers presented recurrent skin herpes infections;
   18% presented CMV infection;
   16% of cases the children’s father was diagnosed with herpes infections;
2. In all examined children was detected high titre of antibodies to CMV;
3. For 88.8% of the children was detected high titre of antibodies to HSV
type 1,2.
4. The deficit of IgA was identified in 75.9% children, and in 27.7% was
   insufficiency of IgG.
5. 63.3% of the children examined had deficiency of citoto-toxic
   lymphocytes (CD8 decreased).
6. The activity of macrophages (B lymphocytes, CD4 decrease) was
   reduced in 22% of those who were examined.

Conclusion: The mixed, persistent herpes infections, frequently affects
cellular immunity, but in combination with other bacterial infections can
induce frequent and severe abnormalities of the humoral immunity, causing
severe evolution of respiratory infections.

Discussions: The herpes virus infection is an important public health
problem for the following reasons:
   the high frequency of congenital infections;
   the character of persistent viral infection;
   the high frequency of immune pathological states.

#76 - IMPACT OF INTRAPLEURAL FIBRINOLYTICS ON THE
OUTCOME OF EMPYEMA IN CHILDREN

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Background: Management of pleural empyema includes chest drain insertion
for free drainage of pleural fluid. Surgical intervention for loculated empyema is required if symptoms do not resolve with drainage alone. Installation of intrapleural fibrinolytics has been shown in some studies in high income countries to be beneficial in childhood empyema. Aim: To compare the outcomes of children with empyema before and after the introduction of intrapleural alteplase at Red Cross War Memorial Children’s Hospital (RCWMCH).

Methods: Clinical, aetiological and outcome data was prospectively collected in children admitted with empyema to RCWMCH between December 2006 and December 2011. Routine pre-emptive intrapleural alteplase (Tissue Plasminogen Activator), administered according to a standard protocol and indications, was introduced in September 2009. Outcomes in children treated with fibrinolytics were compared to the historical cohort who did not receive fibrinolytics. Primary outcome was need for surgery. Secondary outcomes were duration of hospital admission, complications and mortality.

Results: 142 cases of empyema were admitted during the study period with a median age of 17 months (IQR 8–43 months), 81 (57%) were males. After excluding cases where fibrinolytics were contraindicated (36) or no chest drain was inserted (7), data on 99 cases (52 with fibrinolytics; 47 without fibrinolytics) was available for comparison. Demographics, nutritional status, HIV status clinical characteristics and empyema aetiology were similar in both groups. The rate of surgery decreased from 38% (18/47) in patients not treated with alteplase to 10% (5/52) in patients treated with alteplase (RR 0.25; 95% CI 0.1–0.6). The median duration of hospital stay did not differ significantly (alteplase 9.5 days (IQR 7–16); no alteplase 12 days, (IQR 10–20); P = 0.09). Complications relating to empyema (alteplase 10%; no alteplase 13%) and treatment (alteplase 8%; no alteplase 4%) were few and similar in both groups. Overall mortality was low (6 deaths; 4.6%), with 2 deaths occurring in each group respectively.

Conclusion: Introducing intrapleural alteplase in children with empyema resulted in a 4 fold reduction in need for surgery. Intrapleural alteplase should be used in children with empyema.
#124 - THE IMPORTANCE OF EPIDEMIOLOGICAL SURVEYS IN THE DIAGNOSIS OF CHILDREN'S TUBERCULOSIS – CASE STUDY

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Introduction: Bosnia and Herzegovina is among the countries with a high incidence of tuberculosis, with th Directly Observed Therapy (DOTS) program for the treatment of tuberculosis (TB), which includes mandatory vaccinations. Aim of the study is to show importance of epidemiological surveys in the diagnosis of children tuberculosis.

Methods: We retrospectively analyzed four patients of same age who were treated with various form of TB within two years at the department of Pulmology.

Results: All four patients were vaccinated-BCG, with visible scar, denied contact with affected by tuberculosis and with satisfactory social and economic status. In mid-2010 the girl was admitted to the first sub-febrile extended period with dry cough, and with radiological confirmed hilar lymphadenopathy, sputum negative, PPD > 10 mm. After administration of antituberculosis drugs according to protocol, cured. Next year, girl with cavernous form of tuberculosis was hospitalized, bacteriological sputum positive, QuantiFERON positive, previously treated irregularly from childhood asthma with inhalatory corticosteroids. In the same year, we received another two girls who were radiological and QuantiFERON positive. During the treatment of patients, it was found that three girls were in contact with girl with cavernous TB, whose source of infection remains unknown. Girl with cavernous tuberculosis completed successfully nine month, and the other three six-month DOTS treatment protocol.

Conclusion: Carefully investigation the presence of TB contact with affected is of great importance in the diagnosis of TB in children, despite the existence of immunological tests and progress in the identification of Mycobacterium tuberculosis. Suspected TB means prompt diagnosis, therapy and prevention further spread of the disease.

#144 - RELATIVE CONTRIBUTION OF VIRUSES AND CA21+ ACTIVATED CL- CHANNEL 1 TO PNEUMOCYSTIS-ASSOCIATED INCREASED EXPRESSION OF MUC5AC IN AUTOPISED INFANT LUNGS.

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The asymptomatic primary infection by Pneumocystis is probably the most frequent infection of infancy with its consistent peak between 2 and 5 months of age. Pneumocystis goes undiagnosed in infants and is considered innocuous, in contrast with the severe Pneumocystis pneumonia of the immunocompromised host. However, the recent finding of increased expression of MUC5AC, a marker of airway mucus, associated to Pneumocystis in autopsied infant lungs has documented that Pneumocystis-associated pathology also occurs in immunocompetent humans. Viruses may also induce mucus. Therefore, to understand the mechanisms involved and investigate the relative contribution of viruses to this mucus response, we studied common respiratory viruses and CLCA1, a member of the chloride channel family associated with airway mucus secretion, in infant lungs. Fresh frozen lung specimens from legal infant autopsies conducted between 1999 and 2004 at the coroner’s office in Santiago, categorized as Pneumocystis negative or positive were selected in a 1:2 negative/positive age-matched relation blinded to autopsy diagnosis and date of death. The infants, mean age 3.19 [1.0–11.9] months, had died suddenly and unexpectedly (SUID) in the community without hospitalization.

Pneumocystis status of the samples (18 negatives and 37 positives, totaling 55 infants) was re-confirmed using nested PCR specific for human Pneumocystis and, quantified by qPCR using a specific probe against the human Pneumocystis MSG gene. MUC5AC and CLCA1 were studied by western blot using human-actin-gene-normalized determinations for intersample comparisons. Respiratory Syncytial Virus (RSV), Influenza A and B, Parainfluenza virus 1, 2, and 3, and Metapneumovirus, were studied with specific primers by RT-PCR, and Adenovirus by PCR. Viruses were identified in four of the 55 infants; RSV in 3 and adenovirus in 1. Actin-normalized densities of MUC5AC and CLCA1 were significantly increased in Pneumocystis-positive when compared to Pneumocystis-negative infants (P = 0.020 and P = 0.028 respectively), while MUC5AC and CLCA1 expression were not affected when the virus-positive samples were compared with the virus-negative samples (P = 0.405 and P = 0.199 respectively). Interestingly, increasing burden of Pneumocystis organisms (MSG copies/ng human DNA) correlated with increasing expression of CLCA1 (P = 0.007), while MUC5AC levels were unaffected by Pneumocystis burden (P = 0.075). This study confirms that Pneumocystis stimulates the airway secretory system during its primary infection of the immunocompetent infant host. Viruses were 5 times less frequent and did not affect MUC5AC or CLCA1. In addition, results suggest that MUC5AC and CLCA1 responses follow a different activation sequence and that viruses may also induce mucus.

#156 - MACROLIDE-RESISTANT MYCOPLASMA PNEUMONIAE – IS IT RELEVANT?

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Introduction: Macrolide-resistant Mycoplasma pneumoniae has been reported to be rising throughout the world and especially in Asia. How
relevant to clinical practice will this trend be in our management of diseases caused by Mycoplasma pneumonia?

Aim: A preliminary survey was done to document the prevalence of macrolide-resistance in those with positive Mycoplasma results on PCR taken from a throat swab and to correlate it with the clinical features of the patients.

Method: A random survey was taken of 28 patients who were positive on Mycoplasma PCR from 2012 to 2013 and mutations for nt2063 on the 23S rRNA gene was done. The clinical features of those who were positive for the mutation were compared to those without the mutation to identify possible differentiating features which may aid in the diagnosis of macrolide-resistant mycoplasma infection and whether this will affect outcome of the infection.

Results: 28 children with mean age of 7.2 years (Range: 1–14.6 years) were identified. 8/28 (28.6%) was positive for the mutation. The diagnosis ranged from an uncomplicated upper respiratory tract infection to a complicated pneumonia with effusion. Those with macrolide-resistant infection presented with a longer duration of fever at presentation ($P = 0.002$) and also took longer for the fever to resolve ($P = 0.000$). All the children were treated with macrolide, Clarithromycin, with complete resolution of illness.

Conclusion: The estimated prevalence rate of macrolide-resistant mycoplasma pneumonia is about 30%. Those with macrolide-resistant infection were likely to have a longer duration of fever. However all children eventually recovered despite being treated on macrolide even in the presence of the mutation for macrolide-resistance.

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**#157 - FRACTIONAL EXHALED NITRIC OXIDE DURING ACUTE VIRAL BRONCHIOLITIS AND LATER WHEEZING**

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**Rationale:** Hospitalization due to acute viral bronchiolitis (AB) in infants is a major risk factor for recurrent wheezing and asthma like symptoms. In addition to the respiratory syncytial virus (RSV) the role of other viruses and especially rhinovirus (RV) has emerged in recent years. Fractional exhaled nitric-oxide (FeNO) is a marker for eosinophilic airway inflammation and has been shown to be high in asthmatics compared to controls. We have previously shown that FeNO levels decrease during the acute stage of RSV bronchiolitis and return to relatively high levels during convalescence.

**Aim:** To evaluate determinants for recurrent wheezing after AB and to investigate FeNO levels during the acute phase and convalescence also in other viruses.

**Methods:** Children (0–2 years) admitted to the emergency department with AB were recruited. The following data was collected: family and patient’s history, disease severity (bronchiolitis score) and FeNO levels (in ppb). Nasal secretions were collected and PCR was performed for RSV, influenza A-B, para-influenza 1–3, human metapneumovirus, adenovirus, coronavirus, bocavirus and RV. Two and 6 months after the acute disease, FeNO levels were repeated and the occurrence of wheezing episodes was assessed. Recurrent wheezing was defined when two or more wheezing episodes were reported.

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**#163 - PENICILLIN VERSUS CEFUROXIME FOR TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN WHO FAILED ORAL ANTIBIOTIC THERAPY IN THE COMMUNITY**

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**Background:** Adherence to Guidelines for the management of community-acquired pneumonia (CAP) in children is poor. Recently it has been shown that treatment of non-complicated CAP with parenteral penicillin or ampicillin (according to guidelines) is as effective as cefuroxime. Still, this has not been studied in children who failed an oral antibiotic course.

**Aim:** To compare the outcome of treatment with penicillin or ampicillin to cefuroxime in hospitalized children with CAP who received antibiotic treatment prior to their hospitalization.

**Patients and methods:** A retrospective review of the clinical course and outcome of all previously healthy children from 3 months to 18 years old with non-complicated CAP who received an oral antibiotic course in the community and admitted during 2003–2008, in the pediatric departments of Hadassah Medical centers. Clinical course prior to admission, presenting signs and symptoms, laboratory findings at presentation and clinical outcome parameters including number of febrile days, number of days with IV antibiotics, length of hospital stay, change of antibiotics and clinical course 72 hours and 1 week after admission, were compared.

**Results:** Of the 337 children admitted with non-complicated CAP who received antibiotic treatment after failing an oral antibiotic course in the community, 235 were treated with IV cefuroxime, and 104 with IV penicillin or ampicillin. The two groups were similar regarding age, sex, days of fever prior to admission, type of preadmission oral antibiotic treatment and laboratory indices at admission ($P > 0.1$). The cefuroxime treated group had significant better outcomes in total number of febrile days, number of days with IV antibiotic treatment and total number of hospitalization days ($1.2 \pm 1.1$ vs. $1.7 \pm 1.6$, $3.1 \pm 1.3$ vs. $3.9 \pm 2.0$, $3.5 \pm 1.5$ vs. $4.2 \pm 2.0$, respectively, $P < 0.001$). Treatment failure was not significantly different between the two groups ($79.7\%$ vs. $14.4\%$, $P > 0.1$). The odds ratio for being still hospitalized at 72 hr and 7 days was significantly lower for the cefuroxime group ($0.5$ and $0.18$ respectively, $P < 0.05$).

**Conclusion:** In previous healthy children presenting with CAP after failing an oral antibiotic course in the community, treatment with IV cefuroxime appears to be superior to penicillin or ampicillin.
**#164 - EFFECT OF BLACK CUMIN (NIGELLA SATIVA) AS ADDITIONAL THERAPY ON CLINICAL IMPROVEMENT OF PNEUMONIA IN CHILDREN**

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Pneumonia is a major cause of morbidity and mortality in children under 5 years. It is estimated that nearly one-fifth of child deaths worldwide, mainly in Southeast Asia and Africa, are caused by pneumonia. Antibiotics and supportive treatments are standard therapies for pneumonia. Additional therapies are needed both to improve immune system and to provide additional antibacterial effect. Black cumin (nigella sativa) is widely recognized and can be offered as additional therapy, this study aimed to determine the effect of black cumin on clinical improvement of pneumonia in children.

A randomized double-blind clinical trial conducted on 19 subjects aged 6–60 months in Saiful Anwar Hospital. While they had standard antibiotics and supportive therapy, the treatment group also received 200 mg crude extract of black cumin per day during hospitalization, while the other group received placebo. We compared clinical improvement (fever and respiratory distress score) and length of stay between two groups.

There was significant difference in improvement of respiratory distress (p 0.036), but no significant difference in improvement rates of fever (p 0.164). The treatment group had 3 days shorter length of stay compared to placebo group (p 0.039). There was no adverse effect reported during the study.

We conclude that black cumin can improve the rates of improvement of pneumonia in children and is relatively safe.

**Keywords:** pneumonia; black cumin; clinical improvement

**4. Non-infectious Respiratory Disorders**

**#3 - LATE-ONSET NON-INFECTION PULMONARY COMPLICATIONS AFTER PEDIATRIC ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION**

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**Purpose:** Late-onset non-infectious pulmonary complications (LONIPCs) after allogenic hematopoietic stem cell transplantation (HSCT) are associated with substantial post-transplant morbidity. The aim of this study is to assess the incidence, characteristics, and outcomes of LONIPCs in children. Methods: We retrospectively reviewed the medical records of patients aged between 6 and 17 years who underwent allogenic HSCT consecutively at a university hospital between 2007 and 2010. Pulmonary function tests (PFT) and high-resolution computerized tomography (HRCT) of the lungs was performed when the symptoms indicated LONIPCs and could not be explained by infection. Bronchiolitis obliterans (BO) was diagnosed based on persistent radiographic changes, and bronchiolitis obliterans with organizing pneumonia (BOOP) was diagnosed when there were appropriate HRCT findings without clinical evidence of infection by bronchoalveolar lavage or any other tests. Results: Among the 103 patients who were included in the study, 17 (16.5%) developed LONIPCs, and 10 and 7 were further diagnosed with BO and BOOP, respectively. Univariate analyses revealed that the risk for developing LONIPCs was higher in female donor/male recipients, recipients receiving myeloablative conditioning, those who experienced grade 3 acute graft-versus-host disease (GVHD), and those with chronic GVHD (cGVHD) in sites besides the lungs. Multivariate analysis revealed that the only predictive factor for the development of LONIPCs was cGVHD in sites besides the lungs. In addition, early development of cGVHD in sites besides the lungs was a risk factor for the development of LONIPCs. Conclusions: This study showed the increasing incidence and prevalence of LONIPCs after allogeneic HSCT in children. Existence and the early development of cGVHD in sites besides the lungs were risk factors for developing LONIPCs.

**#44 - STUDY OF PHARYNGOMALACIA, A DISEASE POSSIBLY LEFT UNDIAGNOSED**

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**Objective:** Our objective was to identify the characteristics of the cases diagnosed as pharyngomalacia, to give a better understanding of the disease which we believe deserves more recognition.

**Methods:** We have diagnosed 56 infants with pharyngomalacia between 2003 and 2013. The gestational age was between 25 weeks and 41 weeks.
and the birth body weight was between 678 and 3934 g. All cases were diagnosed through flexible fiberoptic endoscopy to confirm collapse of the pharyngeal space. The medical records were evaluated retrospectively to identify symptoms and its onset, age at diagnosis, accompanying diseases, treatment needed, and age at resolution.

Result: The most common symptom was hypoxemic episodes 42/56 (75%), followed by inspiratory stridor 31/56 (55%), and feeding difficulties 27/56 (48%). Symptoms became evident within one month after birth in 34/56 (61%) and the average age at the time of diagnosis was 1.9 months. Airway diseases other than pharyngomalacia were present in 31/56 (55%), and laryngomalacia was most common, seen in 21/56 (38%) of cases. Eighteen cases (32%) had either chromosomal abnormalities, neuromuscular diseases, or multiple anomalies. Nasal CPAP was needed in 20/56 (36%) of cases, tube feeding in 12/56 (21%), and tracheostomy in 7/56 (13%). No cases died. Pharyngomalacia resolved in 43/56 (77%) and the average age at the time of resolution was 6.4 months.

Discussion: Our study shows that pharyngomalacia without laryngomalacia or other airway diseases can cause hypoxemic episodes, inspiratory stridor and feeding difficulties, which from what we have searched is yet to be documented in large numbers in literature. During the same time period we have diagnosed 195 patients with laryngomalacia under flexible fiberoptic endoscopy, which shows that pharyngomalacia is not a rare disease. It may be possible for cases with suspected upper airway diseases to be diagnosed as laryngomalacia or other diseases instead of pharyngomalacia because of the poor recognition of the disease.

Conclusion: Pharyngomalacia on its own can cause hypoxemic episodes, inspiratory stridor and feeding difficulties. Evaluation with a flexible fiberoptic endoscopy is essential in the diagnosis. Many cases resolve with age, but some cases need airway management and/or tube feeding. This disease maybe left undiagnosed and we believe this disease deserves more recognition.

#54 - MCIDAS MUTATIONS CAUSE CILIARY APLASIA

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Background: Primary ciliary dyskinesia (PCD) is a rare disorder, characterized by chronic and recurrent upper and lower respiratory tract symptoms and an increased incidence of situs inversus and male infertility. It is caused by an inborn dysfunction of the motile cilium. Ciliary aplasia (CA) is a subtype of PCD, in which no motile cilium are formed on the respiratory epithelium. So far, more than 25 genes have been identified that can cause PCD. However, no genetic cause has been linked to CA until now.

Methods: We used highly parallel sequencing of a partial exome captured DNA library (DNA library preparation kit TruSeq DNA Sample Prep kit v2, Illumina; Exome capturing kit SeqCap EZ Human Exome Library v3.0, Nimblegen; Sequencing kits TruSeq PE Cluster Kit v3-cBot-BS and TruSeq SBS Kit v3-HS, Illumina; Sequencing apparatus HiSeq 2000, Illumina; Bioinformatic analysis CLC Genomics Workbench, CLC Bio) to find gene mutations in patients with CA.

Results: We report on a patient with a severe phenotype of PCD due to CA (confirmed on repeated nasal biopsy, inclusive cell culture with de novo ciliogenesis). Transmission electron microscopy showed absence of the basal bodies and absence of centrioles. The latter induce differentiation of cilia on the cell surface. She suffered from frequent upper and lower respiratory tract infections, had chronic lung disease, underwent a lobectomy of the lingula for severe bronchiectasis and had fertility problems. She died at the age of 27 years due to pneumonia with respiratory insufficiency. DNA extracted from a blood sample was stored. Exome sequencing revealed a homozygous non-sense mutation (Cys147*) in MCIDAS, the well-conserved human orthologue of multicilin. This mutation has not been reported before in public variation databases. The mutation was confirmed by Sanger sequencing and heterozygous carrier status was demonstrated in both parents. Multicilin is a nuclear protein that has been shown to induce multiciliated cell formation in Xenopus skin and kidney tissue and in cell cultures of mouse airway epithelium (Stubbs et al, Nature Cell Biology 2012). Additionally, it mediates centriole assembly. Therefore, it is an excellent candidate gene for CA. Moreover, we showed that multicilin is expressed in human respiratory epithelium and upregulated during ciliogenesis in a cell culture system. The homozygous non-sense mutation that was found in our patient results in an early stop codon, before the CCDC region of the protein, which is essential for its function. Unfortunately, no tissue of the patient was available to confirm absence of multicilin in respiratory epithelium since she already died. MCIDAS mutations could not be found in several other patients with CA.

Discussion: MCIDAS is a perfect candidate gene for CA and a pathogenic mutation is responsible for CA in one patient.

Conclusion: We report on a patient with ciliary aplasia, probably caused by a homozygous non-sense mutation in MCIDAS.

#69 - STUDY OF PULMONARY FUNCTION AT SCHOOL AGE IN JAPANESE EXTREMELY LOW BIRTH WEIGHT INFANTS – STUDY OF PULMONARY FUNCTION AT 6 TO 12 YEARS OF AGE –

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The survival of extremely low birth weight infant keeps on increasing. In such an age, the presence of subclinical pulmonary function abnormality is suspected even in infants who are thought to have no pulmonary problems. We studied the pulmonary function of Japanese extremely low birth weight infants at school age to look for subclinical pulmonary function abnormalities.

Patients and Methods: Institutions were selected based on the answers of questionnaire on the pulmonary function of extremely low birth weight infants at school age. Pulmonary function was measured in 264 cases (122 male, 142 female, gestational age: 26.2 ± 2.2 weeks, birth body weight: 751 ± 143 grams, age at measurement: 8.5 ± 1.6 years), which satisfied the following 4 criteria: (1) Japanese extremely low birth weight infant, (2) age at measurement 6 to 12 years, (3) clear background, (4) pulmonary function measurement performable. The measurements were compared with normal values in Japanese children, and changes with age and effect of background on school age pulmonary function were evaluated.

Result: Compared with values of spirometry in Japanese children, only 52% had normal pulmonary function. In each age groups, age 6: 41%, age 7: 56%, age 8: 51%, age 9: 57%, age 10: 58%, age 11: 42% had normal results, respectively, and abnormal pulmonary function was common. The percentage of restrictive abnormality were at age 7: 12%, age 8: 23%, age 9: 30%, and increased with age. Factors affecting pulmonary function were palivizumab administration, which had a positive effect, and chronic lung disease and the need for home oxygen therapy, which had a negative effect.

Discussion: Abnormal pulmonary function was common in the study of pulmonary function in extremely low birth weight infants at school age. The
measurement of pulmonary function at school age makes it possible to screen for subclinical pulmonary abnormalities. Improvement with age is not always noted, therefore long term follow up of pulmonary function is thought to be essential.

#91 - FOREIGN BODY ASPIRATION IN CHILDREN: EXPERIENCE FROM 2624 PATIENTS

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Objectives: The objective of this study is to analyze the epidemiological, clinical, radiological and endoscopic characteristics of pediatric foreign body aspiration in Algeria.

Methods: In this retrospective study, the results of 2624 children younger than 18 years admitted in our department for respiratory foreign body removal between 1989 and 2012, were presented. Most of them had an ambulatory rigid bronchoscopy.

Results: The children (62.34% males and 37.65% females) were aged 4 months to 18 years with 66% between 1 and 3 years. Choking was related in 65% of cases. The delay between aspiration and removal was 2–8 days in 65.8% and within 24 h in 9.2%. In the most cases, the children arrived with cough, laryngeal or bronchial signs and unilateral reduction of vesicular murmurs. The examination was normal in 13%. The most common radiologic finding was pulmonary air trapping (40.7%). The aspirated bodies were organic in 66.7%, dominated by peanuts, while sunflower seeds, beans and ears of wheat were the most dangerous. In the other cases, they were metallic or plastic as pen caps and recently scarf pins. The endoscopic removal by rigid bronchoscopy was successful and complete in 97%. Cases with extraction failure (3%) limited to certain FBs, all of them inorganic were assigned to surgery. The complications related to the endoscopic procedure were 0.29% with a mortality of 0.26%.

Conclusion: Foreign body aspiration is a real public health problem in Algeria. The best way to manage it is an early diagnosis and a rigid bronchoscopy removal under general anesthesia used by fully trained staff. The prevention of this domestic accident should consider the population lifestyle and cultural habits to be more effective.

#130 - NATURAL HISTORY OF SNORING IN HONG KONG ADOLESCENTS

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Objective: To determine the natural history of snoring in children and the risk factors for persistence of habitual snoring.

Methods: This study was an extension of our previous cross-sectional telephone survey on the prevalence of sleep problem amongst Hong Kong children in 2002. A follow-up telephone questionnaire survey was conducted 4–6 years after the initial survey. Adolescents who were snoring at least 6 nights a week were defined as habitual snorers. Persistent habitual snorers were the one who were defined as habitual snorers in both surveys. Incident habitual snorers were those who were non-habitual snorers in the 2002 survey but were reported to have habitual snoring in the current survey.

Results: Two thousand and five out of 3,047 eligible subjects were successfully interviewed by phone, giving a response rate of 65.8%. The prevalence of habitual snorers was 12.7% in the current survey. 40.6% of habitual snoring children had persistent habitual snoring. Ninety-one (4.5%) adolescents were persistent habitual snorers. Allergic rhinitis, male gender and higher BMI were identified as significant risk factors of persistent habitual snoring. One hundred and sixty three (8.1%) children were identified as incident habitual snorers. The risk factors of incident habitual snorers included male gender, asthma, higher BMI at follow-up and younger age at the first survey. In the current study, the mean sleep duration was 7.6 hours ± 1.1 hours. The sleep duration from 13- to 18-years-old was less than the lower limit of the international recommendation for sleep duration. Conclusions: 40.6% of habitual snoring children had persistent habitual snoring over 4–6 years period and 8.1% of the initial non-habitual snorers became habitual snorers. Male gender and higher BMI are significant risk factors for both persistent and incident habitual snoring.

#133 - AN INTERNATIONAL PATIENT-REGISTRY FOR PRIMARY CILIARY DYSKINESIA

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Introduction: Primary Ciliary Dyskinesia (PCD) is a rare, genetically heterogeneous disorder that affects approximately 1 in 20,000 individuals. Dysfunction of respiratory cilia results in defective mucociliary clearance and chronic upper and lower airways disease. Recurrent lower respiratory tract infections lead to bronchiectasis and ultimately respiratory failure. The clinical management is currently based on improving airway clearance and controlling respiratory infections through the administration of antibiotics. As there are no evidence-based treatment regimens at all, regimens are largely derived from treatments for patients with airway disorders such as cystic fibrosis. The clinical management of PCD is also confined by the lack of a clearly defined natural course for this disease and features that relate to adverse outcomes. In a rare disease such as PCD, registries are valuable tools that provide information on daily practice not accessible to clinical trials. Within an international consortium, BESTCILIA, we have set up a PCD registry in order to gain insight into the incidence, clinical presentation, treatments and course of the disease.

Methods and results: Items collected in the registry have been generated by an adapted Delphi process. The system is fully compliant to international standards.
guidelines for Good Clinical Practice. Intellectual property rights are fully respected. A web-browser-based data entry system is used involving plausibility checks.

The registry has two levels: Level A comprises a minimal dataset with key items entered for all patients. Level B covers an extended data set of diagnostic, clinical, microbiological and radiological parameters. Furthermore, quality of life is assessed very sensitively by incorporating the newly developed PCD specific quality of life questionnaire PCD-QoL.

Conclusion: The PCD registry will allow (1) collect epidemiological data (e.g. mortality), (2) describe the course of the disease, (3) describe the effects of different treatment regimens, (4) identify genotypic and/or phenotypic features with prognostic relevance and (5) serve as a platform for recruitment of well-defined patient cohorts for randomized clinical trials, what (6) will finally lead to the generation of evidence-based management guidelines.

#148 - PULMONARY HEMOSIDEROSIS – THE HETEROGENEITY OF A GROUP OF PEDIATRIC PATIENTS


Introduction: Pulmonary hemosiderosis (PH) is a rare disease, often idiopathic in pediatric age, even after extensive investigation. We reviewed the PH cases followed at the pediatric department of Centro Hospitalar do Porto (Portugal), in the last 18 years and its evolution with the purpose of better knowledge of this rare disease.

Results: Six children were diagnosed with PH between 1995 and 2013, with age at diagnosis ranging between 2 and 7 years (median age of 3 years) and median time of follow-up 11 years. The initial suspected diagnosis were gastrointestinal hemorrhage, recurrent respiratory infections, bacterial pneumonia, pulmonary tuberculosis and chemical pneumonitis, all associated with severe anemia. The diagnosis of PH was achieved 4 to 36 months after the first symptoms. The initial etiological investigation was inconclusive in all cases, with subsequent detection of anti-neutrophil cytoplasm antibody positive (1 patient), Hashimoto’s thyroiditis (1 patient) and diabetes mellitus (1 patient). All patients received systemic corticosteroids and hydroxychloroquine, with good clinical response in 4 children, 2 of who remained asymptomatic after suspension of therapies. In the remaining 2 cases, one with diabetes mellitus and other with ANCA vasculitiss diagnosed after 14 years of disease, the absence of response to hydroxychloroquine led to its replacement with azathioprine. The latter patient maintained frequent exacerbations progressing to respiratory failure, leading to a change in therapy for rituximab and cyclophosphamide, with good clinical response.

Comments: Pulmonary hemosiderosis initial symptoms are nonspecific and high suspicion is essential for timely diagnosis. This small group of patients showed great heterogeneity on the clinical course, varying from full remission with hydroxychloroquine to alveolar hemorrhage persistence with progression to cardiorespiratory failure and requiring other therapeutic options. Due to the low prevalence of PH, intermittent nature of the disease and variability on the degree of severity, the safety and efficacy of therapeutic immunosuppressive are difficult to assess. Although most PH cases are idiopathic, secondary etiology should be suspected in patients without initial therapeutic response or with association with autoimmune diseases. In these cases, clinical and laboratory surveillance should be maintained in the active search of the best therapeutic approach.

Pediatric Pulmonology

#149 - A RARE CASE OF REFRACTORY ENDOBRONCHIAL CAPILLARY HEMANGIOMA IN A YOUNG INFANT


Introduction: Although rare in pediatric patients, endobronchial tumors can present various pathologic patterns associated with partial or total airway obstruction. Usually benign in infants, diagnosis and management of these tumors remain challenging. Purpose: We report a case of capillary hemangiomia of the left main bronchus, refractory to conventional medical therapy, in a young infant presenting with persistent hyperlucency of the left hemithorax.

Methods/Results: A 6 month-old girl was referred to our institution for persistent hyperlucency of the left lung after recovery from left lower lobe pneumonia. It is the second child of a healthy non consanguineous Caucasian couple, born after a full term pregnancy. She presented two episodes of left lower lobe pneumonia with upper lobe hyperinflation at the ages of 3 and 5 months. On admission, clinical examination revealed mild respiratory distress including tachypnea and hypoventilation of the left hemithorax. The differential diagnosis included congenital lobar emphysema, endobronchial mass, extrinsic bronchial compression, Swyer-James syndrome and foreign body aspiration. Bronchoscopy showed complete obstruction of the left main bronchial lumen by a pulseless, vascularized and depregressive mass causing air trapping of the left lung. Computed tomography demonstrated an endobronchial well delimited mass of 5 mm diameter in the left main bronchus with homogenous and positive contrast enhancement. Magnetic resonance imaging showed no gadolinium contrast enhancement and transesophageal pulsed doppler little or no measurable blood flow. Cardiac tumor markers were not detected either in serum or in urine. The macroscopic aspect and the young age of the patient being highly suggestive of a benign hemangiomia, treatment with corticoids, propranolol and acebutolol were consecutively attempted. As no reduction of the mass volume was observed by successive bronchoscopy, surgical resection and bronchial termino-terminal anastomosis were successfully conducted in order to remove the mechanical obstacle. Anatomopathology and immunohistochemistry confirmed the diagnosis of capillary hemangiomia.

Conclusions: Endobronchial tumors, although rare in infants, should be considered in the differential diagnosis of unilateral hyperlucent lung. In young infants, diagnostic assessment and management remain challenging as airway size and risk of bleeding make endobronchial biopsy and therapy difficult to perform. Age at presentation, localization and anathomopathology should guide therapeutic approach of endobronchial tumors. In this case, the lack of
response of the hemangioma to conventional medical treatment led us to perform a surgical resection.

5. Fetal and Neonatal Respiratory Disorders

#26 - RESPIRATORY DISORDERS AND CONSEQUENT MORBIDITY OF THE “LATE PRETERM” INFANTS (GESTATIONAL AGE: 34-36 + 67 WEEKS)

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Introduction: Late preterm infants (LPIs) are defined as newborns with a gestational age (GA) of 340/7-366/7 weeks. This neonatal population presents a delayed transition from intrauterine to extraterrestrial life and a functional immaturity of the lung structure, associated to high respiratory morbidity; therefore LPIs are prompt to developing respiratory distress syndrome (RDS), transient tachypnea of newborns (TTS) and pulmonary hypertension.

Purpose: To determine the incidence of respiratory disorders of LPIs in a tertiary care perinatal center and their impact on LPI’s morbidity. Patients and Methods: We performed a retrospective analysis of the LPIs delivered in our perinatal center and required admission to the neonatal intensive care unit (NICU) from April 2004 to December 2011. Infants with severe congenital anomalies were excluded. We recorded the incidence of respiratory complications and patients’ evolution.

Results: Out of 10650 deliveries, 1280 newborns (12%) were LPIs; two hundred thirty nine (239) of them were multiple [231 (18%) twins and 8 (0.6%) triplets] while 1041 (81.4%) were singletons. We studied a total of 1527 infants (770 males), 326 (21.3%) of whom were directly admitted to the NICU. Subjects were divided into three groups according to GA (1st: 34–346/7 2nd: 35–356/7 3rd: 36–366/7 weeks). The rate of RDS was markedly declined from 17% at the 1st group to 0.8% at the 3rd group. Infants of the 2nd group were more likely to develop transient tachypnea (10%) than those of the 1st group (4.7%). TPH was recorded in 3 of 340 neonates (0.9%) of the 1st group, 1 of 457 (0.2%) of the 2nd and 2 of 730 (0.3%) of the 3rd group.

Conclusions: LPIs who develop respiratory disorders are susceptible to respiratory failure and therefore they present higher neonatal morbidity and mortality.

#123 - A CASE OF CONGENITAL LOBAR EMPHYSEMA IN THE MIDDLE LOBE

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Introduction: Congenital lobar emphysema (CLE) is uncommon event in neonates. It is characterized by overinflation of pulmonary lobe, and may present as a diagnostic and therapeutic dilemma. This affection can cause a severe respiratory distress with high level of mortality or result in serious morbidity and disability.

Case Report: A 3-week-old male baby weighing 3900g was referred to our neonatal intensive care unit for asphyxia with respiratory distress. After the failure of its management in a Peripheral Hospital. He was delivered as a full term with delayed cry and respiratory distress without any history of infection. Physical examination revealed a tachycpneic at a rate of 55–60/min with subcostal retraction, the cyanosis was generalized (oxygen saturation SpO2 was 66% in air). On examination of the respiratory system, decrease breath sound on the right hemithorax was noted. The cardiac auscultation was normal. The chest X-ray showed hyperinflation on the right side, and right basithoracic opacity and right mediastinal shift. Computed tomography (CT) scan of the thorax supported the X-ray. There was hyperinflation on the right middle lobe with tracheal and mediastinal shift to the left side. The blood parameters were normal. On the echocardiography, there was no evidence of congenital cardiac anomalies or pleural effusion.

After hemodynamic and respiratory stabilization, surgical intervention was performed by right thoracotomy. The right middle lobe looked emphysematous at time resection. Histopathological examination of the excised right middle showed alveolar distension without fibrosis. Post-operative chest X-ray showed expansion of the right upper and lower lobes, with no emphysema or mediastinal shift.

The child was discharged 10 days post-surgical intervention. He was seen as an outpatient at 1, 2 and 6 months of age. He had normal O2 saturations in room air and his respiratory rate was 30–35/min. He was feeding well and gaining weight.

Conclusion: In summary, the diagnosis of CLE may present a diagnostic challenge and a high index of suspicion in neonates with progressive respiratory distress is important if the diagnosis is to be made promptly. The outcome of surgery is good in most cases.

6. Cystic Fibrosis

#58 - BRINGING BAD NEWS: THE DIAGNOSIS OF CYSTIC FIBROSIS IN CHILDHOOD

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Background: The day parents are told their child has Cystic Fibrosis (CF) is imprinted in their memory. The diagnosis changes family life. Parents often show strong emotions (e.g. shock, anxiety) and they need to restructure their lives taking into account CF (Jedlicka-Köhler, Götz & Eichler, 1996; Monestrol et al., 2011).

Aims: The aim of this study is (1) to explore how parents recall hearing the CF diagnosed and the information they received and (2) to explore their current ways of coping.

Methods: Parents (n = 38) of 20 children with CF (diagnosed during the past 5 years) were interviewed using a semi-structured interview about the period around the diagnosis. Coping was assessed using the Utrecht Coping List (Schreurs et al, 1988).

Results: No significant differences between fathers and mothers were found. All parents were informed by the CF specialist, although 20 parents first heard the term ‘CF’ from their local pediatrician or GP. All parents recalled specific details about the diagnosis: the information they were given as well as their innermost thoughts and emotional reactions. Parents were satisfied with the information they received and the way it was provided. Twenty-one parents remembered the doctor showed personal emotions and two thought this unpleasant. The remaining parents were comfortable with the doctor not showing personal emotions. Less than half of the parents (44.3%) mostly used an active problem solving coping style. Present-day passive coping styles were found associated with ratings of negative feelings and thoughts at the time of diagnosis.
Conclusions: All parents were pleased with the detailed disease information they received at the time of diagnosis and many shed a tear. All recalled details, both practical and emotional. When counseling parents it is important to recall these emotions and thoughts, because they seem related to current coping styles. The diagnosis is the starting point of a long-term relationship between patient, parents and CF team. ‘Doing things well from the start’ is crucial and may prevent long-term problems in coping with CF.

Acknowledgements: Special thanks to the parents participating in this study.

#118 - PERSPECTIVES AND EXPERIENCES OF CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS: A SYSTEMATIC REVIEW AND THEMATIC SYNTHESIS OF QUALITATIVE STUDIES

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Introduction: Cystic fibrosis (CF) is a common life-shortening genetic disease with an estimated incidence of 1 in 2500 newborns. Most patients with CF experience chronic pulmonary disease and pancreatic insufficiency, and must adhere to time-consuming and onerous daily treatments and physiotherapy. Limited daily functioning, poor adherence to treatment, low self-esteem, short stature and impaired psychosocial outcomes have been reported. This study aimed to describe the experiences and perspectives of children and adolescents with CF in order to direct care towards areas of importance for patients.

Methods: MEDLINE, Embase, PsycINFO, and CINAHL were searched from inception to April 2013. We synthesized data from qualitative studies, including unstructured interviews and focus groups, that explored the experiences and perspectives of children and adolescents (<21 years of age) diagnosed with CF. For each study, all participant quotations and text under the “results/findings” or “conclusion/discussion” section were extracted and entered verbatim into HyperRESEARCH, a program used for storing, coding and searching qualitative data. We used thematic synthesis to analyze the patterns and relationships within and across themes.

Results: Forty-three articles involving 729 participants aged from 4 to 21 years were included. We identified six main themes with subthemes in parentheses: gaining resilience (accelerated maturity and taking responsibility, acceptance of prognosis, regaining control, redefining normality, social support), lifestyle restriction (limited independence, social responsibility, acceptance of prognosis, regaining control, redefining normality, social support), disease severity (consequential timeliness, hope and optimism), and emotional disempowerment in health management, unrelenting and exhausting therapy, isolation, falling behind, physical incapacity), resentment of chronic treatment (disempowerment in health management, unrelenting and exhausting therapy, isolation, falling behind, physical incapacity), social support (limited independence, social responsibility, acceptance of prognosis, regaining control, redefining normality, social support), lifestyle restriction (limited independence, social responsibility, acceptance of prognosis, regaining control, redefining normality, social support).

7. Respiratory Manifestations of Extra-pulmonary Diseases (including AIDS)

#77 - GRANULOMATOUS AND LYMPHOCYTIC INTERSTITIAL LUNG DISEASE IN A PATIENT WITH COMMON VARIABLE IMMUNODEFICIENCY

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Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by hypogammaglobulinemia and T-lymphocytes dysfunction. The most frequent clinical presentation remains recurrent bacterial infections. Approximately 10–15% of patients with CVID develop granulomatous/lymphocytic interstitial lung disease, which is frequently accompanied by splenomegaly, adenopathy, autoimmune cytopenias and gastrointestinal and hepatic disease. There are no standard guidelines for the treatment of patients with CVID and granulomatous/lymphocytic interstitial lung disease.

A three year old girl was admitted to our hospital with a clinical history of recurrent upper respiratory infections, and splenomegaly. She had a marked decrease of all serum immunoglobulin isotypes and low specific antibody responses. The diagnosis of CVID was based on clinical and laboratory findings and IVIG therapy was started. At the age of 6 years, she presented with cough. Thorax CT revealed mediastinal adenopathy, paranchymal multiple nodular opacities, ground glass opacities and bronchial wall thickening. Lung biopsy revealed non-necrotizing granuloma and lymphocytic interstitial pneumonia. A diagnosis of granulomatous/lymphocytic interstitial lung disease was made and 2 mg/kg/day prednisolone were given. Although the patient’s symptoms improved and there was reduction in the extent of nodularity and ground glass opacification on the HRCT scan, relapses observed with the dose reduction of oral prednisolone during 6 years follow up. At the age of 12 years, in addition to pulmonary findings increase at hepatosplenomegaly and trombostopenia observed. Rituximab therapy was started and azatiopurin was added. Platelet count rose to normal levels and pulmonary radiographic abnormalities decreased.

As a result physicians must be aware of non-infectious complications such as granulomatous/lymphocytic interstitial lung disease in patients with CVID and there is need to determine the best modality of therapy to treat CVID associated granulomatous/lymphocytic interstitial lung disease.

8. Neuromuscular and Chest Wall Diseases (including SIDS)

#125 - MOTOR AND RESPIRATORY SEVERITY OF DUCHARNE MUSCULAR DYSTROPHY

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Purpose: Characterize motor and respiratory severity of Duchenne muscular dystrophy (DMD) patients. Methods: A cross-sectional study was performed in the neuromuscular and neurology departments of a university hospital of tertiary care, where 34 DMD boys were followed-up. Nineteen boys were evaluated for motor [Motor Function Measure (MFM) and 6-minute walk test(6MWT)] and respiratory assessment [respiratory muscle strength, peak cough flow, spirometry and volumetric capnography(VCap)]. The variables were compared between the same group of subjects with DMD (ambulatory and non-ambulatory) and also compared with healthy control subjects (6MWT, spirometry and VCap measures).

Results: Statistical difference (P < 0.05) was found in MFM (between ambulatory and non-ambulatory DMD); 6MWT [lower walked distance, higher rest respiratory rate (RR), rest heart rate (HR) and HR after 9 minutes for DMD compared to controls]; spirometry [lower vital forced capacity (VFC), forced expired volume in one second, forced expiratory flow between 25% and 75%/VFC, maximum forced expiratory flow and higher Tiffeneau index for DMD compared to controls]; and VCap for DMD younger than 11 years [alveolar ventilation per minute, ventilation per minute, tidal alveolar volume, tidal volume, airway dead space, carbon dioxide production, expiratory volume (Ve) and slope of phase III normalized by Ve(Slp3/Ve) compared to controls] and for DMD older than 11 years (lower Slp3/Ve and higher HR compared to controls). Conclusions: Patients with DMD have motor and respiratory deterioration that can be evaluated by the tools used in this study. Longitudinal multicentre studies and follow-up can contribute to a better understanding of the progression of motor and respiratory dysfunction and better management of patients with DMD.

9. Epidemiology, Environmental Risks, Prevention, Socio-economic Cost, Public Health Resources

#23 - SEROTYPE DISTRIBUTION AND DRUG RESISTANCE OF STREPTOCOCCUS PNEUMONIAE ISOLATED FROM CHILDREN WITH COMMUNITY ACQUIRED PNEUMONIA IN JAPAN

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Purpose: To reveal the impact of the heptavalent pneumococcal vaccine (PCV7) and newly approved oral antibiotic (tCONFtloxacin) for children on serotype and drug resistance of Streptococcus Pneumoniae (Sp) isolated from blood and sputum samples of children admitted in hospitals with community acquired pneumonia (CAP) in Japan. Methods: PCV7 and oral tCONFtloxacin (TFLX) were newly approved for children in Japan in February 2010 and August 2009, respectively. The study periods were between April 2008 to March 2009 and April 2012 to March 2013. Children living in Chiba city, Japan, aged under 16 years admitted with CAP in 5 major tertiary hospitals were enrolled in this study, and patient backgrounds were collected. Patients with positive blood culture or cultured sputum (smears Geckler’s group 4 or 5) dominant for microorganisms such as Sp, Haemophilus influenzae (Hi), Moraxella catarralis (Mc) were diagnosed with bacterial pneumonia. Antimicrobial susceptibility of Sp was tested according to CLSI guideline M100-S23, serotypes were determined with Quellung reaction.

For Statistical analysis, the Fisher’s exact test was used to compare between-group differences in patient characteristics and the proportion of PCV7 serotypes in patients with a diagnosis of Sp pneumonia. A logistic regression model adjusted by potential confounders was used to estimate the odds ratio for the PCV7 vaccine effect in relation to the risk of Sp pneumonia.

Results: In this study, 486 and 495 patients under 16 years old were enrolled in 2008 and 2012, respectively. There were significant reductions of the proportion of Sp pneumonia patients (16.4% in 2008 versus 8.3% in 2012, P < 0.001) and the PCV7 covered serotypes (62.5% in 2008 versus 18.4% in 2012).
2012, $P < 0.001$). The number of patients diagnosed with Hi or Mc pneumonia remained unchanged during the two study periods. Patient characteristics were similar between the two periods except for the use of macrolide (19.7% in 2008 versus 29.9% in 2012, $P < 0.001$) and quinolone (0.0% in 2008 versus 9.3% in 2012, $P < 0.001$) as oral antibiotics in outpatient clinics prior to admission. Considering the above confounders, the odds ratio for Sp pneumonia incidence, comparing 2012 with 2008, was 0.59 (95% CI 0.38–0.91, $P = 0.018$), which suggests that PCV7 had the most impact of the reduction of Sp pneumonia in Japan. Although MIC 50 ($\mu$g/ml) of penicillin declined from 0.5 to 0.25, the MIC 50 ($\mu$g/ml) of TFLX increased from $\leq 0.12$ to 0.25 from 2008 to 2012, respectively.

Conclusions: The prevalence of Sp pneumonia in Chiba city showed a significant reduction post 2 years of PCV7 vaccination. Decline in PCV7 serotypes lead to improvement in penicillin sensitivity. Japan is the only country in the world with oral quinolone approved for children. Considering the worsening of TFLX resistance, we should be careful for the use of broad-spectrum antimicrobial agents for children in outpatient clinics.

#28 - PEDIATRIC SLEEP MEDICINE IN ROMANIA - A FORAY INTO THE FIELD OF KNOWLEDGE REGARDING THIS SPECIALTY

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Introduction: During the last thirty years there has been an important ascending evolution of the pediatric sleep medicine, acknowledging the active role of sleep in the physical and mental development of children. Even in those countries where these issues have now been approached for a long time, there are still many questions regarding the underlying aspects related to diagnostic and treatment. This field is still new in Romania, fact which resulted also from this study which applied a questionnaire of evaluation of current knowledge on the sleep matter in children, especially Obstructive Sleep Apnea Syndrome (OSAS). In the last six months of activity only 35% of the respondents have met at least one case of OSAS in children and 53% of the respondents admitted to have little knowledge concerning this disease. The respondents were family doctors as well as doctors of various pediatric specialties and the questionnaire allowed the identification of poor areas for various working groups.

Content: Within this survey performed on 100 validated questionnaires, applied on physicians of different specialties in our country, we have observed physicians’ poor level of information with respect to the obstructive sleep apnea syndrome in children. In the majority of cases the specialists questioned would not assume the role of identifying OSAS patients, 38% of them considering that the family plays the most important role in identifying children and adolescents with OSAS, 44% considered that pediatricians have this responsibility and 12% thought that family physicians should have this responsibility. The physicians mentioned multiple difficulties, most of them described the lack of information, the limited access to polysomnography and high costs. Conclusions: Although, on many occasions, pediatricians recognize sleep problems, it is only rarely that they feel competent in solving them. As a result, parents gather information from magazines, from the Internet, friends or relatives. But this “self-therapeutic” method rarely shows any results. Therefore, it is essential that there are sleep medicine specialists in every country. The development of sleep medicine in Romania, the increase in the level of awareness and building up multidisciplinary teams for the management of these issues represent an important and necessary contribution to our health system. Keywords: pediatric sleep medicine, obstructive sleep apnea syndrome, children, adolescents, survey Romania, physicians

Pediatric Pulmonology

#52 - OUTCOME OF NEONATE WITH TRANSIENT TACHYPNEA (TTN) IN OUR AREA SINCE 2013.

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In 1966, Avery et al, described the clinical features of eight babies with a condition that they attributed to delayed absorption of fetal lung liquid. As we know transient tachypnea in neonatal period (TTN), is a temporary phenomena that its signs and symptoms usually resolve by 3 to 4 days after birth and must not include more hospital stay duration because its costs or morbidity.

In present retrospective case control study, we try to show the span of hospital stay duration of such neonate in our hospital since Oct. 2012 to Oct. 2013. It seems such surveys help us and managers to definite and regulate an acceptable range of hospital stay days for reduce the morbidity and patient costs.

Methods: Fifty six cases were recorded with diagnosis of TTN since past year in our teaching hospital. At first review, we eradicated sixteen patients from study because their concomitant disorders like congenital heart diseases or sepsis. Then we recorded the data include: name-gender- date of birth and hospitalization- gestational age-first minute Apgar-place of birth, the type of delivery-prenatal history and the duration of hospitalization exactly.

Results: From forty neonates, there were 29 (66%) male and 11 (34%) female. Fifty percent of neonates were born by cesarean section and fifteen (37.5%) mothers had positive past history before or among their pregnancy. The common sign and symptom was tachypnea then nasal flaring, grunting, sub or inter costal retractions were occurred respectively, cyanosis was seen in extreme cases (0.5%). Gestational ages were recorded from 32 to 40 weeks and the first signs or symptoms were seen from one to four hours after birth. The duration of hospital stay was from 2 to 16 days and only 14 mothers were urban. Ninety percent of the neonates had at least two nights stay experience in NICU.

Conclusions: Despite currency and availability of health insurance for urban and rural in our area, stay in neonatal intensive care unit includes more cost for patient’s family. According to excellent outcome of such neonates and in comparison with other surveys, it seem we must reduce the duration of hospital stay especially transfer to NICU, not only for its costs but also for the morbidities.

Keywords: Transient Tachypnea Neonates, Hospital Stay Duration, Patient Costs

#107 - INDOOR AIR POLLUTION AND TOBACCO SMOKE EXPOSURE IN AN AFRICAN BIRTH COHORT STUDY.

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Tobacco smoke and indoor air pollution is a risk factor for childhood disease. The contribution of indoor air pollution or tobacco smoke exposure to the incidence, severity and outcome of childhood respiratory illness has not been well studied in African children.
Aim: To describe indoor air pollution and tobacco smoke exposure in a birth cohort in South Africa.

Methods: Indoor air pollution and tobacco smoke exposure were longitudinally measured in children enrolled in the Drakenstein child lung health study, a birth cohort study in a peri-urban area outside Cape Town, South Africa. Indoor air pollution and tobacco smoke exposure were measured at a home-visit conducted antenatally to measure particulate matter 10 μg/m³ (PM10), volatile organic compounds (VOC), nitrogen dioxide, sulphur dioxide and carbon monoxide levels. Urine cotinine in the mother and infant were also measured. Active surveillance for intercurrent lower respiratory tract illness in children was done.

Results: There are high levels of maternal smoking and very high levels of tobacco smoke exposure in infants, Table 1. Most households (69%) without a separate kitchen had benzene (volatile organic compound) levels above ambient standards. Of households with paraffin stoves, 96% had benzene levels above ambient standards, and homes with high density of people per cubic meter had 69% of benzene levels above ambient standard. Table 2.

Conclusion: There are high rates of exposure to tobacco smoke and volatile organic compounds prenatally that may impact on child lung health.

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### #120 - LOW 25-HYDROXYVITAMIN D3 SERUM LEVELS ARE ASSOCIATED WITH PNEUMONIA IN CHILDREN: A CASE-CONTROL STUDY

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**Background:** Pneumonia kills an estimated 1.2 million of children under age five every year. The role of vitamin D in respiratory infections including pneumonia is unclear; therefore, we aimed to determine if low serum 25-hydroxyvitamin D3 is associated with an increased risk of pneumonia in children.

**Methods:** We performed a case-control study of children ages 3–60 months from the Guatemala City metropolitan area hospitalized with community-acquired pneumonia between September and December 2012. Controls were selected from the well-baby/care immunization clinic serving the population from which cases emerged. We analyzed serum 25-hydroxyvitamin D3 levels and conducted parental interviews to assess subject age, height, weight, sex, race, feeding type, vitamin D supplementation, frequency of sun exposure, and maternal education. Complete information was available for 70 (83%) of 84 eligible cases and 68 (60%) of 113 eligible controls.

**Results:** The median (IQR) serum 25-hydroxyvitamin D3 concentration for cases was 23.2 ng/mL (14.4–29.9) compared to 27.5 ng/mL (21.4–32.3) in controls ($P = 0.006$). On multiple regression analysis using an a priori cut-point for vitamin D of <20 ng/mL, children with pneumonia were more likely to have low 25-hydroxyvitamin D3 levels than controls (adjusted odds ratio [aOR] 2.4, 95% confidence interval (CI) 1.1–5.2, $P = 0.02$).

**Conclusions:** Low 25-hydroxyvitamin D3 levels are associated with an increased risk of pneumonia in children. However, it’s possible that the marker 25-hydroxyvitamin D3 is simply a marker for nutritional insufficiency.

10. **Investigation and Diagnostic Tests**

**#22 - ADENOSINE 5'-MONOPHOSPHATE CHALLENGE AS A TOOL FOR ASTHMA DIAGNOSIS AND TREATMENT IN PRESCHOOL CHILDREN**

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**Background:** Challenge test with auscultation to breathing sounds is one of the tools for diagnosis of asthma in young children.

**Purpose:** To test the hypothesis that adenosine challenge test in young children - can assist the physician to diagnose and treat early childhood asthma.

**Methods:** The study is a retrospective cohort study and included 159 children (26–131 months, mean 54.5 months) with recurrent respiratory complaints, which undertook the challenge test in the Lung Institute, Hadassah Ein - Karem Jerusalem, between the years 2004–2010.

**Pediatric Pulmonology**
Results: 73 tests were negative, 86 tests were positive, of which 51.2% had severe score, 17.4% moderate and 31.4% had mild score on the challenge test. Predictability of adenosine challenge test for asthma 3 years after the challenge ranged between 73.3% and 88.89% according to the different ages at the time of the challenge. Significant correlation was found between the severity score of the challenge and a positive diagnosis of asthma 3 years after the challenge ($P = 0.018$) and a positive diagnosis of asthma at school age ($P = 0.018$). Significant correlation was found between the severity score of the challenge and emergency visit to the emergency departments and hospitalizations after the challenge ($P = 0.05$). Positive challenge test reduced the number of visits to emergency departments and hospitalizations in the period of three years after challenge ($P = 0.016$). Positive challenge test influenced toward escalating the asthma treatment ($P = 0.03$) in general and the preventive asthma treatment as lone ($P = 0.01$). Negative challenge test influenced toward reduction in preventive treatment ($P = 0.023$).

It was shown that there is a significant correlation ($P = 0.022$) between the levels of IgE antibodies and the diagnosis of asthma three years after challenge.

Conclusions: Adenosine challenge test is an effective tool for the physician to care for young children who are suspected for the diagnosis of asthma. Challenge test results help the physician to adjust the medication and as a direct result - positively affect the prognosis of these patients. Adenosine challenge test in pre-school children can predict in a good manner which children will suffer from asthma at school age.

**#43 - EVALUATION OF PNEUMOCOCCAL TITERS AND RESPONSE TO 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE IN CHILDREN WITH COUGH**

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PURPOSE: To examine the prevalence and clinical significance of low pneumococcal titers, pre and post 23-valent pneumococcal polysaccharide vaccine (PPSV-23), in pediatric patients ≥2 years presenting with cough.

METHODS: We reviewed 826 charts of children ≥2 years presenting to Ochsner Pediatric Pulmonology Clinic from 2006 to 2012 with a diagnosis of cough. We determined the prevalence of low pneumococcal titers pre and 4–6 weeks post PPSV-23. Low pneumococcal titers were defined as ≤1.2 mcg/mL in >50% of the 14 serotypes tested. Adequate response was defined as doubling of the pre-immunization titer or titer ≥1.2 mcg/mL in at least 50%. Clinical significance was evaluated by examining whether patients with adequate titers post PPSV-23 had clinical improvement in cough, and by determining whether various clinical characteristics were associated with low pneumococcal titers either pre or post PPSV-23. These characteristics included wet cough, duration of cough, abnormal chest X-rays & CT’s, abnormal BAL, history of asthma, tobacco smoke exposure, prior antibiotics for cough, IV antibiotics for infection, and previous diagnoses of pneumonia, otitis media, and sinusitis. STATA was used for statistical analysis. Fisher’s exact test was used to determine statistical significance.

RESULTS: Pneumococcal titers were measured in 276 patients. Abnormal titers were found in 73.2%. Adequate response to PPSV-23 occurred in 77.5%. Inadequate response occurred in 6.3% and 16.2% did not have repeat titers measured. Clinical improvement in cough was documented in 53.5% of patients with adequate response to PPSV-23. Those who were not statistically significant associations between any of the clinical characteristics and low initial pneumococcal titers, except for environmental tobacco smoke (ETS) exposure. Low titers were found in 80% of these patients. None of the clinical characteristics evaluated demonstrated a significant association with poor response to PPSV-23.

CONCLUSION: Our pediatric patients with cough often had low pneumococcal titers, with good response to PPSV-23. Response to PPSV-23 correlated with clinical improvement in cough in >50% of these patients, suggesting post-PPSV-23 may be beneficial in treating pediatric cough regardless of infection history. ETS exposure was associated with low initial titers. ETS exposure has been shown to have a variety of effects on the immune system including alterations in antigen presentation. Our finding suggests poor pneumococcal antibody production may contribute to cough in children with ETS exposure. These children in particular may benefit from evaluation of pneumococcal titers and immunization with PPSV-23. Further studies investigating the role of ETS exposure on immune system function are needed. Larger, prospective studies would also be helpful in predicting which children with cough are likely to benefit from PPSV-23, and which children may have specific antibody deficiency with cough as a presenting symptom.
PFTs done at five years. There was little change in mean FEV1/FVC ratio in the first five years post-BMT (92% predicted at baseline compared to 93% predicted at five years post-BMT). However, there was an overall decline in PFT values at five years post-BMT compared to values at two years (which were already below pre-transplant levels) with regards to FEV1, FVC and TLC values. This was suggestive of a restrictive pattern in lung function several years after BMT, with a decline in FVC (11% fall from two years to five years post-BMT), FEV1 (12% fall) and TLC (3% fall).

CONCLUSION: Our results suggest that, in children undergoing bone marrow transplant, a fall in pulmonary function test values occur three to six months post-transplant, with a partial recovery at one to two years. However, pulmonary function test values were overall reduced at five years compared to values at two years. Our findings emphasise the need for longitudinal respiratory monitoring and follow-up to detect any deterioration in lung function in the years following bone marrow transplant.

#68 - QUANTITATIVE EVALUATION OF THE VENTILATORY RESPONSE TO CO2 IN PRETERM INFANTS.

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Background: The incidence of apnea in preterm infants is higher than in term infants because of the immature respiratory center. However, there are few reports evaluating the respiratory center in preterm infants. We have evaluated the respiratory center quantitatively by measuring the Ventilatory Response to CO2 (VR CO2) and reported the normal values in term infants and the VR CO2 of 29W-33W CGA was not significantly different from that of 34W-36W CGA. It is shown quantitatively that the respiratory center of preterm infants is physiologically premature than that of term infants which may play a role in the high incidence of apnea in preterm infants. The VR CO2 of preterm infants does not increase until 36 weeks CGA, on the other hand the administration of theophylline increases the VR CO2. Therefore regular administration of theophylline is effective in preterm infants with apnea. In the future, the VR CO2 in preterm infants after 37 weeks CGA should be evaluated in order to investigate how the respiratory center matures.

11. Therapeutic Procedures

#15 - COMPARISON OF NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) AND CPAP WITH INTERMITTENT PRESSURE IN PRETERM NEWBORNS

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Objective: To describe differences in clinical indicators and in the failure of two noninvasive pressure systems in preterm newborns.

Methods: Cross-sectional, prospective, analytical and observational cohort study. The study included 80 infants, who received noninvasive ventilation. The infants were randomly divided into two groups: 40 infants used nasal continuous positive airway pressure (cpap) and 40 used cpap with intermittent positive pressure. The infants were observed over the first 48 hours. Respiratory rate, heart rate, and oxygen saturation were recorded. Apnea, progression of respiratory distress, nose bleeding and agitation were defined as outcome variables of pressure support failure.

Results: The infants were classified as very low weight (1.337 ± 0.422 g and 30.3 ± 2.4 weeks), 55% were males. No significant difference in birth characteristics was observed between groups. Pressure support failure was observed in 55% children receiving cpap and in 30% receiving cpap with intermittent pressure, indicating an association between noninvasive ventilation failure and cpap without intermittent pressure (p=0.01, odds ratio 22), apnea was the main consequence of cpap failure. The clinical variables did not differ significantly between treatment modalities.

Conclusion: No difference in clinical indicators was observed between the two noninvasive positive pressure modalities. However, a higher frequency of pressure support failure was significantly associated with the use of cpap without intermittent pressure.

12. Cellular and Molecular Biology

#1 - B-TYPE NATRIURETIC PEPTIDE INHIBITS ANGIOTENSIN II-INDUCED PROLIFERATION AND MIGRATION OF PULMONARY ARTERIAL SMOOTH MUSCLE CELLS

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Pediatric Pulmonology
BACKGROUND: Pulmonary vascular remodelling, characterized by disordered proliferation and migration of pulmonary arterial smooth muscle cells (PASMCs), is a pathognomonic feature of pulmonary arterial hypertension (PAH). Pharmacologic strategy targeting on anti-proliferation and anti-migration of PASMCs may have therapeutic role for PAH, but is still lacking. The aims of the present study were to investigate the effects and underlying mechanisms of B-type natriuretic peptide (BNP) on angiotensin II (Ang II)-induced proliferation and migration of PASMCs.

METHODS: Vascular smooth muscle cells isolated from rat pulmonary artery were cultured and used at passages 3–5. Proliferation and migration of PASMCs were induced by Ang II and evaluated by MTT test and Boyden chamber assay, respectively. PASMCs were incubated with Ang II, with or without BNP pretreatment to determine its effects on proliferation and migration. In addition, potential underlying mechanisms including Ca2+ influx, oxidative stress, MAPK and Akt signaling and the cGMP/PKG pathway were also examined.

RESULTS: BNP inhibited Ang II-induced PASMC proliferation and migration dose dependently. In addition, BNP attenuated intracellular calcium overload caused by Ang II. Moreover, Ang II-induced ROS production was mitigated by BNP, with associated down-regulation of NADPH oxidase 1 (NOX1) and reduced mitochondrial ROS production. Finally, downstream signal transduction including ERK1/2 and Akt activated by Ang II were also counteracted by BNP. Of note, these effects of BNP were all inhibited by Rp-8-Br-PET cGMPS, a PKG inhibitor.

CONCLUSIONS: BNP inhibits Ang II-induced PASMC proliferation and migration. These effects are potentially mediated by decreased calcium influx and reduced ROS production by NOX1 and mitochondria, through the cGMP/PKG pathway. Therefore, BNP may have a valuable role in the prevention of pulmonary vascular remodelling.

#2 - EFFECTS OF PNEUMONIA AND MALNUTRITION ON THE FREQUENCY OF MICRONUCLEI IN PEDIATRIC PATIENTS

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The aim of this study was to evaluate the effects of bacterial pneumonia and malnutrition on the frequency of micronuclei (MN) in peripheral blood of pediatric patients through flow cytometric analysis. Patients and Methods: The study was an analytical case-control study carried out on 35 malnourished children with bacterial pneumonia and 20 well-nourished children with bacterial pneumonia, in addition to 20 healthy children as controls. Complete physical examination including; anthropometric measurement, Chest roentgenograms were done for all cases. Assessment of MN was done by FACSCalibur flow cytometry. Results: The frequency of micronucleated reticulocytes (MN-RETs) was higher both in the malnourished children with pneumonia and well-nourished children with pneumonia than the controls. Within the malnourished children with pneumonia, patients with kwashiorkor had more micronucleated mature erythrocytes (MN-RBCs) and MN-RETs than patients with marasmus. Conclusion: Pneumonia is associated with an increased frequency of MN and this increment is more pronounced in children with severe malnutrition especially kwashiorkor group.

#6 - DECREASED AMBIENT OXYGEN TENSION ALTERS THE EXPRESSION OF ENDOTHELIN-1 IN ALVEOLAR MACROPHAGE

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Abstract Streptococcus pneumoniae is an important pathogen of pneumonia in human. Human alveolar epithelium acts as an effective barrier and is an active participant in host defense against invasion of bacterial by production of various mediators. Sirtuin 1 (SIRT1), the prototypic class III histone deacetylase, is involved in the molecular control of lifespans and immune responses. The current study aimed to examine the role of SIRT1 in mediating S. pneumoniae-induced human β-defensin-2 (hBD2) and interleukin 8 (IL-8) mRNA expression in the alveolar epithelial cell line A549 and the underlying mechanisms involved. A549 cells were transfected with S. pneumoniae for indicated times. The levels of hBD2 and IL-8 mRNA were evaluated by real time quantitative reverse transcription - polymerase chain reaction (qRT-PCR). The expression of SIRT1 was detected by Western blot. S. pneumoniae increased the expression of SIRT1 protein, hBD2 and IL-8 mRNA. The SIRT1 inducers resveratrol enhanced S. pneumoniae-induced gene expression of hBD2 but decreased IL-8 mRNA levels. Blockade of SIRT1 activity by the SIRT1 inhibitors nicotinamide reduced S. pneumoniae-induced hBD2 mRNA expression but increased its stimulatory effects on IL-8 mRNA. S. pneumoniae-induced activation of extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK). SIRT1 expression was attenuated by selective inhibitors of ERK and p38 MAPK. The hBD2 mRNA production was decreased by pretreatment with p38 MAPK inhibitor but not with ERK or JNK inhibitor. Whereas the IL-8 mRNA expression was controlled by phosphorylation of ERK. These results suggest that SIRT1 mediates
the induction of hBD2 and IL-8 gene expression in A549 cell by S. pneumoniae. SIRT1 may play a key role in host immune and defense response in A549.

#168 - THE EFFECT OF IMMUNOTHERAPY, PROBIOTICS AND NIGELLA SATIVA IN THE NUMBER OF CD4+ IL-4+ CELL, TOTAL IGE LEVEL AND ASTHMA CONTROL TEST (ACT) SCORE

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Asthma is a chronic inflammatory disorder of the airways dominated by Th2. Immunotherapy has benefits for asthmatic patients. Its long duration of treatment is often caused drop out of treatment. Probiotics and Nigella sativa as immunomodulator for asthma expectantly could increase the efficacy of immunotherapy. The aims of this study was to evaluate the therapeutic efficacy of immunotherapy combined with probiotics and Nigella sativa in the number of CD4+ IL-4+ cells, Total IgE level and Asthma Scoring Test. A total of 31 children with mild asthma were evaluated and then randomized to receive immunotherapy or immunotherapy plus Nigella sativa or immunotherapy plus probiotic or immunotherapy plus Nigella sativa plus probiotic openly for 14 weeks. We used subcutaneous HDM immunotherapy (build up phase), 2 × 109 mixed live bacteria Lactobacillus acidophilus and Bifidobacterium lactis and 15 mg/kg/day Nigella sativa. Number of CD4+ IL-4+ cells was evaluated using flowcytometri of PBMC isolated from peripheral blood and analyzed using BD Cell quest Pro software. Total IgE level was measured using Enzyme Chemiluminesence Immunoassay by Roche Elecsys 2010. The children were accompanied by their parents while they answer ACT questions. There was no significant difference in the pre and post test mean number of CD4+ IL-4+ cells in all three treatment group. The Total IgE level was decreased significantly in the immunotherapy+ probiotic+ Nigella sativa group (p 0.022). The ACT score were increased in the immunotherapy+ Nigella sativa group (p 0.001), in the immunotherapy + probiotics group (p 0.004), and immunotherapy+ Nigella sativa+ probiotics group (p 0.000). Correlation test found a significant association between the number of CD4+ IL-4+ cells, Total IgE level and ACT score in all groups. The combination of immunotherapy, Nigella sativa and probiotics could decrease the Total IgE level thus improve the clinical symptoms.

13. Pediatric Pulmonology in Developing Countries

#16 - ROLE OF ZINC IN SEVERE PNEUMONIA: A RANDOMIZED DOUBLE BIND PLACEBO CONTROLLED STUDY

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Background: Pneumonia is a leading cause of morbidity and mortality in children. Objective: The aim of study was to evaluate the efficacy of Zinc supplementation in treatment of severe pneumonia in hospitalized children. Design/Methods: A double blind randomized, placebo- controlled clinical trial conducted at a tertiary care centre of a teaching hospital. Children with diagnosis of severe pneumonia were randomly assigned to receive supplementation with either elemental zinc or placebo by mouth at the time of enrollment. From day 2, they received 10 mg of their assigned treatment by mouth twice a day for 7 days along with standard antimicrobial therapy. Results: The baseline characteristics like age, sex, weight, weight Z score, height, height Z score, weight for height Z score and hemoglobin were comparable in both study groups. The respiratory rate, chest indrawing, cyanosis, stridor, nasal flaring, wheeze and fever in both groups recorded at enrollment and parameters did not differ significantly between the two groups. The outcome measures like time taken for resolution of severe pneumonia, pneumonia, duration of hospital stay, nil per oral, intravenous fluid, oxygen use, treatment requiring 2nd line of drug and 3rd line drug were evaluated and found to be same. Conclusion: The present study did not show a statistically significant reduction in duration of severe pneumonia, or reduction in hospital stay for children given daily zinc supplementation along with standard antimicrobial therapy. Therefore, zinc supplementation given during the acute episode does not help in short term clinical recovery from severe pneumonia.

Keywords: Pneumonia, Children, Zinc

#20 - ROLE OF METHYL PREDNISOLONE TREATMENT IN SEVERE MYCOPLASMA PNEUMONIAE PNEUMONIA IN CHILDREN

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Objective To investigate the therapeutic effects of methylprednisolone on severe MPP. Methods Sixty-two children with severe MPP were enrolled to receive azithromycin combined with methylprednisolone (treatment group, n = 26) or receive azithromycin alone (control group, n = 36). Clinical symptom changes (defervescence time), hospitalization time, C-reactive protein (CRP) levels, and pulmonary radiographic images were assessed at the end of the study. Results Patients in the treatment group experienced defervescence from 4 to 16h after enrollment, whereas no defervescence was observed among patients in the control group. Atelectasis rate was 2/26 in the treatment group and 11/36 in the control group (P < 0.05). The mean defervescence time was 8.8 ± 3.8 h in the treatment group and 52.9 ± 16.2 h in the control group (P < 0.01). The mean hospitalization time was 7.5 ± 1.4 d in the treatment group versus 11.3 ± 3.5 d in the control group (P < 0.01). Within three months of follow-up, 23/26 patients in the treatment group showed complete pulmonary infiltration absorption, and 23/36 patients in the control group showed the same result (P < 0.05). No significant difference in the mean fever duration prior to admission and the CRP mean value (P > 0.05) between the treatment group and the control group was observed. Conclusions Early methylprednisolone therapy with adequate macrolide content is helpful in the treatment and quick recovery of children with severe MPP. Keywords: Children; Mycoplasma pneumoniae; methylprednisolone; Pneumonia; pulse; severe

#103 - FACTORS INFLUENCING OUTCOME OF VENTILATED NEONATES IN INTENSIVE CARE UNIT IN A DEVELOPING COUNTRY

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Background: Large number of neonates in NICU require mechanical ventilation with a high fatality.

Objective: To find out the factors influencing outcome of ventilated neonates in ICU.

Materials and methods: This study was conducted from March 2006 to December 2009 in the ICU of Dhaka Shishu (Children) Hospital, Bangladesh. Neonates consecutively put on mechanical ventilator during the study period were enrolled. For each ventilated neonate, information included age, sex, admission weight, gestational age and primary diagnosis. Observations at the time of initiation of ventilation included PIP, PEEP, FiO2, SaO2 and ABG analysis. Complications encountered during ventilation and duration of ventilation was noted. Relevant investigations were done. Finally, outcome was recorded. For data entry and analysis SPSS version 17 was used.

Results: Total 225 neonates were put on mechanical ventilator. Out of them 96(42.67%) survived. Mean weight and gestational age was significantly low among non-survivors (P<0.05). Perinatal asphyxia (37.3%), preterm LBW with refractory apnoea or respiratory failure (29.4%) and neonatal sepsis (15.7%) contributed majority of cases. There was significant relation found between mortality and pneumonia cases (P<0.05). Weight <1500 gm and gestation <32weeks, mean initial arterial pH and HCO3, initial PH <7.1, high PCO2, BE and high initial FiO2 to maintain oxygen saturation, hyponatremia, hypokalemia, complication during ventilation were associated with mortality (P<0.05). Significant association was found between complication related to ventilation and outcome (P<0.05). Ventilator associated Pneumonia (VAP) and Sepsis showed high mortality.

Conclusions: Early identification of need for respiratory support and initiation of ventilation before metabolic derangement should be necessary. Proper ET tube care and control of infection should be ensured. Fluid and electrolyte balance should be look after meticulously.

#115 - THE ROLE OF THE HIGH-RESOLUTION LUNG CT IN THE DIAGNOSIS AND CLASSIFICATION OF CHILDREN BRONCHIOLITIS OBLITERANS.

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Objective: To explore the role of the high-resolution lung CT in the diagnosis and classification of children bronchiolitis obliterans.

Methods: We retrospectively summarize the HRCT sign of 147 cases of children bronchiolitis obliterans, diagnosed in Beijing Children’s Hospital during April 2001 to April 2012. Compared with the HRCT sign of children asthma diagnosed in the same period and try to find the differences. We divide the 147 cases into 2 different groups according to their clinical severity and try to find the differences between CT findings. BO children were followed up.

Results: In BO patients, there are 147cases of Mosaic perfusion sign, 86 cases of bronchial wall thickening, 80 cases of bronchiectasis, 44 cases of mucus plug and 32 cases of atelectasis. The control group, only show 2 cases of Mosaic perfusion sign. The difference is statistically significant. The severe BO children show more bronchiectasis in HRCT than mild children. The signs of HRCT of 49 cases of BO who were followed up persist.

Conclusion: Mosaic perfusion sign, bronchial wall thickening and bronchiectasis are the most common sign in HRCT of children bronchiolitis obliterans. The severe patients show more bronchiectasis in HRCT. The signs of HRCT of BO persist.

Keywords: children bronchiolitis obliterans diagnosis HRCT

Pediatric Pulmonology

#116 - EARLY DETERMINANTS OF LUNG FUNCTION IN AFRICAN INFANTS

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There is limited data on early lung function in African infants despite a high prevalence of respiratory disease.

Aim: To assess antenatal and early life factors associated with low lung function in early infancy in a low and middle income setting.

Method: Infants enrolled in the Drakenstein Child Lung Health study, a birth cohort study in a peri-urban area of South Africa, had lung function at 6–10 weeks of age. Infants were not tested within 2 weeks of a respiratory tract infection. Lung function was measured in unseeded infants during sleep using standardised methodology. Measurements, made with the infant quietly breathing through a face mask and bacterial filter, included tidal breathing (TBFLV), exhaled nitric oxide (NO) and sulphur hexafluoride multiple breath washout (MBW) measures using an ultrasonic flow meter and chemoluminescent NO analyzer. Information on antenatal and birth exposures was prospectively collected with questionnaires and urine cotinine antenatally, at birth and post-natally.

Results: Four hundred and thirty seven infants were tested at a mean age of 6.8 (SD 2) weeks, corrected for prematurity. Fifty percent of infants were male, 34% were exposed to maternal smoking in pregnancy and 43% were exposed to passive maternal smoke exposure. Median gestational age at birth was 39 weeks (IQR: 38–40) and birth weight 3kg (IQR: 2.7–3.4). Testing was successful in 420/437 (96%) of children for MBW, 434/437 (99%) TBFLV and in 430/437 (98%) for exhaled NO. Birth weight was positively associated with total tidal volume at a corrected age of 7 weeks: for every 1kg increase in birth weight there was an average 5 ml increase in tidal volume at 7 weeks (P<0.001, 95%CI 4.26 to 6.4). Both maternal smoking and passive maternal smoke exposure during pregnancy were associated with changes in TBFLV and NO measures: ratio of time to peak tidal expiratory flow over total expiratory time (tPTEF/Ei) was 5% lower (95%CI −8.3 to −2; P<0.01) for infants whose mothers smoked and 3.7% lower (95%CI −6.7 to −0.8; P=0.01) for infants with passive maternal smoke exposure compared to infants whose mothers did not smoke or have passive smoke exposure. NO output (VNO) was 1.3 mL/sec-1 higher (95%CI 0.1–2.4; P=0.03) for infants whose mothers smoked and 1.3 mL/sec-1 higher (95% CI: 0.3–2.4; P=0.01) for infants with passive maternal smoke exposure compared to infants whose mothers did not smoke or have passive smoke exposure. Smoke exposure had no significant effect on MBW measures. Prematurity (<37 weeks) was not associated with low lung function at 7 weeks in this cohort. Analyses were adjusted for infant length, weight, birth weight and length, gender, smoke exposure and prematurity.

Conclusions: Intrauterine and early life exposures have a significant impact on lung growth and function in early infancy which may constitute a risk for subsequent respiratory illness.

Funding: Thrasher Research Fund, Bill and Melinda Gates Foundation, The Wellcome Trust
#122 - DIAGNOSTIC AND INTERVENTIONAL BRONCHOSCOPY IN CHILDREN: MOROCCAN EXPERIENCE

Author:

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INTRODUCTION: Congenital and acquired lesions of the pediatric airway frequently pose perplexing problems in children, infants and newborns. Prompt investigation into the etiology and early intervention are essential to decrease the morbidity and to prevent some tragic events. Bronchoscopy grants access to the lesion sites for either diagnostic or therapeutic purposes.

MATERIAL AND METHODS: From January 2009 to December 2013, totally 224 endoscopic procedures, including 98 flexible and 126 rigid endoscopic procedures were performed in 236 pediatric patients at pediatric department of Hassan II hospital in morocco.

RESULTS: The median age of our patients was 52 months (range 5 months–15 years). They were 61% males. Interventional bronchoscopy was indicated for foreign body inhalation in (54.7%), stridor (21.6%), dyspnoea (14%). Bronchoscopy for diagnostic was performed for recurrent/persistent pneumonia(32%), wheezing that does not respond to appropriate therapy (16, 5%), and persistent atelectasis (14.2%). The X ray showed lung hyperinflation in 28% of patients, segmental or lobar pneumonia in 23% of cases, atelectasis in 15%, emphysema in 5%.

Interventional bronchoscopy was performed in 122 patients, foreign body was organic in 98 cases (peanut in 46.8% patients, almond in 16.1%, sunflower in 13.6% seeds, olive in 7.3%, metal screw in 5.9%) and inorganic in 12 cases (pins 45.4%, pieces of plastic 32.6%, metallic screw 17.3%). For 6 patients rigid bronchoscopy was necessary to resects obstructive granuloma due to tuberculosis or sequelae of a foreign body.

Diagnostic bronchoscopy was indicated for 114 patients. The commonest finding were foreign body in 24%, tuberculosis in 12.4%, airways malacia in 11.1%, External compression of trachea / bronchi in 9.6%, structural deformity in 8.9%, hydatid cyst membrane in 2.6%.

There was not post operative major complication. Only reasonable bleeding in 10 patients, bronchospasmy in 5 cases, transient hypoxemia in 4 childrens, and post bronchoscopy fever in 3 patients. These complications were managed accordingly and all patients recovered without any serious consequences.

CONCLUSION: The development that bronchoscopy has experienced in the recent years has been spectacular, especially in the field of pediatrics. Both the diagnostic and the therapeutic applications of bronchoscopy have increased considerably.

#143 - ASSOCIATED FACTORS TO THE INAPPROPRIATE MANAGEMENT OF ACUTE BRONCHIOLITIS IN COLOMBIA

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OBJECTIVE To determine whether there are factors associated to the inappropriate management of acute bronchiolitis in Colombia

METHODOLOGY: Observational Analytic Study of type Cross Sectional. 267 physicians were surveyed during the second half of 2013. Logistic regression models were fitted to identify whether there were factors associated to the possibility to assign an inadequate treatment during the infant’s stay in the emergency room and hospitalization.

RESULTS A total of 267 surveys were conducted to physicians in 8 different cities of Colombia. In relation to the type of hospital, 164 (61.4%) of respondents were practicing their care activities in university hospitals, and 57 (21.3%) in non-university hospitals. With respect to the academic level of the physicians surveyed, it was noted that 75 (28.1%) were physicians fellows, 69 (25.8%) pediatricians, 48 (18%) general physicians, 32 (12%) medical interns and 18 (6.7%) pulmonologists or neonatologists. Based on survey responses, 80 (30%) physicians would assign an inappropriate handling to infants with bronchiolitis in the emergency department and 66 (24.7%) during hospitalization. Of caregivers surveyed, 232 (86.9%) confirmed their institutions had acute bronchiolitis management guidelines and 31 (11.6%) did not have them. In the case they had them, 41 (15.4%) said no to apply them. Bivariate analysis confirmed that for both sceneries to work in an university hospital (P = 0.00), become a significative factor associated with a better chance of receiving appropriate management. Additionally, academic level was significant factor associated with a better chance of receiving appropriate treatment in the hospitalization scenario. Multivariate analysis concluded that for the case of hospitalization, to work in an university hospital was associated, with the ability to receive appropriate management (OR 0.40 95% CI 0.17–0.92, P = 0.031). Besides, decision making in the Pacific Coast Region (OR 4.68 95% CI 1.11–19.7 P = 0.03) and Coffee Region (OR 4.95 95% CI 1.10–16.48 P = 0.03) in Colombia was also associated with the possibility of prescribing an inappropriate treatment at the same stage.

CONCLUSION: The study showed that in Colombia 30% of physicians surveyed may assign improper treatment for acute bronchiolitis in emergency room and 25% of them in hospitalization. The existence of guidelines does not guarantee the application of them as 29% of the physicians decided not to apply them. To work in an university hospital reduced by 60% the chance of being assigned to improper treatment during hospitalization. It is necessary to develop continuing medical education activities with emphasis on Hospitals that have no physicians on training and in the Regions of Colombia that were mentioned. It must be ensured greater adherence to management guidelines of the institutions.

#161 - ETIOLOGY AND OUTCOME OF LOWER RESPIRATORY TRACT INFECTION IN CHILDREN

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Background: Lower respiratory tract infection (LRTI) remains the leading cause of mortality in children worldwide. Mixed viral-bacterial infections are common. The respiratory viruses pave the way for airway colonization bacteria. There were severe acute respiratory infection (SARI) surveillance in Indonesia including Hasan Sadikin General Hospital. Aim of the study to investigate the respiratory pathogens and outcome of the disease.

Methods: Since 2007–2009 NIHIRD, Ministry of Health Indonesia developed SARI surveillance. The study enrolled 352 children hospitalized with LRTI (pneumonia and bronchiolitis). Blood culture for bacteria and PCR Luminex of nasopharyngeal swab for viral detection were assayed in 160 subjects. Outcome of LRTI was observed until discharge.

Results: Of the 160 subjects, bacterial cultures positive in 61 blood specimens. The most common bacteria is coagulase negative staphylococci (CONS) 35 (57%), Serratia marcescens in 10 (16%), Pseudomonas aeruginosa 7 (11%), Staphylococcus aureus 2 (3%), others 8 (13%). Viral infections were identified in 44 subjects. The most common viruses are Influenza A 18 (41%) and Coxsackie virus 18 (41%), Rhinovirus 3 (7%), Parainfluenza virus 3 (7%), Respiratory syncytial virus (RSV) in 1 (2%) and Influenza B 1 (2%). Mixed viral-bacterial infections were detected in 21 subjects. The outcome of LRTI was 6 (4%) death, four subjects positive
CONS, and 2 subjects with mixed-infection by CONS and viruses (Coxackie and Rhinoviruses). Conclusion: The proportion of mixed viral-bacterial infection in LRTI in children is high. The most common cause of mortality are CONS and mixed viral CONS.

Keywords: Etiology-LRTI-Outcome

14. Clinical and Radiology Cases

#42 - BLOODY PLEURAL EFFUSION AT A GIRL OF 10 YEARS OLD

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Bloody pleural effusions are very rare in children, excluding trauma. This could lead to false diagnosis and to delay the treatment accordingly. A girl of 10 years old is admitted to our clinic, as an emergency, for fever, cough, abdominal and chest pain, anorexia, malaise. Onset of the disease is 9 months before, when she got abdominal pain, poor appetite, was treated for parasitosis and got analgesics seemingly with good evolution. After 1 month she was readmitted for cough and abdominal pain. Clinical examination, lab tests, abdominal ultrasound, chest radiograph showed bilateral pleural effusions. Thoracectomy evacuate small amount of bloody pleural exudate in which no microorganism was isolated. After 3 weeks of antibiotics she was better and she was discharged. Two weeks after, she came back with the same symptomatology. She had bilateral pleural effusions and at repeated thoracectomy bloody pleural liquid was identified. Diagnosis of tuberculosis was done, even QuantiFERON-TB, ADA in blood tests showed the presence of inflammatory markers, no positive autoimmunity tests, serum amylase and BAL amylase were high. She had anti-TB drugs for 4 months. During this time she continued to suffer of cough, abdominal and chest pain and repeated hemoptysis. In our clinic after clinical exam, she had chest radiography and bronchoscopy with bronchoalveolar lavage (BAL). No microorganism was found but measuring Gold Score for hemosiderin laden macrophage was found 94. Blood tests showed the presence of inflammatory markers, no positive autoimmunity tests, serum amylase and BAL amylase were high. Abdominal ultrasound, chest and abdominal MRI – established the diagnosis: mediastinal pancreatic fistula, bilateral bloody pleural effusion, chronic pancreatitis.

She had caudal pancreactectomy, fistulectomy, spleen was preserved. Post surgery evolution was good. The histopathology result confirms chronic pancreatitis and pseudo pancreatic cyst. We emphasize the difficulity of the diagnosis explained by the rareness of pleural and pulmonary complications of pancreatitis at pediatric age and by the developing of a fistula and not a typical pancreatic pseudo cyst image. Causes of bloody pleural effusion and of pancreatic diseases in children are discussed.

#45 - A CASE OF SEVERE COMBINED IMMUNODEFICIENCY (SCID)

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Pediatric Pulmonology

Severe combined immunodeficiency (SCID) includes a group of rare life-threatening disorders. At least 15 different single gene defects result in profound deficiency in T- and B-lymphocyte function. The estimated annual incidence of SCID is approximately one case per 50,000 live births. SCID usually is diagnosed when an infant has repeated or chronic unusual infections or complications following live vaccines (BCG or viral vaccines). We report a seven month old girl who presented with left axillary lymphadenitis, difficult wound healing after BCG vaccination and pneumonia. SCID was diagnosed – T-, B-. All attempts to clarify the etiology of the pneumonia (blood cultures, sputum, gastric aspirate, PCR for viruses) failed. She was treated with antibiotics, trimethoprim and sulfamethoxazole and anti-tuberculous chemotherapy (comprising Isoniazid, Rifampicin, Ethambutol), intravenous immune globulin. After partial improvement of the symptoms of pneumonia and BCG lymphadenitis the patient was sent for hematopoietic stem cell transplantation. The case adds up to the wellknown discussion about BCG vaccination - when and whether to do it.

#61 - CONGENITAL SYSTEMIC ARTERY-PULMONARY ARTERY SHUNT IN A MASSIVE HEMOPTYSIS CHILD: CASE REPORT

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Background: Congenital Pulmonary Arteriovenous Malformation (PVM) is a communication between artery and vein in lung. According to the source of supply vessel PVM can be divided into three types. Shunt between pulmonary artery and pulmonary vein (95%). Shunt between pulmonary artery and systemic artery with pulmonary artery to pulmonary vein shunt. Shunt between pulmonary artery and systemic artery without pulmonary artery to pulmonary vein shunt.

Case presentation: A 9-year-old girl presented with recurrent hemoptysis for 4 months. Her past history was normal. She tested negative for pneumonia, tuberculosis, idiopathic pulmonary hemosiderosis, auto-immune disease and hematological disease. The results of CXR showed atelectasis or infiltration. CT scans showed extensively diffuse infiltration in pulmonary parenchyma but was normal 9 days later. Based on Digital Subtraction Angiography (DSA), which showed the right and left bronchial arteries were aberrant with bronchial artery to pulmonary artery shunt in right middle and low lobe, she was diagnosis as pulmonary artery-systemic artery shunt without pulmonary artery to pulmonary vein shunt. She was treated by Transcatheter Embolotherapy (TCE). During 6-year of follow-up the patient remained well without recurrence.

Conclusions: Congenital pulmonary artery-systemic artery shunt can be the rare cause for massive hemoptysis in children. It had no specific sign of CXR and CT scans. It was confirmed by DSA. TCE can be used as treatment. Follow-up should be recommended with its unclear natural history and the long-term effects of TCE.

#102 - RARE COMPLICATION OF FOREIGN BODY ASPIRATION – CASE REPORT

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Despite significant advances in emergency airway management and endoscopic technology, airway foreign bodies still lead to significant morbidity and pose an important risk of death in the pediatric population. We overview the possible complications of foreign body aspiration through a case report. An 18 month old boy was referred to the oncologist because of bilateral neck swelling, following a few days of cough, low grade fever and flue-like symptoms. On physical examination subcutaneous emphysema was found, with weakened breath sounds on the right. CXR showed mediastinal shift, right-sided air trapping, pneumomediastinum and subcutaneous emphysema. Since the patient ate fish on the day before, tracheal or esophageal injury was suspected and an emergency CT examination of the neck and chest was performed. Besides the above-mentioned findings, a foreign body was detected in right main bronchus. A piece of peanut was removed via bronchoscopy. Because of pneumomediastinum, a mediastinal drain was inserted. After surgery the patient’s condition improved, but three days later bilateral PTX was detected, and pleural drains were inserted. The patient recovered completely. Foreign body aspiration is a life-threatening condition occuring most frequently in children under the age of four. Parents should be educated to avoid giving nuts to young children and to keep them in baby seats during meals.

#165 - HEMOPTYSIS IN PEDIATRIC PRACTICE - THREE DIFFERENT CASES

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Hemoptysis can range from blood-streaking of sputum to the presence of gross blood in the absence of any accompanying sputum. It’s a symptom in variety of diseases of upper or lower respiratory tract as well as some with vascular origin. The most common source of hemoptysis is the airways disease (inflammatory diseases, neoplasms, foreign body and airway trauma, fistula between a vessel and the tracheobronchial tree).

We present three different cases of children admitted in the clinic in which the only initial symptom is hemoptysis.

The first case is well developed 17 year old girl, without any significant premorbidity but with a very hazardous behavior and many risk factors (including drug, alcohol and tobacco abuse). At the admission the X-ray was suggestive for massive bilateral pulmonary in both lower lobes of the lung. At the careful examination, specific diagnostic tests and follow up Goodpasture Syndrome was diagnosed, and she received an appropriate treatment.

The second case is well developed 11 year old boy, without any significant premorbidity. On the X-ray oval shape behind the heart shadow was found. After CT scan, the patient was transferred for surgical removal of hyalide cyst.

The third case is of a 9 year old boy with signs of mild mental and physical retardation, with repeated pneumonias in early childhood. On the X-ray and the CT scan – localized bronchiectasis were found and appropriate treatment was conducted.

These cases illustrate different entities with an onset with only one symptom – hemoptysis. Careful diagnosis and imaging examination helps for the correct treatment. While surgery remains the only truly definitive therapy for massive hemoptysis, it should not be used in the acute emergent setting unless it cannot be avoided.
Background: Hospitalised bronchiolitis imposes a significant health burden upon young children globally, particularly in Indigenous children. In settings where children have high rates of nasopharyngeal bacterial carriage and frequent prolonged illness, macrolides may be beneficial. We aimed to determine if 3 once-weekly doses of azithromycin (30 mg/kg) vs. placebo improve clinical outcomes (length of hospitalisation and duration of supplemental oxygen). Secondary aims include (i) effect of treatment on respiratory readmissions to hospital within 6 months; (ii) whether macrolide-resistant respiratory pathogens in nasopharyngeal swabs (NPS) influence clinical severity; (iii) the short term impact of azithromycin on macrolide resistance patterns of respiratory pathogens in the nasopharynx; and (iv) point prevalence and diversity of respiratory viruses.

Methods: Indigenous children aged ≤24 months were enrolled in a placebo-controlled randomised trial from two Northern Australian and one New Zealand hospital from 2010 to 2013. Primary endpoints were monitored 12 hourly until discharge. NPS were collected at baseline and 48 hours. Children were reviewed clinically on day-21 to determine presence of persistent respiratory symptoms and signs. Respiratory readmissions within 6 months post discharge were recoded. All investigators, care providers, and participants remain blinded to treatment groups until the final chart review.

Results: The mean age of 219 children randomised was 7 months (SD = 5). One family withdrew consent after enrolment and another refused NPS. summarises the results. The most common viruses found at baseline were respiratory syncytial virus (RSV) 91/215 (42%) and human rhinovirus (HRV) 79/215 (37%). Respiratory bacteria detected at baseline include Haemophilus influenzae 78/217 (36%), Moraxella catarrhalis 80/217 (37%) and Streptococcus pneumoniae 42/217 (19%). At day-21, a wet cough was present in 29/218 (13%), crackles in 22/218 (10%) and wet cough plus crackles in 40/218 (18%) children. 50/186 (27%) children have had a persistent symptoms 3 weeks post hospitalisation is high. We will report the primary and secondary outcomes by treatment group after breaking treatment codes in April 2014.

Support: NHMRC (grant 605809), NHMRC Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children (grant 1040830).GBM is supported by a NHMRC scholarship (grant 1055262).

Conflict of Interest: None

#67 - TUBERCULOSIS EMPYEMA: A CASE REPORT

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Empyema due to tuberculosis usually occurs in older children and is rarely associated with miliary disease. It is a complication of plural tuberculosis, which is responsible for 5% of the tuberculosis in children in endemic regions.

Objective: Describe a case of empyema due to tuberculosis in a 6 year old girl.

Methodology: The information needed for the study was obtained from hospital records.

Case report: IMM, a 6 year old girl from Belém, Pará, Brazil was admitted after experiencing progressive dyspnea, fever and productive cough for 16 days and had a previous admission to another hospital. A chest X-ray exposed opacification of the right hemithorax and pneumothorax. She underwent a chest tube drainage procedure in which green, purulent fluid was drained.

Cytology of pleural effusion: Neutrophils 99%; Lymphocytes 1%; Glucose 10 mg/dl

Ph 6.98; TST: 00 mm; Gastric lavage: 3 negative samples; HIV serology test: dot-ELISA negative. Intravenous(IV) Piperacillin-Tazobactam was started and she exhibited no fever for 18 days. Later, complications evolved despite antibiotic therapy and she still had drainage of purulent fluid. Chest Computedized Tomography (CT) showed a large right pneumothorax with fluid and bronchopleural fistula. Thoracoscopoy with decortication was performed and a double chest tube inserted. The antibiotic was changed to imipenen and vancomycin.

Another chest CT was implemented and showed air fluid level and pulmonary collapsing. She underwent a flexible bronchoscopy on the 57th
day and the bronchoalveolar lavage (BAL) showed AFB. A standardized treatment regimen of 2 RHZ/4RH (R-Rifampicin; H- Isoniazid; Z- Pyrazinamide) for Tuberculosis was started and after 67 days she was discharged from the hospital.

Conclusion: Tuberculosis in children remains difficult to diagnose. In this case, the acute non-typical form of the disease delayed a proper diagnosis and treatment.

#70 - ADVERSE EFFECTS OF ANTITUBERCULOUS TREATMENT IN CHILDHOOD

Author:

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Tuberculosis is a disease requiring multi-drug treatment for a prolonged time. Simultaneous use of multiple drugs increases the risk for side effects. Seventy five patients with a prediagnosis of tuberculosis were followed between 2007 and 2012. Among these 61 were diagnosed with tuberculosis infection and 14 with tuberculosis disease. Six of the patients in the tuberculosis disease group were diagnosed with pulmonary tuberculosis, two with urinary and two with tuberculosis lymphadenitis. The remainder were diagnosed with tuberculosis arthritis, periartitis, endobronchial and military tuberculosis. Patients diagnosed with tuberculosis infection received isoniazid for 6 months (5–10 mg/kg/day). Except for a patient with elevated liver function tests, no adverse events were documented. Patients diagnosed with tuberculosis disease were initially started on a 3 or 4-drug regimen for two months (isoniazid 10–15 mg/kg/day, rifampin 10–15 mg/kg/day, pyrazinamide 30–40 mg/kg/day, ethambutol 15–25 mg/kg/day) followed by a 2-drug regimen for 4–16 months (isoniazid 10–15 mg/kg/day, rifampin 10–15 mg/kg/day). Treatment was delayed in two patients with elevated liver function test results. Seven patients had elevated serum uric acid levels and they were encouraged to drink water and were prescribed allopurinol. Hyperuricemia is the most common side effect of the patients who were treated with pyrazinamide and these patients may require oral hydration therapy and allopurinol during the course of antituberculous regimen treatment.

#71 - ANALYSIS OF THE USE OF TOBACCO AND MARIJUANA IN JUNIOR HIGH SCHOOL IN 10 SCHOOLS IN THE WESTERN REGION IN SÃO PAULO – BRAZIL

Author:

Lotufo J. (Pediatrics, USP – São Paulo, Brazil)

Introduction: the use of tobacco and marijuana is appearing increasingly early in Brazil and worldwide. Although being the fourth country in the number of ex-smokers, the precocity of tobacco use in Brazil concerns us. Smoking and the use of marijuana are pediatric diseases, for they start at the age of 12 (+/-2) and must be understood as a reason for prevention by pediatric pulmonologists.

Methodology: We screened 2814 questionnaires from students of 10 schools in the western region of São Paulo, on the initiation of tobacco use. These were teenagers from Junior High School and High School, with ages ranging from 10 to 17 years.

Results: 48% were boys and 52% girls.

18% of them deny having received any guidance on drugs and tobacco. About tobacco, 90% deny having smoked in the past year, 3% of them use tobacco less than once a week, 1% of them once or more times a week, 2% of them use it daily, 1% of them twice or more times a day and 3% did not answered this question.

About marijuana, 90% have never used, 2% used less than one time a week, 1% use once or more times a week, 1% of them use it daily, 1% twice or more times a week and 5% did not answer this question.

The reasons to try smoking for the first time were:

1. Because I wanted to and friends offered (4%) 2. Because friends offered and I couldn’t refuse it (1%)
3. Out of curiosity (9%)
4. Because it is charming (1%)
5. 5% did not answer and 80% have never used it.

When asked about the use of cigarettes, 80% said to help reduce bad feelings, 1% to do things they wouldn’t be able to, 5% because it is tasty, 1% because they are already used to doing it, 1% because their friends do it, and 9% did not answer it.

Of those who did not use tobacco products, 57% because they know it is harmful, 10% because “it’s against their principles”, 4% are afraid, 3% have never had the opportunity and 15% have never used them. 4% did not use for other causes, and 7% did not answer.

When asked about the best way to prevent the use of drugs, 57% said it would be family guidance, 8% radio and TV, 3% teachers, 4% school material, 12% school campaign and 16% did not answer it.

Conclusion: Pediatric Pulmonologists and Pediatricians must get involved in the tobacco control issues, and anti marijuana, mainly in the prevention, for Junior High and High School students (11–17 year olds) are already trying it and are becoming early users. And Pediatric Pulmonologists are not mentioned as a way of prevention of drug use among teenagers. There has to be a change. The brief intervention (using 3 minutes of the medical appointment to talk about tobacco and marijuana) should be part of our medical appointments.

#72 - IMPORTANT DETAILS OF A SMOKING CESSATION CLINIC, RELATED TO PEDIATRICS AND PEDIATRIC PULMONOLOGY.

Author:

Lotufo J. (Pediatrics, USP – São Paulo, Brazil)

Introduction: Active smoking is the first cause and passive smoking is the third leading cause of preventable death in the world. I started a smoking cessation clinic by treating smoking parents of children with asthma. 3000 people are currently being treated with therapy related to drug addiction and psychological and behavioral dependence.

Methodology: we evaluated the situation of teenagers in the smoking cessation group, and all the important facts related to Pediatrics.

Results:

1. 24% of children aged zero to five years old who come to the Emergency Department of Pediatrics, have urine positive for cotinine levels (nicotine derived), which means, they had close contact with cigarette in the past 36 hours (index ranged from 6.9 to 273 ngammas /ml of blood).
2. 3% of those who come to us in order to quit smoking, started smoking before age ten, 53% before age15, and 86% before 20 years of age.
3. There was no seeking for treatment for smoking cessation before age 20.
4. From 20 to 25 years of age, only 21% quit smoking, and from 25 to 30 years of age, 30% quit smoking.

Evaluation:

1. Passive smoking is real in children, it is important to quit smoking at home.
2. Smoking begins increasingly early and it starts in the pediatric phase.
3. The teenager is not worried about quitting smoking, for the age group that seeks treatment ranges mainly from 40 to 60 years of age.

Pediatric Pulmonology
Abstract

4. The rate of smoking cessation is lower by the age of 30, if compared to the rate after the age of 30 (45 to 50%)

Discussion: Smoking starts in the pediatric phase of life, and pediatricians and pediatric pulmonologists do not spend time in making the prevention of the disease called “Nicotine Dependence”. Young people are not interested in quitting smoking (pre-contemplation stage) and the pediatricians need to guide them on this regard (action stage).

Young university students are still teenagers, and even with potential for 6000 smoking students at USP campus (20% of the population) a clinic created for this age group did not succeed for lack of demand. Young people are not interested in quitting smoking.

Conclusion: pediatricians and pediatric pulmonologists need to embrace this issue about smoking, as well as of other drugs, for its beginning is increasingly early. We need to make tobacco prevention in the pediatric care, guide smoking parents properly and discuss this issue in every medical appointment.

#87 - THE EFFECT OF BODY MASS INDEX (BMI) ON PULMONARY FUNCTION IN SCHOOL AGED CHILDREN

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Introduction: Data on pulmonary function abnormalities as complications of obesity in children are limited and conflicting. Therefore, it is of great importance to study the effect of high BMI on pulmonary function parameters in children.

Methods: Healthy children between 9 and 15 years of age were recruited. The parents were given a detailed questionnaire. All the responders underwent a detailed clinical assessment.

High BMI group (obese & overweight) had BMI for age and sex more than 85th percentile according to Centre for Diseases Control reference charts. (Overweight - 85th - 95th and Obese >95th percentile). The control group had BMI between 3rd and 85th percentile. All the children in high BMI and a subgroup of normal children (control) underwent spirometry.

Exclusion criteria were respiratory infections within 2 weeks, chronic respiratory disorders and neuromuscular system disease.

Weight (kg) and standing height (cm) were measured with a calibrated weighing scale and a stadiometer. Alpha Touch Vitalograph Spirometer in accordance with the American Thoracic Society and European Respiratory Society Guidelines was used for testing. All children performed forced expiratory maneuvers. The best of at least three technically acceptable values for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), maximum mid-expiratory flow rate (FEF25-75%), and flow volume curves were selected.

Study was approved by the Ethics Committee, University of Sri Jayawardenepura.

Statistical analysis: Pearson’s chi square test to evaluate potential association and student’s t test to assess differences were used with categorical and ratio-scale variables among the two groups with SPSS for Windows. The level of significance was set at 5%.

Results: A total of 405 school children participated. Of them 93 were excluded (did not fulfill the inclusion criteria or refused consent for spirometry). Finally 307 children were invited to perform spirometry. Of them 32 were absent on the day of test or could not cooperate to do a good test. Twenty percent (55/275) had high BMI, 30 were overweight and 25 were obese. Eighty percent (220/275) were between 3rd and 85th centile. Finally 55 high BMI children and a representative sub-group of 64 (64/220) randomly selected normal weight children underwent spirometry.

No significant difference noted in age, gender, height, exposure to cigarette smoke (P = 0.552) and family history of atopy (P = 0.458) between the 2 groups.

BMI has no significant relationship to any of the pulmonary function parameters (FVC (t = 1.708, df = 117, P = 0.175), FEV1/FVC (t = 1.796, df = 117, P = 0.75) and FEF 25-75% (t = 1.060, df = 117, P = 0.291).

No significant difference in pulmonary function was evident between obese and the overweight.

Conclusion: In conclusion, we have shown that pulmonary function does not correlate with body mass index and there is no reduction in pulmonary function values in children with high BMI.

#134 - INFLUENZA VIRUS INDUCED DAMAGE TO THE PULMONARY EPITHELIAL-ENDOTHELIAL BARRIER

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Acute respiratory distress syndrome (ARDS) is a fatal complication of influenza virus infection that is observed in both paediatric and adult patients. Clinically, ARDS is characterised by severe respiratory insufficiency and a high case fatality rate. The severity of this disease is reflected in the lung lesions of infected patients. During the acute phase of ARDS, patients display diffuse alveolar damage characterised by the accumulation of fluid and leukocytes in the alveoli. Central to the development of these pulmonary lesions is damage to the epithelial-endothelial barrier. Destruction of this barrier results in fluid leakage from interstitium, fibrin deposition and pulmonary haemorrhaging. At present, the specific mechanisms by which influenza virus damages the epithelial-endothelial barrier remain unclear. Previous studies have suggested that the ability of influenza virus to infect the pulmonary endothelium and cause endothelial cell apoptosis results in vascular permeability and oedema. Others have suggested that the pro-inflammatory cytokines produced in response to influenza virus play a more significant role in lung damage. Pro-inflammatory cytokines may damage the lung via the recruitment and activation of leukocytes. Alternatively, pro-inflammatory cytokines can damage tight junctions between epithelial cells and facilitate intercellular fluid permeability – although this has yet to be demonstrated in the case of influenza virus infection. Here, we use an in vitro model to assess how influenza virus damages the pulmonary epithelial-endothelial barrier. Briefly, epithelial cells are seeded on the upper half of a transwell membrane whilst endothelial cells are seeded on the lower half. These cells are then grown in co-culture for approximately seven days and then influenza virus is added to the upper chamber. The presence of influenza virus damages this barrier, as determined by a significant decrease in the trans-epithelial resistance (TER) overtime. Interestingly, we show that whilst the addition of influenza virus results in the infection of epithelial cells, endothelial cells are not infected. Instead, endothelial cells facilitated increased cytokine production by epithelial cells. This increased cytokine production was associated with a significant decrease in the expression of tight junction by epithelial cells. Our data therefore suggest that endothelial cells may play an important role in influenza virus induced ARDS by triggering cytokine production by epithelial cells. This then in turn disrupts epithelial cell tight junctions and facilitates paracellular permeability and pulmonary oedema.

#147 - SLEEP-RELATED RESPIRATORY EVENTS AND SLEEP STRUCTURE IN HYPOXIC-ISCHEMIC ENCEPHALOPATHY NEONATES

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Objective: To determine whether sleep-related respiratory events are more common in hypoxic-ischemic encephalopathy (HIE) neonates compared to normal controls and to investigate if sleep structure is impaired in HIE patients.

Method: HIE neonates were recruited in the neonatal wards from June to August in 2011. Newborns recovered from neonatal pneumonia were served as controls. All the subjects and controls had the polysomnography performed in the Sleep Unit for at least 4 hours. Sleep stage was scored and respiratory events were analyzed by technicians who were unaware of the subjects’ conditions.

Results: Twenty-two full term infant with mild to moderate HIE and eleven control neonates were included into the study. There were no differences regarding age, gender, height and weight between the two groups. The percentage of indeterminate, quiet, and active sleep of total sleep time was 39.9, 29.4 and 30.6 respectively in the HIE group, and 29.1, 33.7 and 37.2 respectively in the control group. The percentage of indeterminate sleep was increased and REM sleep was decreased in the HIE patients compared to the controls (P = 0.002 and P = 0.031 respectively). There was no difference regarding the percentage of quiet sleep between the two groups (P = 0.12).

The HIE patients had a higher apnea/hypopnea index and hypopnea index compared to the controls (P = 0.002 and P = 0.031 respectively). There was no difference regarding the percentage of quiet sleep between the two groups (P = 0.12).

The HIE patients had a higher apnea/hypopnea index and hypopnea index compared to the controls (P = 0.002 and P = 0.031 respectively). There was no difference regarding the percentage of quiet sleep between the two groups (P = 0.12). The HIE patients had a higher apnea/hypopnea index and hypopnea index compared to the controls (P = 0.03, and P = 0.01 respectively), while no difference were found with respect to obstructive apnea index, central apnea index and Mixed apnea index (P = 0.08, P = 0.57 and P = 0.49 respectively).

Conclusions: HIE neonates had increased proportion of indeterminate sleep and decreased proportion of active sleep. Further more, HIE patients were more likely to have apneas and hypopneas compared to the controls.

#162 - PERFORMANCES OF A VALVED HOLDING CHAMBER WITH DIFFERENT INHALED CORTICOSTEROIDS

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In young children with asthma, the use of a pressurised metered dose inhaler (PMDI) with a valved holding chamber is recommended. The objective of this study was to evaluate the performances of a valved holding chamber with different inhaled corticosteroids.

In this study, the performance of a valved holding chamber called Tipshaler (Protec’som, France) was evaluated with beclomethasone (QVAR®, 100 μg/dose, MEDICIS, Canada) and ciclesonide (Alvesco®, 200 μg/dose, Takeda, Canada). The method according to the European Pharmacopoeia used a constant flow rate (30 L/min) was used. Particle size distribution was measured using a NGI cascade impactor (Copley Scientific, Nottingham, United Kingdom). The beclomethasone and ciclesonide concentrations were assayed by spectrophotometry at 239 nm and 243 nm respectively.

In the trachea, the mass of beclomethasone was higher with pMDI alone in comparison with Tipshaler (11.6 ± 0.4 μg vs 1.2 ± 0.2 μg, P < 0.05). In addition, deposition of fine particles of beclomethasone was similar with pMDI alone compared to Tipshaler (77 ± 1 μg vs 75 ± 1 μg, P < 0.05). Concerning ciclesonide, in the trachea, the mass of drugs was lower with Tipshaler compared to pMDI alone (2.4 ± 0.7 μg vs 16.0 ± 0.6 μg, P < 0.05). However, the fine particle dose was higher with the pMDI alone compared to Tipshaler (158 ± 1 μg vs 153 ± 1 μg, P < 0.05).

In conclusion, the use of valved holding chamber reduces the deposition of ultra-fine particles of inhaled corticosteroids in the trachea and allows efficient lung deposition of drugs.
Index

A
Abdulkadir MB., 65
Abdulkarim AA., 65
Abreu F., 86
Acerbi D., 54, 55
Acuna RH., 59, 60, 83
Adnan Custovic, 8
Alberts A., 82
Almeida CC., 75
Alonso Bernardo LM., 51, 58
Amiel, J., 46
Amir Kugelman, 26
Andrew Bush, 2, 11, 43
Andrew Colin, 23
Anne B Chang, 10, 15, 29
Anthony K., 78
Ardhani RY., 69
Armoni Domany K., 62, 68
Asensi Monzo MT., 51, 58
Aslan AT., 87
Aubin-Lemay C., 64
Avenshtein A., 77
Avital A., 77
Axelrod FA., 63

B
Babaei H., 76
Badkar G., 64
Bahececi Erdem S., 75
Bang KW., 69
Bar Aluma BB., 63
Bar-Yoseph R., 57
Barhom A., 44
Barlianto W., 81
Barry W., 76
Baronio R., 55
Barreto M., 56
Baumann SF., 62
Baumann SS., 62
Beltran C., 60
Bentur L., 57
Berankova K., 44
Berceo sanz A., 51, 58
Berger P., 53
Best E., 64
Biedebach S., 53
Bisgaard H., 67
Blich BO., 68
Boon M., 46, 49, 57, 70
Bosch, B., 46
Bouabdellah Y., 73
Boufersaoui B., 71
Bouharrou A., 73
Boukhettala NB., 89
Boulerice-Turcotte A., 64
Bozzone A., 56
Breuer BO., 68
Breuer O., 44
Brigitte Fauroux, 35
Bruce K. Rubin, 33, 42
Brunherotti MA., 79
Brzostek J., 55
Bustamante R., 45, 67
Bustos Y., 83
Byrnes C., 64
Byrnes CA., 85

C
Caiazzo I., 56
Callén Blecua MT., 51, 58
Campisano M., 56
Can D., 75
Cano Garcimunio A., 51, 58
Carvaljal Urueta I., 51, 58
Carzana E., 55
Casares Alonso I., 51, 58
Casimir G., 72
Castillo Laita JA., 51, 58
Castro-Rodriguez JA., 61
Catherine M. Owens, 31
Chan H., 71
Chan YH., 67
Chandra Kusuma MS., 69, 81
Chang AB., 86
Chang B., 49, 75
Charatsi A., 72
Charlotte H. Dean, 25
Chawes B., 54
Chay OM., 52
Chen IC., 80
Chong CS., 50
Chong CY., 67
Christmann M., 53
Chun YH., 69
Ciurlia G., 54
Cohen S., 77
Cohen-Cymberknob CM., 68
Colberg-Poley A., 48
Correia J., 72
Cortés Rico O., 51, 58
Counil F., 64
Craig JC., 74
Cuppens H., 70

D
Daban K., 78
Dabbah H., 56
Dagan AD., 63
Dai ZK., 80
David Shouseyov, 17, 37
De Boeck K., 46, 57, 70
de Bruyne JA., 57
Deanovic M., 62
De Wachter E., 74
Diaz V., 54
Ding SG., 81
Domínguez Aurrecoechea B., 52, 58
Donata Girosi, 6
Dore-Veillette S., 64
Dougherty G., 48
Drouot X., 54
Dumas M., 64
Dupont L., 46
Durán Iglesias C., 52, 58
Dzinovcic M., 66

E
Efrati OE., 63
Eichler I., 63
Eickmeier O., 53
Eitan Kerem, 16
El Omairi N., 73
El Omairi Nissrine N., 83
Elgalal A., 55
Elaine Vrijlandt, 28
Eyns H., 74

F
F. Vermeulen, 32
F.G.A. Versteegh, 13
Fayon M., 53
Fernández Carazo C., 52, 58
Fitzgerald D., 74
Forns Serrallonga D., 51, 58
Foucher R., 88
Frans De Baets, 20
Freihat R., 48
Freitas A., 72

G
Gallo M., 67
García Merino A., 51, 58
Gary W.K. Wong, 29
Gács E., 84
Genel F., 74
Gerber JS., 77
Gie RP., 76
Gilchrist F., 47
Giovanni A. Rossi, 6
Gkiougki E., 73
Gkiougki E., 73
Goeminne P., 46
Goh A., 52, 67
Goh DY., 50, 78
Gonçalves AC., 86
Govoni M., 54, 55
Gray DM., 82
Grimwood K., 87
Grolle Onnebrink J., 48
Guedes M., 72
Gugliani V., 56
Gulez N., 75
Abstract S91

Pediatric Pulmonology

Gut G., 62
Gut G., 68

H
Haiza Hani H., 59
Hakim F., 57
Hall GL., 82
Hananias K., 67
Hanson C., 74
Hanssens L., 72
Hasegawa H., 69, 70, 79
Hasniah AL., 59
Havermans T., 49, 73
Heather J. Zar, 1, 14, 37
Henmi N., 69, 79
Hishiki H., 49, 75
Hoffman EP., 48
Hogg J., 46
Honkova L., 44, 60
Hoshina J., 69, 79
Hsu JH., 79, 80
Hu YH., 84
Huertas RM., 60
Huseni S., 48

I
Ibraheem RM., 65
Imai T., 85
Ishiwada N., 49, 75
Issaev V., 84
Iturra P., 45, 67

J
Jackowska, T., 45
Jacobsen NJ., 86
Jamalludin AR., 59
Jamieson N., 70
Jaspers M., 70
Jean-Paul Praud, 34
Jing W., 58
Johnson AR., 65
Jorissen M., 57, 70
Jose A. Castro-Rodriguez, 3

K
K De Boeck, 18
Kabachieva R., 84, 85
Kaczmarek J., 55
Kappos A., 66
Karkiner CS., 75
Kasper J., 56
Kaufmann HK., 63
Kavandi S., 76
Kerem E., 44
Kerem KE., 68
Kim HH., 69
Kim HS., 69
Kim JT., 69
Kirkpatrick C., 88
Kovacs E., 85
Kuehni C., 71
Kuiken T., 88
Kuna P., 55
Kunling S., 58
Kurlandsky L., 65
L
La Penna F., 56
Lablans M., 71
Lammertyn E., 46
Lavie ML., 63
Lee EK., 69
Lee JS., 69
Lee JT., 78
Lefevre N., 72
Leigh M., 71
Lemire C., 64
Lenney W., 47
Leonard MB., 77
Leonardi KM., 79
Levi-Schaffer F., 44
Levin G., 77
Lim MT., 50, 78
Lin L., 64, 80
Liu CH., 59
Livnat G., 57
Liyanimate G., 88
Loges N., 48
Loo LH., 67
Lotufo J., 87
Lucas J., 71
Lucci G., 55
Lui LC., 75

M
Macari A., 56
Macleman C., 85
Malfroot A., 74
Mamathuba R., 66
Mamun MA., 81
Mansbach A., 72
Maria Angela Tosca, 6
Marijke Proesmans, 19
Martin Ibáñez I., 51, 58
Martin L., 64
Martinez S., 60
Matthews Griese, 21, 24
McCallum GB., 85
Mckay CC., 85
Melo AP., 79
Mentzer D., 63
Migdal M., 63
Minai Y., 44
Minic, P., 46
Miteva D., 85
Miyoshi Y., 69
Miyoshi Y., 79
Mobberley C., 86
Mokria-Serbinova S., 55
Moneo Hernández I., 51, 58
Montano D., 60
Montón Álvarez JL., 51, 58
Mora Gandarillas I., 51, 58
Morais L., 72
Morcillo AM., 75
Morell Bernabe JJ., 51, 58
Morris PS., 85
Moscusco S., 84
Mulliez J., 54
Murcia García J., 51, 58

N
Nacaroglu HT., 75
Nagasawa K., 49, 75
Nagashima K., 49, 75
Narayan O., 47
Natalie Mazur, 12
Nathan AM., 57
Naumova E., 84
Nemeth B., 85
Neron C., 64
Ng D., 71
Ng E., 71
Nicolella Solari, 6
Nielsen K., 71
Nino G., 48, 61
Norcliffe-Kaufmann I., 63
Nucci A., 75

O
Olbrich H., 48
Olivianto E., 69, 81
Oloyede IP., 49
Omran H., 48, 71
Oros M., 76
Oulmaati A., 73

P
Pacchiarotti C., 56
Pakaski S., 62
Pancham K., 48
Pedraza AM., 59
Pennekamp P., 48
Pereira L., 86
Perenoskva P., 84, 85
Perez F., 45, 67
Perez GF., 48
Petr Pohunek, 1, 39
Petrova G., 85
Petsky HL., 57
Piccinno A., 54
Pohunek P., 44, 55, 60
Poli G., 54
Ponce CA., 45, 67
Ponce N., 45
Porde TP., 89
Prerna Crespo M., 51, 58
Praud JP., 64
Preciado D., 48
Proesmans M., 57, 70, 73
Pugaleanti A., 52

Q
Quentin C., 72

R
Radic V., 62
Raidt J., 48, 71
Ramamurthy MB., 50, 78
Reed F., 64
Reis G., 72
Reznichenko Y., 55
Ribeiro JD., 75
S92  Abstract

Ribeiro MA., 75
Rito T., 86
Robert Olcese, 6
Rodriguez CR., 91, 58
Rodriguez CE., 95, 60, 83
Rodriguez-Martinez CE., 61
Rojas DA., 45, 67
Rose M., 48
Rosewich M., 53
Rossi P., 63
Saad K., 80
Saad K., 80
Sarouk IS., 63
Schatz A., 79
Schindler R., 77
Schulze J., 53
Scu M., 55
Sejal Saglani, 5, 9
Senra V., 79
Shah G., 81
Shanmugam S., 57
Shen KL., 84, 89
Short K., 88
Siao V., 53, 54
Siddarta B., 69
Silva B., 86
Silveira CS., 79
Simunkova P., 60
Singh D., 54
Singh R., 44
Singh-Grewal D., 74
Sivan Y., 62, 68
Sive A., 85
Slogotskaya L., 65
Sloots TP., 85
Sly P., 82
Smith E., 82
Soegiono LS., 81
Soferman R., 62, 68
Sossa-Briceno MP., 61
Sovic A., 46
Springer C., 77
Srikantha JT., 78
Stelmac I., 55
Steyaert H., 72
Stojnic, N., 46
Strom BL., 77
Suvaranant S., 83
Sun JH., 84
Ta Tack J., 73
Taelman A., 49
Takahashi S., 49, 75
Tan MS., 80
Tan PL., 78
Tauler i Toro E., 51, 55
Tee N., 67
Teoh OH., 52, 67
Thavagnanam S., 57
Thomas B., 50, 52
Thoon KC., 67
Tiwar A., 56
Tong A., 74
Trenholme A., 64
Trian T., 53
Tsaturu S., 69, 79
Turcanu T., 66
Uchiyama T., 69, 79
Udin MF., 69
Uhlker J., 44, 60
Ulrich Wahn, 4, 6
Urrego F., 78
Uckert F., 71
Vaes P., 74
Vajner L., 60
Valla J., 72
Van Bever HP., 50
Van Raemdonck D., 46
Vanaudenaerde B., 46
Vanker A., 76
Varela MM., 83
Vargas, SL., 45, 67
Varinder Singh, 38, 41
Varoli G., 55
Velasque Lopez AA., 77
Verbeke E., 46
Verleden G., 46
Verleden S., 46
Vermeulen PL., 57
Verschakelen J., 46
Versteegh LA., 85
Vertommen A., 73
Verwey C., 66
Villa MP., 56
Villegas MS., 78
Vilozni DV., 63
Vlachos-Mayer H., 64
Vukas E., 67
Wallmeier J., 48, 71
Wang J., 81
Wasa M., 69, 79
Wei W., 58
Werner C., 48, 71
White AV., 85
Whitley H., 47
Willekens J., 74
Willemse L., 82
Wong P., 52
Wrotek, A., 45
Wu JR., 80
Xie D., 77
Xu BP., 84
Xu ZF., 88
Yamada Y., 69, 79
Yang L., 51
Yang XF., 89
Yao Y., 84
Yiallouros P., 71
Yoon JS., 69
Zaia JE., 79
Zaleska-Ponganis, J., 45
Zaluu MA., 57
Zampoli M., 66
Zandakov D., 81
Zar H., 66
Zar HJ., 76, 82
Zhipeng Z., 82
Zielen S., 53

Pediatric Pulmonology