Paediatric Respiratory Reviews publishes four issues a year and contains commissioned articles relevant to the continuing medical and professional development of paediatricians, primary care physicians, and other healthcare professionals specialising in the diagnosis, treatment and management of paediatric respiratory disease. The commissioned review-based articles cover all aspects of global paediatric respiratory disease, function, diagnosis, management and therapy. Subjects covered include epidemiology, immunology and cell biology, physiology, occupational disorders and the role of allergens and pollutants. Through selected reviews readers also have the opportunity to acquire Continuing Medical Education credits.

The journal additionally welcomes submitted editorials, educational reviews and short communications (which will be peer-reviewed), on all aspects of paediatric respiratory medicine and which support the educational aims of the journal.

Editor-in-Chief
Dominic Fitzgerald
The Children's Hospital, Westmead, New South Wales, Australia
Email: prrjournal@elsevier.com

Associate Editors
Ian Balfour-Lynn
Royal Brompton Hospital
London, UK
Ernst Eber
Department of Paediatrics,
Medical University of Graz,
Austria
Bruce K. Rubin
Department of Pediatrics Virginia Commonwealth University School of Medicine Richmond, VA, USA

Editorial Board
Paul L.P. Brand
Isala Klinieken
Amalia Children's Clinic
Zwolle, The Netherlands
Pascual Chiarella
Departamento de Pediatría, Universidad Peruana Cayetano Heredia, Peru
Brigitte Faureaux
Armand Trousseau Hospital
Pierre et Marie Curie University Paris, France
Gilberto B. Fischer
Universidade Federal de Ciências da Saúde, Porto Alegre, Brazil

Editorial Advisory Board
John Henderson
ALSPAC, Bristol, UK
Petr Pohnsek
2nd Medical Faculty of Charles University,
University Hospital Motol, Prague, Czech Republic
Dorota Sands
Klinika Pediatrii, Instytutu Matki i Dziecka,
Warsaw, Poland
Varinder Singh
Department of Pediatrics, Lady Hardinge Medical College and assoc Kalawati Saran
Children's Hospital, New Delhi, India

Managing Editor
Annette Fowler
Elsevier, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB
Tel: ++44 1865 843672
E-mail: prrjournal@elsevier.com

Founding Editor
Warren Lenney
Consultant Respiratory Paediatrician, Stoke-on-Trent, UK
Abstracts of the

10th International Congress on Pediatric Pulmonology

25–27 June 2011, Versailles, France

The CIPP X organization warmly thanks for their valuable support in this E-publication:

[Logos: TEVA, Abbott]

Published as Supplement 1 to
Paediatric Respiratory Reviews, Volume 12, 2011
Oral Presentations .......................................................... S1
I. President’s Address ...................................................... S1
II. Keynote Speakers ........................................................ S1
III. Obstructive Lung Disease ........................................... S7
   III.1. Obstructive Lung Disease – Where genome meets environmentome ........................................ S7
   III.2. Obstructive Lung Disease – Pro/Con debate: immunotherapy for asthma .................................. S9
   III.3. Obstructive Lung Disease – Pro/Con debate: asthma inflammatory assessment improves asthma care ......................................................................................... S13
   III.4. Obstructive Lung Disease – Lung diseases in children: immunity, viruses or genes? ....................... S16
   III.5. Obstructive Lung Disease – Asthma epidemiology and treatment .................................................. S21
IV. Infection, Inflammation & Other Topics ....................... S27
   IV.1. Infection, Inflammation & Other Topics – Gastroesophageal reflux ................................................ S27
   IV.2. Infection, Inflammation & Other Topics – Cystic fibrosis ............................................................. S37
   IV.3. Infection, Inflammation & Other Topics – East and West: global perspective on childhood respiratory diseases ........................................................................................................ S39
   IV.4. Infection, Inflammation & Other Topics – Childhood respiratory infections: the new frontiers .......... S43
   IV.5. Infection, Inflammation & Other Topics – What happens to the child with lung disease as a young adult? .................................................................................................................. S45
V. Pearls ................................................................. S48
   V.1. Pearls – The art and science of bronchoscopy ............................................................................. S48
   V.2. Pearls – Respiratory physiology and immunology ........................................................................ S52
VI. French Sessions ...................................................... S57
VII. Oral Communications from Young Investigators ............. S61
Posters ........................................................................... S67
   A. Bronchial asthma and other chronic obstructive pulmonary diseases ........................................ S67
   B. Bronchopulmonary and pleural infections (including tuberculosis) .............................................. S72
   C. Noninfectious respiratory disorders ......................................................................................... S77
   D. Fetal and neonatal respiratory disorders ...................................................................................... S81
   E. Cystic fibrosis ............................................................................................................................ S83
   G. Respiratory manifestations of extra-pulmonary diseases (including AIDS) ..................................... S84
   H. Neuromuscular and chest wall diseases (including SIDS) .......................................................... S85
   J. Epidemiology, environmental risks, prevention, socio-economic cost, public health resources .......... S86
   K. Investigation and diagnostic tests .............................................................................................. S87
   L. Therapeutic procedures .......................................................................................................... S89
   M. Cellular and molecular biology .............................................................................................. S91
N. Pediatric pulmonology in developing countries ............................................................... S93
P. Miscellaneous ........................................................................................................... S96

Author index........................................................................................................... S101
Oral Presentations

I. President’s Address

I.1 Foreword

A. Colin. Miller School of Medicine, University of Miami, Miami, FL, USA

It gives me great pleasure to welcome all to the tenth meeting of The International Congress of Pediatric Pulmonology – CIPP, at historic Versailles.

Since its inception in 1994 CIPP remains the only global meeting that is fully dedicated to pediatric pulmonology. As of last year’s congress in Vienna we moved from an alternate-year to an annual program, and the meeting this year is the test of this new paradigm. As the travel distances between continents and countries have been reduced to hours, understanding of commonalities and differences of medical practices and cultures between developed and developing countries, has become vital. And as the Congress has matured from a local meeting to one with a global reach, we have continually attempted to give a voice to medicine from more remote places. The participation of delegates from 74 countries at our most recent meeting is a testament to the success of this mission and the reputation and reach of our message.

With the hope of a balanced program we are striving to engage some of the leading authorities on the major topics of the day, in which chronic lung disease, anergy and non-specific clinical and radiological signs make definitive diagnosis even more challenging. Scoring systems have been especially variable with poor reliability for diagnosis. Interferon-gamma release assays do not seem to offer substantial improvements over the tuberculin skin test for the diagnosis of TB infection except in HIV-infected, very young or malnourished children. Definitive microbiologic diagnosis and antimicrobial susceptibility has become increasingly important in children given the issues of pill burden, adherence and the emergence of drug resistant isolates. Sputum induction has increasingly been shown to be useful and safe and provides a good specimen for microbiologic confirmation even in infants. Recent data suggest that sputum induction may be feasible in primary care settings. Development of capacity for microbiologic diagnosis in children at all levels of health care systems is needed. The use of new, rapid molecular based diagnostic tests on sputum offers further promise.

Global guidelines on the management of TB in children and in HIV-infected children have recently been published, including a revision of recommended drug dosages of the first-line TB drugs for children, with increased dosages now advised based on pharmacokinetic evidence. Providing appropriate therapy including fixed drug combinations that contain such higher TB drug doses remains a challenge. The incidence of multidrug resistant (MDR) disease in children, in which M. tuberculosis is resistant to both isoniazid (INH) and rifampicin is unclear due to lack of microbiologic data, but worldwide the incidence of MDR cases is approximately 3 to 4% of the TB caseload.

The resurgence in TB incidence has been driven by the HIV epidemic, with dual epidemics occurring in a number of low or middle income countries. HIV-infected children have a much higher risk for developing TB and for disease progression compared to immunocompetent children. Conversely, TB accelerates the progression of HIV. Dual treatment of TB and HIV remains difficult due to pill burden, potential for side effects, adherence issues and drug interactions. The use of HAART is now advocated early as soon as a child is diagnosed with HIV, but adjustments in antiretroviral therapy may be needed with concomitant TB treatment especially when rifampicin is used. Immune reconstitution inflammatory syndrome (IRIS) occurring in the context of unrecognized TB infection or during TB treatment remains a particular challenge in HIV-infected children who commence antiretroviral therapy. Renewed interest in prevention of childhood TB has focused on the development of improved vaccines, and on specific preventative strategies in HIV-infected children including early use of HAART.

II. Keynote Speakers

II.1 Advances in childhood tuberculosis

H.J. Zar. Department of Paediatrics and Child Health, Red Cross War Memorial Children’s Hospital, University of Cape Town, South Africa

Recent renewed global interest in TB and better funding for TB research has led to advances in the understanding, diagnosis, prevention and management of childhood TB. Childhood TB cases contribute approximately 15 to 20% of all TB cases, increasing to up to 40% in some high TB burden countries. The World Health Organization (WHO) recently instituted a policy of reporting childhood TB cases for 2 age groups, those 0–4 years and 5–14 years, to improve the measurement of childhood TB burden. Measurement of the burden of childhood TB has been hampered by the difficulty of definitive diagnosis due to non-specific clinical and radiological signs, paucibacillary disease, and lack of capacity for microbiologic diagnosis. Increasingly, TB has been recognised as a cause of acute pneumonia in children that is difficult to clinically or radiologically distinguish from other pathogens. Diagnostic uncertainty has been compounded by the HIV epidemic in which chronic lung disease, anergy and non-specific clinical and radiological signs make definitive diagnosis even more challenging. Scoring systems have been especially variable with poor reliability for diagnosis. Interferon-gamma release assays do not seem to offer substantial improvements over the tuberculin skin test for the diagnosis of TB infection except in HIV-infected, very young or malnourished children. Definitive microbiologic diagnosis and antimicrobial susceptibility has become increasingly important in children given the issues of pill burden, adherence and the emergence of drug resistant isolates. Sputum induction has increasingly been shown to be useful and safe and provides a good specimen for microbiologic confirmation even in infants. Recent data suggest that sputum induction may be feasible in primary care settings. Development of capacity for microbiologic diagnosis in children at all levels of health care systems is needed. The use of new, rapid molecular based diagnostic tests on sputum offers further promise.

Global guidelines on the management of TB in children and in HIV-infected children have recently been published, including a revision of recommended drug dosages of the first-line TB drugs for children, with increased dosages now advised based on pharmacokinetic evidence. Providing appropriate therapy including fixed drug combinations that contain such higher TB drug doses remains a challenge. The incidence of multidrug resistant (MDR) disease in children, in which M. tuberculosis is resistant to both isoniazid (INH) and rifampicin is unclear due to lack of microbiologic data, but worldwide the incidence of MDR cases is approximately 3 to 4% of the TB caseload.

The resurgence in TB incidence has been driven by the HIV epidemic, with dual epidemics occurring in a number of low or middle income countries. HIV-infected children have a much higher risk for developing TB and for disease progression compared to immunocompetent children. Conversely, TB accelerates the progression of HIV. Dual treatment of TB and HIV remains difficult due to pill burden, potential for side effects, adherence issues and drug interactions. The use of HAART is now advocated early as soon as a child is diagnosed with HIV, but adjustments in antiretroviral therapy may be needed with concomitant TB treatment especially when rifampicin is used. Immune reconstitution inflammatory syndrome (IRIS) occurring in the context of unrecognized TB infection or during TB treatment remains a particular challenge in HIV-infected children who commence antiretroviral therapy. Renewed interest in prevention of childhood TB has focused on the development of improved vaccines, and on specific preventative strategies in HIV-infected children including early use of HAART.
Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease that develops as a consequence of perinatal/neonatal lung injury, and it is one of the most important sequelae of premature birth. The diagnosis of BPD is currently based on the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the respiratory support required at 36 postmenstrual weeks. BPD almost always occurs in neonates who are delivered at a gestational age of less than 30 weeks and who have a birth weight of less than 1500 g. These are about 1.5% of all newborns and BPD develops in about 20% of them. Today BPD is mainly a developmental disorder in which the immature lung fails to reach its full structural complexity. Longitudinal studies on children with BPD identified, at all ages, increased rates of chronic coughing and wheezing, a greater need to use inhaled asthma medications and a significant airflow obstruction. Children who have survived BPD and children with asthma share some clinical and functional characteristics, but available evidence suggests that the two obstructive lung diseases do not have the same underlying airway inflammation. Spirometric values reflecting airflow, such as FEV₁, are consistently lower in survivors of BPD into adolescence and young adulthood than in controls born at term rising the concern that the chronic lung disease after premature birth may predispose to the development of a chronic obstructive pulmonary disease (COPD)-like phenotype with aging. This is an open question that only follow-up and lung function studies extended to middle-age and beyond will answer. Unfortunately, no pathologic data are available elucidating which structural and pathophysiological alterations underlie the clinical and functional pulmonary abnormalities seen at long-term in some subjects delivered prematurely. A relevant question is whether the long-term pulmonary consequences of prematurity and BPD essentially depend on a non-progressive reduction of the airflow caliber, due to a stabilized, non-progressive structural damage of the airways, or instead reflect an active airway disease. Chronic lung disease of prematurity can no longer be considered only a pediatric disease and also family doctors and chest physicians should be aware of this “new” Chronic Obstructive Pulmonary Disease.

References

II.3 Diagnosis and management of ciliopathies
A. Bush. Department of Paediatric Respiriology, Imperial School of Medicine at National Heart and Lung Institute; and Royal Brompton Hospital, UK
Correspondence: Correspondence: A. Bush. Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. Tel.: +44 207 351 8232; fax: +44 207 351 8763. E-mail: a.bush@rbh.nthames.nhs.uk

Introduction:
If Nitric oxide (NO) was the molecule of the 1990s, cilia are the organelles of the 21st century. There has been an explosion of knowledge in the understanding of the disparate functions of cilia, and of disease caused by their dysfunction. This presentation will discuss the spectrum of ciliopathy, but focus mainly on the diagnosis and management of primary ciliary dyskinesia (PCD). Most of the other ciliopathies are the province of non-respiratory paediatricians.

There are three groups of mammalian cilia:
- Primary cilia: (which are NOT abnormal in PCD) have 9 outer doublets, no central pair, and are probably non-motile. There is only one per cell, they are found on many cell types, and probably function as chemo-, osmo- and phototransduction sensors
- Nodal cilia: These are primary in structure, but motile with a circular, rotator beat. They are found in the embryonic node and determine organ situs
- Motile cilia: These have the classic 9+2 structure, and are responsible for propelling mucus along epithelial surfaces (or propelling single cell organisms through liquid). There are around 200/respiratory epithelial cell.

Ciliary assembly includes complex intraflagellar transport, including retrograde recycling of proteins. The process involves at least eight Bardet-Biedl-Syndrome (BBS) proteins. Ciliary signal transduction involves the hedgehog signaling pathway, and canonical and non-canonical Wnt pathways.

The extended spectrum of ciliopathy: Syndromic Manifestations:
Mutations in more than 40 genes have been associated with ciliopathy. Many are complex, overlapping genetic disorders, and each syndrome may be related to many different underlying mutations, some of which have been identified as part of the ciliosome [1]. The more important are listed below.
- Joubert syndrome (J BTS): is characterized by hypotonia, ataxia, psychomotor delay, irregular breathing pattern, oculomotor apraxia with cerebellar and brainstem abnormalities
- Meckel-Gruber syndrome (M KS): overlaps with J BTS. Features include posterior fossa defects, cystic dysplastic kidneys, hepatic duct proliferation and polydactyly.
- Senior-Loken syndrome (SL S): is characterized mainly retinal disease (retinitis pigmentosa (RP) and congenital blindness, and renal disease (nephronophthisis, polycystic disease and cystic renal dysplasia)
- Orofacial digital syndrome (OF D): is characterized by oral cavi ty, facial and digital malformations, cystic kidney disease and central nervous system abnormalities
- Leber’s congenital amaurosis (L CA): this early presenting syndrome is characterized by poor visual function, often with nystagmus and reduced or absent papillary responses, photophobia, keratoconus and hyperopia.
- Bardet-Biedl-Syndrome (BBS): This syndrome includes rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism and renal disease (renal dysplasia, cystic tubular disease, nephronophthisis, focal glomerular sclerosis), and detrusor instability. Among the many secondary features are speech disorders, developmental delay and behavioural disorders, strabismus, cataracts and astigmatism, brachydactyly or syndactyly, ataxia and poor coordination, hypertonia,
anomia, diabetes, fibrocystic liver disease, Hirschsprung's disease, cardiovascular abnormalities and sometimes craniofacial abnormalities (brachycephaly, bi-temporal narrowing, male frontal balding, large ears, a short and shallow philtrum, nasal anomalies, mid-facial hypoplasia and mild retrognathia).

- Alstrom’s syndrome (ALS): is characterized by cone-rod dystrophy, obesity, sensorineural hearing loss, dilated cardiomyopathy (60% develop cardiac failure), insulin resistance syndrome and developmental delay. Males have hypogonadism. Renal failure may be early, but unlike in BBS, cognitive function is relatively preserved and there are no digital anomalies.

- Jeune asphyxiating thoracic dystrophy (JATD): this syndrome falls within the province of paediatric respirology, because mild cases may have prolonged survival, and severe cases are doing better with thoracic expansion procedures. The characteristic skeletal findings are a very narrow thorax with short ribs; hypoplastic 1st and 2nd toes, 5th digit syndactyly and rhizomelic limb shortening. Diagnosis can be made by a skilled paediatric bone radiologist from the radiological appearances, including regular metaphyseal ends. There may be post-axial polydactyly, brachydactyly, hydrocephalus, retinitis pigmentosa and renal aplasia, glomerulosclerosis and cystic renal disease including nephronophthisis, and pancreatic and hepatic fibrocystic disease. A case of intestinal malrotation and disordered motility in a neonate’s syndrome has recently been reported [2]. JATD is genetically heterogeneous, but cases with mutations in IFT80, which is important in intraflagellae transport has been implicated.

- Ellis van Creveld syndrome (EvC): this can be confused with JATD, but can be distinguished by the nail dysplasia and the appearances of the upper lip. 60% have heart defects, which are rare in JATD. EvC is characterized by short limbs and ribs, post-axial polydactyly and dysplastic nails and teeth. The EvC protein localizes to the base of cilia.

- Sensenbrenner syndrome (cranioectodermal dysplasia): This is similar to EvC, but has the additional features of renal cysts with dolicocephaly, sparse and slow-growing hair, epicanthal folds, disorders of dentition, brachycephaly and a narrow thorax.

**Organ-specific manifestations:**

- Single or multiple organ disease, not part of a syndrome, is part of ciliopathy. Kindreds have been described in which several different single organ manifestations of ciliopathy have been manifest.

- Congenital heart disease: Complex congenital heart disease, especially with disorders of laterality have an increased prevalence in PCD. Children with these abnormalities should be carefully screened for PCD.

- Renal disease: The best known is polycystic kidney disease (PKD), which can be associated with liver cysts, and may present in childhood as well as adult life. Disease is due to mutations in polycystin 1 or 2. Interestingly, polycystin 1 is expressed in respiratory epithelium [3], and there is a higher than expected prevalence of bronchiectasis is non-PKD renal disease. Nephronophthisis presents with childhood renal failure, and imaging shows normal kidney size with loss of corticomedullary differentiation and increased echogenicity. More than 10% have external renal features, including renal cysts, fibrocystic liver disease, skeletal dysplasia and hypoplasia of the cerebellar vermis. Renal dysplasia is characterized by small kidneys, unilateral or bilateral. The kidneys have increased echogenicity and there is loss of fatty tissue. On liver biopsy, there are no identifiable cysts.

- Liver disease: these are heterogeneous. Congenital fibrocystic diseases of the liver are characterized by any of congenital hepatic fibrosis, bile duct dilatation and cyst formation.

- Retinal disease: Disorders of retinal photoreceptors manifesting as a progressive loss of peripheral vision. Retinitis pigmentosa is a common ophthalmoscopic appearance.

**Primary ciliary dyskinesia:**

Classical PCD is a disease of the upper and lower respiratory tracts, with associated mirror image arrangement in nearly half of all cases. Extended kindreds with PCD and other ciliopathies such as retinitis pigmentosa have been described.

**When to suspect PCD:**

Many symptoms are very non-specific, and the key is to maintain a high index of suspicion, and take a really focused history [4].

- Antenatally: Diagnosis of abnormal situs or complex congenital heart disease.

- Newborn period: Rhinorrhea from birth, respiratory distress with no obvious cause; abnormal situs; complex congenital heart disease; testing because of a positive family history.

- Childhood: Chronic productive cough (which should be differentiated from recurrent acute cough, which is usually normal in childhood), atypical 'asthma' not responding to treatment, idiopathic bronchiectasis, rhinosinusitis, and severe oesothelial disease should all prompt consideration of PCD as part of the spectrum.

**Diagnosis of PCD:**

PCD must be distinguished from secondary ciliary abnormalities caused by viral infection or pollution, for example. Since so many symptoms of PCD (cough, rhinitis) are very non-specific, it is essential that the diagnosis is confirmed in a centre with expertise in testing. If there is doubt, testing should be repeated after a time interval.

- Screening tests: Nasal NO is very low in PCD, but also in other conditions. A high nNO with a low risk history virtually excludes the diagnosis. There is only scant information on this test in infants, so results should be interpreted cautiously. Other screening tests include radio-isotope clearance and the saccharin test, which last is very difficult to interpret in children.

- Tests of ciliary motility: Ciliated epithelium is obtained by nasal brush biopsy. Ciliary beating should be recorded digitally, and beat frequency and pattern noted.

- Ciliary structure: this is determined by transmission electron microscopy, sometimes with computerized edge enhancement. Note that undoubted cases of PCD with normal ultrastructure have been reported.

- Ciliary culture: This is only needed in cases of doubt. If ciliated epithelium is regrown in culture, secondary ciliary defects disappear, whereas primary abnormalities persist and can be identified by motility studies and electron microscopy.

- Genetic studies: The ciliary protein contains over 1000 polypeptides, and there is presumably an elaborate assembly apparatus, so numerous genes can likely cause PCD, of which fewer than 20 have been identified. Hence genetic studies may occasionally confirm a doubtful diagnosis, they cannot be used to exclude one.

**Management of PCD:**

There are no worthwhile randomized controlled trials of treatment, protocols are highly variable, and either empirical or based on cystic fibrosis (CF) [4]. These have been reviewed recently [refs]. It is recommended that children are seen in a dedicated PCD clinic, with full facilities for monitoring lung function and hearing.

- Lower respiratory manifestations: airway clearance is encouraged with chest physiotherapy and exercise. Antibiotics are prescribed for positive cultures, and given continuously if there are repeated isolates of a particular organism. If Pseudomonas aeruginosa is isolated, then eradication regimes are as for CF. If the child is thought also to have coincident asthma, then inhaled corticosteroids and bronchodilators are prescribed. The use of anti-
inflammatory and mucociliary agents such as rhDNase is based on isolated reports.

- Upper respiratory manifestations: in general, conservative management is best. Chronic secretory otitis media tends to improve with age, and tympanostomy tubes should be avoided. Functional endoscopic sinus surgery may be rarely needed. Chronically discharging ears are almost invariably infected with *Pseudomonas aeruginosa*, and are treated with ciprofloxacin ear drops.

- Other manifestations: Male adults may need assisted conception service, and intracytoplasmic sperm injection (ICSI) should be offered. Management of associated diagnoses is beyond the scope of this article.

**Prognosis of PCD:**

Unfortunately, diagnosis of PCD is frequently delayed until well after bronchiectasis has developed. Although in many patients lung function can be stabilized, a recent report suggests as many as 3% of infants may show deterioration in lung function [5], and some PCD patients have had to undergo lung transplantation.

**Learning points:**

1. Ciliary dysfunction is implicated in an ever-widening spectrum of diseases.
2. Children with complex congenital heart disease with disorders of laterality should have the diagnosis of PCD considered as a serious possibility.
3. There is a higher than expected prevalence of bronchiectasis in renal disease – beware the kidney patient with a cough!
4. There needs to be a high level of suspicion for the diagnosis of PCD in many contexts, otherwise diagnosis will be delayed until after the onset of bronchiectasis.

**References**


**II.4 Inflammation and sleep disordered breathing: review for the pediatric pulmonologist**

A.D. Goldbart1,2. 1Department of Pediatrics and 2the Sleep-Wake Disorders Unit, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Correspondence: Aviv D. Goldbart, MD, MSc. Department of Pediatrics, Sleep-Wake Disorders Unit, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva 84101, Israel. Phone/Fax: +972 8 624 4465. E-mail: avigold@bgu.ac.il

Keywords: Inflammation, leukotrienes, obstructive sleep apnea, sleep-disordered breathing

Sleep disordered breathing (SDB) represents a spectrum of breathing disorders, ranging from snoring to obstructive sleep apnea (OSA). The latter is a prevalent disorder in children (2% to 3%) that is associated with neurobehavioral, cognitive, and cardiovascular morbidities. Inflammatory changes were observed in upper airway samples from children with OSA, and systemic inflammation, as indicated by high-sensitivity C-reactive protein (hsCRP) levels, has been shown to decrease after adenotonsillectomy. Inflammation is correlated with some OSA-related neurocognitive and cardiovascular functions and anti-inflammatory treatments for children with mild OSA are associated with major clinical and polysomnographic improvement. The role of biomarkers in the diagnosis and management of OSA, and the role of anti-inflammatory treatments, remains to be clarified.

This review examines the role of inflammation in the pathophysiology of sleep-disordered breathing, related morbidity and potential effects of anti-inflammatory therapy.

**Introduction:** A search for the key words inflammation and sleep in children reveals that even snoring children without any gas exchange abnormalities may present with poor neurocognitive performance and behavioral morbidity, suggesting that mechanisms like intermittent hypoxia and sleep fragmentation are not responsible for all known OSA-associated morbidity.

Oxidant stress and inflammation are associated with sleep disruption as well as intermittent hypoxia, in rodent models of sleep apnea. Antioxidants like green tea (containing catechin polyphenols), when given to rodents, can attenuate intermittent hypoxemia-induced neurobehavioral deficits by reducing lipid peroxidation, and inflammation.

Although adults with sleep disordered breathing (SDB) present with inflammatory changes locally in the airway and systemically, it is harder to evaluate the role of inflammation in the pathogenesis of SDB in adults, and occasionally in adolescents due to common morbidities (e.g., obesity and the metabolic syndrome), in contrast to children.

Children with SDB present with local (upper airway apparatus) inflammatory changes and systemic correlates. The measured inflammatory changes reflect activation of specific pathways such as the lipoxygenase pathway, which is involved in other inflammatory conditions such as asthma and allergic rhinitis. The hope is that the knowledge gathered in the field will improve future diagnostic and therapeutic abilities.

**The upper airway:** The association between inflammatory measures of the upper airway and development of SDB in adults led several investigators to examine children. Cysteinyl leukotrienes for example are well recognized inflammatory mediators and potent neutrophil chemoattractants and activators. The leukotrienes are metabolites of arachidonic acid and their effect occurs after their interaction with their receptors. The receptors of these mediators (cysteinyl leukotriene receptors 1 and 2 [CYS LT1-R and CYS LT2-R]) are expressed on several tissues including the nasal mucosa and the lungs. The expression of LT1-R and LT2-R was studied in tonsils of 2 distinct groups: OSA and RI (recurrent infectious tonsillitis without OSA). Messenger RNA encoding for LT1-R and LT2-R was detected in the tonsils of all children. LT1-R and LT2-R proteins were over-expressed in the tonsils of children with OSA.

Children with OSA had a significantly greater percentage of spumut neutrophils than did children without OSA after an overnight polysomnography. LT1-R is primarily expressed in myeloperoxidase-positive cells (usually neutrophils) within upper airway lymphoid tissues in children with SDB. Leukotriene concentration (both LTB4 and LTC4/LTD4/LTE4) is increased in the adenotonsillar tissue of the patients in the OSA group, compared with children with RI. Moreover, LT pathways mediate intrinsic proliferative and inflammatory signaling pathways in mixed cell cultures prepared from dissociated adenotonsillar tissues from children with OSA.

Furthermore, global cell proliferative rates from mixed OSA tonsils cultures were significantly higher than RI, with CD3, CD4, and CD8 cell proliferation being higher in OSA; however, values were in a highly proliferative state in the tonsils of children with OSA.

A different technique to assess the airway is by exhaled condensates that can be easily obtained from children noninvasively and are better for defining the role of inflammation in the pathogenesis of diseases that involve the airway than peripheral measures in urine or blood samples that provide remote and indirect measures about the airways. OSA severity-dependent increases in leukotriene concentrations (LTB4 and LTC4/LTD4/LTE4) emerged in exhaled...
condensates from children with OSA, while Prostaglandins were not affected by the condition. It is therefore suggested that inflammatory surrogate markers in the exhaled breath condensate may serve as a noninvasive means of clinically assessing children with SDB. Interestingly, there is also an increase in LTB4 in exhaled condensates of adults with OSA, and the concentration of the lipid mediator is positively correlated with the severity of OSA. Systemic inflammation: Obstructive SDB is associated with cardiovascular disease in adults, and elevated hsCRP levels have been proposed as a link between the 2 disorders. Tauman and colleagues were the first to report on increases in plasma hsCRP levels among American children with SDB. Subsequently, a group from Greece reported that hsCRP levels are not significantly increased in children with SDB. Larkin and associates approached 143 adolescents and showed that hsCRP levels (adjusted to BMI) demonstrated a dose response with SDB above a threshold apnea hypopnea index of 5 theorizing that pediatric SDB may confer additional cardiovascular risk beyond that of obesity. The conflicting issue of obesity among children with SDB was addressed by Tauman who examined 244 children and found that children with SDB displayed increases in plasma hsCRP and IL-6 levels independent of obesity. The differences found among the diverse groups of children assessed in several pediatric sleep centers raises the question of confounders that may alter the levels of hsCRP independent of SDB. The “key suspects” are genetic (Greek vs American), or environmental causes like diet (Mediterranean vs western high-fat/high-carbohydrate) or physical activity that can also affect hsCRP.

Inflammatory biomarkers: Several investigators have tried to assess other inflammatory measures in children with SDB. IL-6 levels were reported higher and IL-10 levels were lower in children with OSA, indicating systemic inflammation as a constitutive component and a consequence of OSA in many children, even in the absence of obesity. Similar to the reported elevations of leukotrienes in adenoids, tonsils, and exhaled condensates, LTB4 and Cys LT circulating levels are also elevated in children with SDB compared with controls decreasing following adenotonsillectomy. The over-expression of Cys LT1 receptor, is found also on circulating neutrophils drawn from children with SDB. There are significant decreases in the levels of hsCRP three months after surgery that correlate with the reduction in the severity of apnea after adenotonsillectomy. Kaditis and associates showed that Urine excretion of CysLTs is related to SDB severity in children, suggesting that SDB promotes CysLTs biosynthesis.

Inflammation, morbidity and the role of obesity: Several pediatric studies were able to link inflammation to morbidity. Circulating hsCRP levels were higher in children with OSA, particularly in those who developed neurocognitive deficits, suggesting that the inflammatory responses can increase the risk for neurocognitive dysfunction. Echocardiographic documentation of increased pulmonary pressure in young children with OSA are related to nocturnal hypoxemia and systemic inflammation, which also decrease (per echo) following adenotonsillectomy. Endothelial dysfunction is highly prevalent in children with SDB, correlating with systemic inflammation, and may persist, particularly in the context of high genetic background risk for cardiovascular disease. Taurine suppression of the morning plasma concentrations of CRP appeared in children with OSAS, and appear to be proportionate to the severity of daytime sleepiness. Obesity prevalence continues to increase in children. One of the conditions whose prevalence is increased by obesity in children is OSA. OSA in non-obese children recruits similar inflammatory mechanisms as those activated by obesity, and synergistically augment the degree of their respective unfavorable consequences. Obesity also may affect the outcome of surgery in OSA. A recent study showed that obesity and apnea hypopnea index at diagnosis are the major determinants for surgical outcome.

Anti-inflammatory therapy: Although steroids are considered one of the most potent anti-inflammatory drugs, not all children respond to them. For example, fewer than 10% of patients with asthma do not respond to steroids. Indeed, although reduced ligand binding to corticosteroids or defects in glucocorticoid receptor translocation to the nucleus and binding to the glucocorticoid-binding response element can explain some cases of corticosteroid-resistant asthma, altered relations in the expression of the 2 human isoforms of glucocorticoid receptors (GCR), GCRα and GCRβ, in lung tissue have emerged as the most likely and major determinants of corticosteroid insensitivity. A study looking at the the 2 human isoforms of glucocorticoid receptors (GCR), GCRα and GCRβ, found that they are expressed in pediatric adenotonsillar tissue, and more abundant in OSA patients. These findings along with the high GCRα/GCRβ ratio suggest a favorable profile for topical steroid therapy in SDB. A short course of systemic prednisone was ineffective in treating SDB. Intranasal fluticasone, given for 6 weeks, assessed in a randomized, placebo-controlled, trial in 25 children, decreased the frequency of obstructive apneas, but not the parent symptom score. Four weeks’ open study of nasal budesonide improved both polysomnographic parameters and symptoms in children with mild SDB. The authors reported continued clinical effect for several months. Intranasal budesonide for 6 weeks improved polysomnographic and radiographic parameters, with the effect persisting for at least 8 more weeks.

An open study with montelukast, a Cys LT1-R antagonist, showed significant improvement in respiratory and EEG polysomnographic parameters, as well as reduction in adenoid size. Twenty-four children started and completed a 16-week course, in contrast to 20 children who were not offered the drug. Effects of montelukast on SDB were assessed also in a double blind placebo controlled fashion. All the 30 children completed the study. Montelukast treatment resulted in a significant reduction of Apnea Index, as well as in adenoid size. In contrast, children who received placebo displayed no significant changes in the same measures after the 12-week period. Sleep complaints (per validated questionnaire) improved significantly in the montelukast group in contrast with placebo.

The effect of a combined anti-inflammatory approach in children with residual SDB after surgical treatment was studied in twenty-two children. They were offered intranasal budesonide and oral montelukast after surgery. In contrast to 14 children who were not offered the medications, there was a significant difference in the polysomnographic and radiographic measures up to 4 months after surgery, suggesting a new approach for residual SDB after adenotonsillectomy.

Unsolved questions: Currently, there is not enough data to conclude whether the inflammatory mechanisms are a component of the cause of this syndrome or its consequence. Also, larger well-controlled prospective studies with anti-inflammatory medications are needed before any recommendations can be made. Finally, information regarding the effects of therapy on long-term sequel remains to be elucidated and deserves further investigation.

References
[4] Gozal D, Capdevila OS, Kheirandish-Gozal L. Metabolic alterations and systemic inflammation in obstructive sleep apnea among nonobese and...

II.5 RSV and asthma: the chicken or the egg?

T.V. Hartert. Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Center for Asthma & Environmental Sciences Research, 6107 MCE, Nashville, TN 37222–8300, USA. Phone: +1 615 322 3412; fax: +1 615 936 1269. E-mail: tina.hartert@vanderbilt.edu

Correspondence: Tina V. Hartert, M.D., M.P.H. Division of Allergy, Pulmonary and Critical Care Medicine, Center for Asthma & Environmental Sciences Research, 6107 MCE, Vanderbilt University School of Medicine, Nashville, TN 37222–8300, USA. Phone: +1 615 322 3412; fax: +1 615 936 1269. E-mail: tina.hartert@vanderbilt.edu

Keywords: Respiratory syncytial virus, lower respiratory tract infection, bronchiolitis, asthma, recurrent wheezing

RSV and asthma: the chicken or the egg?

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections (LRTIs) during infancy, and almost all children have been infected at least once by age 2 years. By age 2, almost all children have been infected with RSV and most have been infected twice. The initial RSV infection is usually the most severe, causing bronchiolitis, in 20–30% of infants. However, for reasons that are not fully understood, the immune response to RSV is incomplete and reinfection with RSV occurs throughout the life.

There are well-established links between RSV illness and asthma. First, it is well established that among infants who require hospitalization for RSV bronchiolitis, as many as 20–40% in various studies develop asthma by age 13 years. Second, viral infections are the most frequent and important cause of asthma exacerbations in children, implicated in up to 85% of disease exacerbations. While these data convincingly demonstrate that infants who develop viral-associated bronchiolitis have a high risk of developing asthma, and animal studies demonstrate biologically plausible mechanisms through which RSV may contribute to asthma, these studies cannot answer the question of whether RSV contributed to asthma inception or was merely the first manifestation of reactive airway disease in a genetically predisposed child. The aims of this overview are to review the evidence of the relationship between RSV infection and subsequent asthma.

Studies of the influence of RSV infection on the risk and severity of childhood asthma: The occurrence of recurrent wheezing after RSV LRTI has been recognized for decades. We and others have demonstrated that children hospitalized for RSV bronchiolitis during infancy are more likely to have subsequent episodes of wheezing and asthma during the first decade of life compared with children without a history of a bronchiolitis hospitalization during infancy [1–7]. Whether this risk persists throughout adolescence and into adult life is less clear, as longitudinal studies suffer from significant patient drop-out. Those studies which follow children longitudinally past 10 years suggest that RSV may no longer be significantly associated with asthma risk. The association of increased asthma risk among infants with RSV LRTI during infancy is consistent in most studies, and most pronounced during the first 6 years of life. Two ongoing longitudinal studies of infants with RSV bronchiolitis suggest that RSV infection does increase the risk of wheezing and later childhood asthma [1,2]. Sigurs and colleagues reported an increased prevalence of asthma or recurrent wheezing and allergic sensitization in children with RSV bronchiolitis at multiple timepoints, including at age 18, where 39% of the children who had suffered from RSV bronchiolitis in infancy were documented to have asthma or recurrent wheezing compared to only 9% in the control group. Somewhat different results were obtained in the Tucson Children’s Respiratory Study which prospectively enrolled 1246 infants born between 1980 to 1984 [1]. In this study, LRTI with confirmed RSV infection was associated with increased risks of infrequent and frequent wheezing at age 6, but the risk was reduced as children became older, and was not statistically significant by age 13 years. Taken together, these studies demonstrate that severe RSV bronchiolitis is associated with a 30 to 40% increased risk of subsequent asthma, at least within the first decade of life. The difference in asthma risk after the first decade of life between the two studies might be simply due to the differences in the populations studied, as well as the severity of infant RSV infection between the two groups. Recently, follow up of the children at age 22 years in the Tucson Children’s Respiratory Study has been reported. Asthma at age 22 years has been found to be associated with recurrent wheezing at age 6 years [7]. Although the relationship between RSV infection in early childhood and later asthma development was not significant at age 13 years in this cohort of children, a revisit of the association of asthma at age 22 years with RSV infection during early childhood will provide insights into the importance of this early life event.

The causal relationship of RSV infection on the development of wheezing and asthma: Is the increased association of asthma following RSV infection an epiphenomenon due to enhanced airway inflammation and injury among those genetically predisposed to develop asthma, or does RSV alter the host defense, lung and/or immunity and truly cause asthma? A few recent studies have been aimed to address this question. We identified a dose-dependent relationship between increasing infant bronchiolitis severity and both increased asthma risk and increased asthma severity among a population-based cohort of children covered under a US state-based health insurance plan, the TABS (Tennessee Asthma & Bronchiolitis Study) cohort [4,8]. This has been replicated using data from a managed care organization by Escobar and colleagues [6]. In the TABS study, we specifically evaluated the causal role of winter viral respiratory epidemics in the development of asthma among nearly 100,000 infants in a retrospective birth cohort [8]. We did this by investigating the relationship between infant age at the first winter viral peak following birth and subsequent asthma risk during the fifth to sixth year of life. Infants who were 4 months old at the peak of winter viral season were more likely to develop both clinical bronchiolitis and childhood asthma. Despite the winter viral peak shifting by nearly two months over the six winter viral seasons studied, the risk of asthma shifted in any given year with the shift in the peak of the winter viral peak such that infants born approximately 4 months prior to the first winter viral peak they encountered following birth were at the highest risk of developing childhood asthma. This strongly suggests a causal role of early RSV infection on asthma development. Three additional studies provide evidence, however, to dispute RSV causality. In a population based study among Denmark twins [9], Thomsen and colleagues fitted genetic variance components and direction of causation models to over 8,000 twin pairs [9]. A model in which RSV hospitalization causes asthma was rejected, whereas one in which asthma causes RSV hospitalization was not. In another attempt to detect the causality between RSV and asthma, Stensballe and colleagues reported that the effect of RSV hospitalization on asthma was only short term (2 months after RSV hospitalization) and no longer significant 1 year later [10]. Lastly, a study of 37 monozygotic twin pairs discordant for severe RSV bronchiolitis in infancy indicated no differential effect of severity of RSV infection on subsequent asthma development. These studies utilized RSV bronchiolitis information from patient registries. Twins who were discordant for RSV hospitalization were highly likely to be discordant for RSV infection given the known high infectivity. Therefore, any conclusion about causality suffers from the misclassification of twins not hospitalized with RSV infection to an unaffected group. In addition, asthma was defined at an early age in two of the three twin studies. Children were considered as having asthma as early as infancy or by age 3 years,


T.V. Hartert.
which may well reflect children with “transient early wheezing” but not asthma.

The impact of prevention or treatment of RSV on asthma risk:
Ultimately to address the question of whether RSV infection during infancy causes asthma, showing that prevention or delay in infant infection prevents asthma will be necessary. There is very limited data, in the form of two small studies, which suggest that RSV immunoprophylaxis may lower the likelihood for the development of asthma. The first is a small investigation of 13 children identified retrospectively as having received RSV immunoprophylaxis, showing that receipt of RSV immunoprophylaxis during infancy may have long-term effects on respiratory and immunologic parameters relevant to the development of asthma [12]. The second study is an industry-sponsored investigation of open-label compassionate-use RSV immunoprophylaxis among a European cohort of preterm infants showing decreased wheezing outcomes among infants receiving immunoprophylaxis. There are substantial limitations to the design and selection of subjects, including use of RSV immunoprophylaxis on a compassionate use basis with no delineated indications nor standard recommendations for use in each child [13]. In addition, the age of the children in this investigation at follow-up was only 19–43 months. Lastly, an open-label study assessing the impact of treating (not preventing) active RSV bronchiolitis with the antiviral agent ribavirin showed a reduction of the risk of asthma and allergic sensitization at age 6 years among children 2 years and less who did and did not receive ribavirin for RSV bronchiolitis [14]. This study also has limitations, in that those who did and did not receive ribavirin differed significantly in age of RSV bronchiolitis, prematureity and disease severity.

Summary: To summarize the evidence in support of a role of RSV in asthma causation there is: (1) Ecological evidence of increasing rates of infant bronchiolitis in the last ten years mirroring the 5-year offset increases in asthma at age 5 years among these same children; (2) Dose–response relationship with a positive severity-dependent association with both asthma risk and asthma morbidity; (3) Known common host immune factors for both diseases, with persons with asthma known to be at increased risk for viral infections and invasive bacterial infections; (4) Genetic evidence with genes predisposing to asthma also linked to susceptibility and severity of RSV infection; and lastly (5) Causal evidence with demonstration for the first time that timing of birth in relationship to when RSV circulates independently predicts asthma development, with birth timing conferring a nearly 30% increase in risk of early childhood asthma. Ultimately, however, showing that prevention or delay in infant infection prevents asthma will definitively answer the question of whether RSV causes asthma, and potentially provide an important primary asthma prevention strategy.

References

III. Obstructive Lung Disease

III.1. Obstructive Lung Disease – Where genome meets environment

III.1.1 The clinical relevance of asthma genetics
F. Martinez. Regents’ Professor, Director, BIOS Institute, Director, Arizona Respiratory Center, Swift-McNear Professor of Pediatrics, University of Arizona, USA

There different approaches have been attempted to elucidate the genetic basis of asthma and other complex diseases. Initially, most studies consisted of assessment of association between polymorphisms in candidate genes and asthma and asthma-related traits. These studies provided replicated evidence for association in many different genes [1]. Simultaneously, other studies applied a second approach, namely, linkage analysis between asthma and highly polymorphic markers distributed in a roughly uniform way in the genome. Although these latter studies yielded some promising results [2], they proved relatively insensitive to identifying areas of
the genome in which there was clear evidence of the presence of asthma-related genetic variation. During the last 5 years, the advent of a third phase was received with great enthusiasm by the scientific community. The availability of hundreds of thousands of single nucleotide polymorphisms distributed in all human chromosomes opened the possibility to assess direct associations between these markers (and implicitly those in linkage disequilibrium with them) and asthma. As a result of these major technical advances, a number of major genome-wide association studies (GWAS) of asthma have been published [3]. These studies have identified several new genes with polymorphisms that are associated with asthma in a highly replicable manner, but still, only a small fraction of the genetic variance of asthma is explained by these GWAS-discovered polymorphisms. With few exceptions (e.g., IL-13), these studies have been unable to replicate most of the associations reported in candidate genes during the first phase. Moreover, most of the genetic variants associated with asthma are very common in the population, and their sensitivity and specificity are too low to allow their use in clinical practice to predict asthma risk.

Of great interest to the practicing clinician would also be genetic variants associated with response to therapy, and there have been advances in this area as well, with polymorphisms having been identified that predict response to inhaled corticosteroids. Unfortunately, the previously reported associations between the Arg/Cly locus in the beta-2-adrenergic gene and response to short-acting and long-acting beta-agonists have been replicated with variable success and are not likely to provide clinically important information.

All in all, identified associations between asthma and common genetic polymorphisms have increased our understanding of the biological mechanisms involved in asthma pathogenesis, but have yet to provide us with new tools for asthma diagnosis or personalized treatment.

References


III.1.3

Before the first breath is taken: the role of in utero environment

A. Custovic. University of Manchester, UK

In order to understand the development of asthma and propose strategies for primary prevention, it is essential to establish when and how the initial imprinting on the immune system occurs. It can be argued that in utero period may be the critical period in developmental programming. There is mounting evidence that environmental exposures during this period may have important influence on evolving function. It has been suggested that initial priming of the T cell system to environmental allergens may occur before birth, and a series of immunoproliferation studies reported differential stimulation of CBMC by mitogens and a variety of allergens. However, subsequent studies have demonstrated that the magnitude of immunoproliferative responses cannot be used as evidence for in utero sensitisation to inhalant allergens, but may suggest that there are differences at birth between neonates with and without family, possibly caused by genetic differences. Although twin studies provide clear evidence of a genetic component underlying the development of asthma, genetic studies have produced heterogeneous results with little replication [1]. Heritable changes in gene expression that occur in the absence of alterations in DNA sequence (epigenetics) may partially explain some of the inherited component of asthma. Epigenetic modifications are transmitted from one cell generation to the next [2] and can be inherited through the germ line [3]. Interestingly, children have an increased risk of asthma if their grandmother smoked during their mother’s foetal period, and the risk is even greater if both the grandmother and mother smoked during pregnancy [4], providing an example of an environmental exposure affecting the asthma epigenome. There has been substantial progress in
understanding the epigenetic mechanisms through which in utero environmental exposures can alter gene expression. Environmental exposures relevant to asthma development (e.g. microbial exposure, diet, tobacco smoke etc) can induce epigenetic changes in gene expression and alter disease risk, which may in part explain the environment-driven epidemic of asthma [5].

References

III.2. Obstructive Lung Disease – Pro/Con debate: immunotherapy for asthma

III.2.1 Immunotherapy for asthma – Pro

D.P. Skoner. Director, Division of Allergy, Asthma & Immunology, Department of Pediatrics, Allegheny General Hospital, Pittsburgh, Pennsylvania Professor of Pediatrics, Drexel University College of Medicine, West Virginia University School of Medicine, USA Correspondence: E-mail: dskoner@wpahs.org

Introduction: The guidelines from the second National Heart, Lung, and Blood Institute (NHLBI) recommend that all asthma patients who require daily therapy be evaluated for allergens as possible contributing factors. Testing can be used as the basis for recommendations on allergen avoidance or to support treatment with specific immunotherapy. In the case of suspected Aeroallergens, panels usually include approximately 40 antigens. Antigens should be selected on the basis of history and regional differences (Li 2002).

The understanding of asthma pathogenesis has evolved dramatically in the past 25 years, and research is continuing on links between clinical features of disease and biologic patterns. A complex interplay between host factors (e.g. genetics) and environmental exposures occurring at crucial times in immune system development is thought to be responsible for the development of asthma (NHLBI EPR-3, 2007). Environmental factors that can contribute to asthma include the following: (1) allergens such as dog dander, cat epithelia, mold (Alternaria), cockroaches, and house dust mite species; (2) viral respiratory infections (including respiratory syncytial virus, parainfluenza virus, and rhinovirus); and (3) inhaled irritants (tobacco smoke, air pollution, and occupational sensitizers).

Atopy, the genetic predisposition for the development of an immunoglobulin E (IgE)-mediated response to common Aeroallergens, is the strongest identifiable predisposing factor for developing asthma. Viral respiratory infections are one of the most important causes of asthma exacerbation and may also contribute to the development of asthma. The importance of IgE antibody in asthma: The IgE-mediated inflammatory cascade is a key underlying component of allergic asthma (NHLBI EPR-3, 2007). In IgE-mediated asthma, antigens can trigger asthma symptoms. Antigens are presented to cells involved in the immune response.

In response to antigen stimulation, B lymphocytes differentiate into plasma cells (the epsilon switch), which produce and release IgE antibodies into the blood (Storms 2002).

IgE circulates in the blood, eventually binding to high-affinity IgE receptors (FcεRI) on the surface of mast cells in tissue or peripheral-blood basophils. When the subject subsequently reencounters the offending allergen, binding of the allergen with IgE induces the release of inflammatory mediators, leading to the bronchoconstriction characteristic of an exacerbation (MacGlashan 1997). IgE is a key underlying component of asthma in many asthma patients.

Data from several population-based studies indicate that the overall geometric mean levels of IgE in the general population range from 200IU/mL to 400IU/mL, with variation according to age, sex, and geographic distribution (Burrows 1989 and Dolan 2002). Burrows (1989) investigated the relationship between IgE levels and the risk of developing asthma. In this study, it was noted that the risk of asthma increases as total serum IgE concentration increases. A study investigated the association of self-reported asthma and serum IgE levels in a general population. These data are from a stratified cluster sample of 2657 patients from white non-Mexican-American households in which the association of self-reported asthma with serum IgE levels and skin-test reactivity to allergens was investigated. Blood samples were obtained from subjects aged 26 years, and serum IgE levels were measured. The authors noted that regardless of the patients’ allergy status or age group, the prevalence of asthma was closely related to the serum IgE level (P < 0.0001). At 7 levels of total IgE concentrations, after correction for age, sex, smoking habits, and skin-test index in a logistic analysis, the odds ratio of having asthma increases linearly with the serum IgE level.

Several studies have examined the importance of cockroach allergens in patients with asthma. A cohort study of elderly nonsmokers with asthma aged 260 years demonstrated that the presence of cockroach-specific serum IgE was associated with more severe asthma, as reflected by an increase in airway obstruction and hyperinflation (Rogers 2002). In another study conducted in inner cities, 50% of inner-city bedrooms had high levels of allergens (Rosenreich 1997), 41% were exposed to high allergens and skin test positive, and black race and low socioeconomic status were independently associated with cockroach reactivity (Sarpong 1996). High allergen levels, in those IgE-sensitized, were associated with more days of wheezing, 3-fold increase in hospitalizations, and 78% more visits for asthma.

Some studies have examined the possibly synergism between allergens and viruses in asthma exacerbations. Children who were admitted to the hospital with an acute exacerbation of asthma were tested for allergic sensitization (skin prick test, total & specific IgE levels), allergen exposure (home – hoover lounge & bedroom, mold, carpet/forage, sex, smoking habits, and skin-test index in a logistic analysis, the odds ratio for asthma admission was highest for the group that was sensitized, and exposed, and infected with a virus (Murray 2005).

Reduction of environmental allergen levels in asthma: Other studies have determined if allergen avoidance can affect asthma outcomes. Van der Heide et al. (1997) studied air-cleaners with respect to their capacity to capture airborne allergen particles and to determine clinical and biologic effects of asthma and aeroallergens over six months in 45 patients with allergic asthma. The study groups were as follows: 1) Group 1, the intervention consisted of the application of active air-cleaners in living rooms and bedrooms; 2) Group 2, placebo air-cleaners were used in combination with allergen-impermeable mattress covers; and 3) Group 3, the same intervention was performed as in Group 2 but with active air-cleaners. In patients in whom both active air-cleaners and mattress covers were used, there was a small (less
than 1 doubling dose) but statistically significant improvement of provocative concentration of histamine causing a 20% fall in forced expiratory volume in one second (PC20) observed (from 5.96 mg to 9.02 mg/mL). Also, the amount of dust and house dust mite allergen collected in the filters was significantly correlated with an improvement of peak flow variation.

In another study, Morgan et al (2004) evaluated 937 children, aged 5 to 11 years, with atopic asthma in a 1-year, randomized, controlled trial of home-based, environmental intervention. Interventions consisted of education and remediation for exposure to both allergens and environmental tobacco smoke. For every 2-week period, the intervention group had fewer days with symptoms than those in the control group both during the intervention year (3.39 vs 4.20 days, \(P < 0.001\)) and the year afterward (2.62 vs 3.21 days, \(P < 0.001\)). They also had greater declines in the levels of allergens at home (eg, dust mites and cockroach) on the bedroom floor (\(P < 0.001\)): a finding that was correlated with decreased asthma-related complications (\(P < 0.001\)).

**IgE-based immunotherapy in allergy and asthma:** Immune-based therapies have also been tested in patients with asthma. Durham et al (1999) conducted a randomized, double-blind, placebo-controlled trial of the discontinuation of immunotherapy for grass-pollen allergy in patients in whom 3 to 4 years of this treatment had previously been shown to be effective. Scores for seasonal symptoms and the use of rescue antiallergic medication, which included short courses of prednisolone, remained low after the discontinuation of immunotherapy, and there was no significant difference between patients who continued immunotherapy and those who discontinued it. The authors concluded that immunotherapy for grass-pollen allergy for 3 to 4 years induced prolonged clinical remission accompanied by a persistent alteration in immunologic reactivity.

A humanized, monoclonal anti-IgE antibody (omalizumab) has also been extensively tested in patients with more severe asthma in randomized, double-blind, placebo-controlled trials. The study designs for two pivotal studies (Busse 2001, Solèr 2001) included four phases: 1) **Run-in phase:** On entry into the study, patients were switched from their currently prescribed inhaled corticosteroid (ICS) to an equivalent dose of BDP. After 2 weeks, the dose of BDP was adjusted to maintain previous asthma control. A stable BDP dose was maintained for 4 weeks before randomization. A mean total symptom score during the last 2 weeks of the run-in period of \(\geq 3\) was required for eligibility for randomization; 2) **Steroid-stable phase:** Patients were randomized to receive either placebo or omalizumab by subcutaneous injection. The baseline BDP dose was maintained during the 16-week steroid-stable phase; 3) **Steroid-reduction phase:** During the 12-week steroid-reduction phase, the dose of BDP was reduced by approximately 25% every 2 weeks until it was totally eliminated or asthma symptoms worsened. If symptoms worsened, BDP was increased by \(\geq 25\%\). For the final 4 weeks of this phase, each patient was maintained on the lowest effective dose of BDP that did not result in worsening of symptoms; and 4) **Extension phase:** In the 24-week extension phase, treatment options were more relaxed. Twelve weeks of follow-up ended the study. The study was blinded for 1 year. Blinding in extension allows one to examine the durability of benefit (Lanier 2003)

Fewer patients receiving omalizumab + inhaled corticosteroids (ICS) experienced exacerbations in both the steroid-stable and steroid-reduction phases of both studies. Reductions in exacerbations were not seen in patients who had FEV1 of \(\geq 80\%\) at the time of randomization or in patients who required oral steroids as maintenance therapy. An asthma exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the patient’s baseline BDP dose. In the pooled data from the two studies, omalizumab + BDP was associated with a significant reduction in the mean number of exacerbations that required a systemic steroid burst per patient versus placebo + BDP. Moreover, omalizumab improved total asthma symptom scores, daytime symptom scores, and nighttime symptom scores compared with placebo in the steroid-stable and steroid-reduction phases in both studies (\(P \leq 0.05\)). Improvement was seen beginning at week 4 of treatment, and was observed throughout the remainder of the study period.

In a 6-week, randomized, double-blind, placebo-controlled study of 24 rhinitis patients with ragweed allergy (Lin 2004), omalizumab caused a significant decrease in basophil FceRI expression at all time points compared to baseline (\(P < 0.001\)) and compared to placebo treatment (\(P < 0.001\)). Maximum inhibition of FceRI expression occurred within 14 days of omalizumab treatment and was maintained for the duration of the study. No significant changes in FceRI expression were found in the placebo group at any time point.

In a randomized, double-blind, placebo-controlled study (Fahy 1997), sputum was collected over a 24-hour period both before and after antigen challenge in 19 allergic asthmatic patients. Omalizumab significantly reduced the percentage of eosinophils (a marker of inflammation) in induced sputum after 9 weeks of treatment, as compared with baseline (pretreatment) levels (\(P = 0.02\)). This reduction in sputum eosinophils was seen both before and after antigen challenge. The placebo group was not significantly different either before or after antigen challenge compared with baseline.

Collectively, these studies have led to the following statement in the NHLBI EPR-3 guideline (NHLBI EPR-3, 2007): “The development of monoclonal antibodies against IgE has shown that reduction of IgE is effective in asthma treatment. These clinical observations further support the importance of IgE to asthma.”

A large number of other immunotherapy trials have also been conducted. In 2 large retrospective studies (Pajno 2001 and Purello-D’Ambroso 2001), subcutaneous immunotherapy appeared to prevent the onset of new atopic sensitizations as determined by skin prick testing. In a large randomized, controlled, but not blind study of SCIT (the Preventative Allergy Treatment study), pollen immunotherapy reduced the risk of the onset of asthma in children who had allergic rhinitis and no asthma (Moller 2002). This preventive effect was observed to persist in the same patients for 2 years after the termination of SCIT (Niggemann 2006).

There is also evidence for disease modification when allergen immunotherapy is delivered subcutaneously. However, until recently, such evidence has been lacking for SLIT. Durham et al (2010) investigated the sustainability of efficacy one year after a 3-year period of daily treatment with the SQ-standardized grass allergy immunotherapy tablet Grazax (Phleum pratense 75,000 SQ-T/2,800 BAU). They conducted a randomized, double-blind, placebo-controlled, phase III trial including adults with a history of moderate-to-severe grass pollen induced rhinoconjunctivitis that was inadequately controlled by symptomatic medication use. The results for 257 subjects at follow-up were analyzed. As expected based on the results of previous studies, significant improvements in efficacy were consistently shown during 3 years’ of active treatment. One year after treatment ended, the active treatment group showed sustained reductions in mean rhinoconjunctivitis symptom scores (26%, \(P < 0.001\)) and medication scores (29%, \(P = 0.022\)) when compared with placebo. These levels of efficacy were similar to those observed during the 3-year treatment period. Likewise, the differences in percentages of symptom- and medication-free days were significant during the 3-year period and one year after treatment. Moreover, the active group also reported sustained and significant improvements in quality of life. Immunologic changes paralleled the clinical changes. Importantly, no safety issues were identified. The authors concluded that the three years of treatment with the SQ-standardized grass allergy immunotherapy tablet resulted in consistent clinical improvement and immunologic changes that were sustained for one year after treatment was stopped, which is consistent with disease modification and associated long-term benefits.
Most of the previous sublingual specific immunotherapy (SLIT) studies were conducted in Europe and only a few controlled trials were conducted in the United States. Thus, experience using SLIT in North American populations was very limited until the recent conduct of a ragweed trial, and subsequently, two grass trials, one in children and one in adults. Both of the latter studies used a Timothy grass allergy immunotherapy tablet. Importantly, Timothy grass is cross-reactive with Festuca species, including rye, meadow fescue, bluegrass/junie, orchard/cocksfoot, redtop/bent/velvet, and sweet vernal.

In the ragweed SLIT trial, Skoner et al. (2010), conducted a randomized, double-blind, placebo-controlled trial to identify a safe and effective maintenance dose range of sublingual standardized glycerinated short ragweed pollen extract in adults with ragweed-induced rhinoconjunctivitis. Patients (n=115) with ragweed-induced rhinoconjunctivitis were randomized to placebo (n=40), medium-dose extract (4.8 mcg Amb a 1/d; n=39), or high-dose extract (48 mcg Amb a 1/d; n=36). Subjects were administered a 1-day (rush) dose-escalation regimen in May of 2006 with placebo or ragweed pollen extract in incremental doses until the maximum tolerable or scheduled dose was reached. Daily dosing was then maintained during the fall ragweed pollen season (August to October). Patient diaries were used to monitor nasal and ocular symptoms and medication use, and the primary endpoint was symptom score. Thirty-two of 40 subjects (80%) in the placebo group, 27 of 39 (69%) in the middle-dose group, and 23 of 36 (64%) in the high-dose group tolerated the maximum scheduled dose. The average cumulative dose administered through the entire treatment course was 498±185 mcg Amb a 1/mL in the medium-dose group and 494±1487 mcg Amb a 1/mL in the high-dose group. The mean maximal tolerable dose was estimated to be 3.21 (±1.64) and 30.54 (±16.14) mcg Amb a 1 in the medium-dose- and high-dose groups, respectively. A 15% reduction in the total rhinoconjunctivitis symptom score was observed in both active treatment groups compared with placebo during the entire ragweed pollen season, but the difference was not statistically significant (p>0.10). However, an analysis of covariance which corrected for pre-seasonal symptoms found that both mean daily symptom scores (0.19±1.16 vs 1.00±2.30) and medication scores (0.0003±1.64 vs 0.63±1.06) for the entire pollen season were significantly reduced in the high-dose versus placebo groups, respectively (p<0.05). In addition to improvement in these clinical outcomes, immunologic changes were also observed. Ragweed-specific IgG, IgG4, and IgA antibodies were increased after treatment in the medium- and high-dose groups, but not in the placebo group. Safety was carefully evaluated in this study as well. The frequency of adverse events was similar between the placebo and active treatment groups, but oral-mucosal adverse events occurred more often with active treatment. A total of 202 adverse events (placebo, n=67; medium-dose, n=65; high-dose, n=70) were reported, with frequency ranging from 56% in the high-dose group to 73% in the placebo group. Thirteen of the 202 events (6%) were classified as severe, 4 events (2%) were considered serious, and 1 additional event was considered life-threatening. Three of the 13 severe events were reported by 2 subjects in the placebo group, and 10 of the severe events were reported by 6 subjects in the active treatment groups. The 4 serious events occurred in 1 subject in the placebo group (gall bladder surgery), 1 subject in the medium-dose treatment group (life-threatening blood clot in the leg), and 1 subject in the high-dose treatment group (spontaneous abortion, n=1; sigmoid diverticulitis, n=1). No asthma-related events occurred. Oral-mucosal events occurred more often with medium-dose (13%) and high-dose (11%) treatment than with placebo (0%; P=0.01).

This study showed that standardized glycerinated short ragweed pollen extract administered sublingually at maintenance doses of 4.8 to 48 microg Amb a 1/day was safe and induced favorable clinical and immunologic changes in ragweed-sensitive subjects. However, the study did fail to meet its primary endpoint, showing that additional trials will be needed to establish efficacy.

In the first grass SLIT study, Blaiss et al (2011) investigated the efficacy and safety of Timothy grass allergy immunotherapy tablets (grass AIT) in North American children with grass pollen-induced allergic rhinoconjunctivitis with or without asthma. In that study, 345 subjects (5–17 years) were randomized to receive once-daily grass AIT (2800 bioequivalent-allergen-units [BAU], 75,000 SQ-T, –15 ug Phl p 5) or placebo beginning ~16 weeks before the 2009 grass pollen season and continuing intra-seasonally. The majority of subjects (89%) were multisensitized. The primary endpoint, which was the total combined score (TCS) of the daily symptom score (DSS) and daily medication score (DMS) for the entire grass pollen season (assessed via e-diary), improved in the grass AIT group by 26% (P=0.001) versus placebo. Furthermore, the DSS, DMS, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores versus placebo improved by 25% (P=0.005), 81% (P=0.006), and 18% (P=0.04), respectively. Furthermore, itchy and watery eye symptoms individually improved by 28% in the grass AIT group relative to placebo for a combined average improvement of 28% (P=0.003). In parallel, the eye symptom RQLQ domain score significantly improved in the grass AIT group by 29% relative to placebo (P=0.005). Adverse events were largely local, mild and transient. No investigator-assessed systemic allergic reactions were reported, but one grass AIT-treated subject experienced an event indicating a systemic reaction (lip angioedema, dysphagia, and cough). The authors concluded that once-daily Timothy grass AIT effectively treats Timothy grass pollen-induced allergic rhinoconjunctivitis in predominantly multisensitized North American children.

The second grass SLIT study was similar to the study conducted in children, but instead enrolled adults. Nelson et al (2011) investigated the efficacy and safety a grass allergy immunotherapy tablet (AIT) (oral lypophilisate, Phleum pratense, 2800 BAU) in allergic rhinoconjunctivitis patients with or without asthma. In that study, 439 adults with Timothy grass pollen-induced allergic rhinoconjunctivitis were randomized to once-daily grass AIT or placebo beginning approximately 16 weeks before and continuing through the 2009 grass pollen season. Similar to the study in children, the majority of subjects (85%) were multisensitized. The primary endpoint, which was the total combined score (TCS) of the daily symptom score (DSS) and daily medication score (DMS) for the entire grass pollen season (assessed via e-diary), improved by 20% in the grass AIT group compared with the placebo group (P=0.005). Likewise and similar to the study performed in children, there were there were improvements in the AIT group relative to placebo for the DSS (18%, P=0.02), DMS (26%, P=0.08) and RQLQ (17%, P=0.02). Furthermore, itchy and watery eye symptoms were improved in the grass AIT group by 20% and 35%, respectively, for an average improvement of 26% relative to placebo (P<0.001). The eye symptom RQLQ domain score was improved in the grass AIT group by 21% relative to placebo (P=0.01). The majority of adverse events were mild local reactions that were transient, with no treatment-related serious adverse events in active subjects, one treatment-related serious adverse event in a placebo subject, and no reports of anaphylactic shock. The authors concluded that grass AIT was effective and well-tolerated in a predominantly multisensitized North American adult population with Timothy grass pollen-induced allergic rhinoconjunctivitis.

The conduct of two grass SLIT trials conducted in children and adults was also carefully evaluated. The most common treatment-emergent adverse events (TEAEs) were oral pruritus, throat irritation, and nasopharyngitis in the pediatric study, while they were oral pruritus, throat irritation, and upper respiratory tract infection in the adult study. The TEAEs asthma and urticaria were rare (≤4%). Treatment-related adverse events (TRAEs) were reported by 122/175 (70%) of AIT subjects and 43/169 (25%) of placebo subjects in the pediatric study, and by 155/213 (73%) of AIT

Oral Presentations/Paediatric Respiratory Reviews 12S1 (2011) S1–S56
subjects and 62/225 (28%) of placebo subjects in the adult study. The majority of TRAEs were mild or moderate; <2% of subjects had severe TRAEs. Also, the majority of TRAEs were local, application site reactions that began shortly after treatment initiation and were reported for one to two days only. The rate of development of new local application site adverse events diminished with treatment over time. Very few subjects discontinued because of adverse events (pediatric study: AIT=13/175; placebo=5/169; adult study: AIT=11/213, placebo=8/225). One subject from each study received epinephrine in response to an AIT-related reaction (pediatric study: moderate [lip angioedema/dysphagia/cough]; adult study: mild [flush/rash/chest discomfort]) at first dose. One other subject (pediatric study) reported a possible AIT-related systemic reaction (dyspnea, chest discomfort, neck pruritus, racing heart, mouth pain). No serious or life-threatening AIT TRAEs or new safety concerns were reported for either study. The authors concluded that Timothy grass AIT was generally safe and well tolerated in North American adults and children. The incidence and severity of AEs were similar across age groups, which supports use of the same dose of grass AIT in the different age groups. The recent update of the ARIA guideline addressed whether immunotherapy should be used in patients with AR and asthma using evidence-based recommendations (Brozek 2010). In patients with allergic rhinitis and asthma, they suggested subcutaneous specific immunotherapy for treatment of asthma with moderate-quality evidence. They also suggested SLIT for treatment of asthma with low-quality evidence. Both of these recommendations placed a relatively high value on possible reduction of asthma symptoms and a relatively low value on avoiding adverse effects and limiting the cost of specific immunotherapy. Summary: Collectively, the above studies document the importance of IgE antibody in asthma and the improvement in asthma and asthma outcomes by modulation of the levels of environmental allergen or allergen-specific IgE antibody. The safety of subcutaneous and sublingual immunotherapy has been well-documented. Immunotherapy, specifically SLIT, is ideally suited to the treatment of children due to the convenience and avoidance of pain associated with subcutaneous immunotherapy, and opportunities for long-term disease modification. In contrast, current therapies, including inhaled corticosteroids, do not result in long-term disease modification and have undesirable side effects in children such as growth suppression, even at low doses and possibly with an effect on final adult height (CAMP 2000, Guibert 2006, Petrisko 2008, Strunk 2009). Concerning side effects also extend to long-acting beta agonists (severe exacerbations and increase in asthma-related deaths, Chowdhury 2010) and leukotriene receptor antagonists (suicidality, Philips 2009).

References


III.2.2 Immunotherapy for asthma – Con

A. Custovic. University of Manchester, UK

The efficacy of subcutaneous [1] and sublingual [2] immunotherapy in asthma is modest. This form of treatment is appropriate for allergic asthma with mild disease – however, this is the patient group with eosinophilic asthma, who generally responds well to standard anti-inflammatory treatments. Given the efficacy of standard pharmacological treatment and the real risk of adverse effects, the potential small benefits have to be weighed against the side-effects [3]. Not surprisingly British Thoracic Society Guideline on the Management of Asthma does not endorse the use of subcutaneous immunotherapy, and states that “immunotherapy can be considered in patients with asthma where a clinically significant allergen cannot be avoided” [4] but that “the potential for severe allergic reactions to the therapy must be fully discussed with patients” [4]. The BTS guideline is clear about sublingual immunotherapy, stating that “it cannot currently be recommended for the treatment of asthma in routine practice” [4]. It would be important to have evidence to compare the effect of immunotherapy to that of standard pharmacotherapy – unfortunately, such evidence comparing the roles of immunotherapy and pharmacotherapy in the management of asthma is lacking. It has often been stated that immunotherapy offers a possibility to change the natural history of asthma. However, it is important to emphasise that whilst the idea of preventative effect of SIT was suggested by some randomised, controlled (but not placebo controlled) [5] studies, this possible effect is as yet not proven. Thus, more studies are required to establish whether immunotherapy might have a role in primary prophylaxis of asthma [4].

Several different strategies to improve immunotherapy have been evaluated for their safety (e.g. genetically modified hypoallergenic allergen derivatives, recombinant allergens, allergens modified with immunostimulatory DNA sequences composed of unmethylated CpG repeats – allergen/ISS conjugates and peptide immunotherapy) and larger scale-efficacy studies are ongoing. The results of appropriately designed and powered studies are awaited with interest.

References


- Monitoring asthma control and titrating anti-inflammatory therapies (especially ICS).
- Predicting asthma exacerbations.
- Understanding mechanisms (this is a research context and irrelevant to the debate, and will be not discussed further).

It is my contention that although inflammetry may be useful in future, and has been shown to be beneficial in some small, and short term studies, at the moment it has NOT been shown to be useful in a clinical context in children, in terms of showing medium to long term real benefits in children. The mere writing of manuscripts in journals (an addictive practice to which this author is very prone!) is good for individual academics, and may even as a spin-off advance the sum of human knowledge, but is very far from being the same as showing clinical value. This in part relates to the complexities of the problem.

**Inflammetry: the tools:** Inflammation is clearly a complex process. A pro-inflammatory stimulus (allergen, infective agent, pollutant) has to be sensed, and, depending on a number of factors, either or both of the innate and adaptive immune systems react. In terms of airway inflammation, this will involve signals to the bone marrow from respiratory epithelial and dendritic cells, the mobilisation of inflammatory cells (including stimulating division of haemopoietic progenitor cells in the bone marrow) and their trafficking across the endothelium into the airway. So the first issue is to frame the right question: what aspect of inflammation should be measured? For example, a blood measurement may be ideal for looking at signalling to the bone marrow, but very far from relevant to the airway lumen.

Within the airway itself, there may be discordance between mucosal inflammation (endobronchial biopsy) and luminal inflammation (sputum or bronchoalveolar lavage (BAL)) [1], and between proximal and distal inflammation [2]. We do not know which is most important, and it seems very unlikely that a single biomarker can cover all aspects of the inflammatory process. Indeed, given the different compartments and the many different mediators involves, as shown by proteomic and other studies, a reductionist approach to using a single measurement as a window onto complex processes seems naive and almost bound to fail.

Another often forgotten methodological issue is the difference in the requirements between measurements useful for showing differences between groups (and therefore giving a guide to mechanisms) and those which are helpful in monitoring individuals; in the latter, any overlap between individuals with (say) uncontrolled asthma dilutes the value of the measurements, whereas in the former overlap is expected and may not impair the utility of the marker in mechanistic studies. So for example distal nitric oxide (NO) production is affected by asthma control, but the overlap is too great for it to be useful distinguishing between well and poorly controlled individuals [3].

The earliest proof of concept study in adults used measurement of bronchial hyper-responsiveness (BHR) as a surrogate for inflammation [4]. It is now realised that there is only a loose relationship between inflammation and BHR, and also BHR is both time-consuming to measure and not applicable if there is pre-existing severe airflow obstruction, so this parameter will not be considered further.

The characteristics of the ideal inflammmometer are given in the Table. Unfortunately, none such exists. The two most popular non-invasive markers, uncontrolled NO measured at 50 ml/sec (FeNO50) and induced sputum. The performance of both is compared against the ideal in the table.

**Diagnosing asthma:** Asthma is notoriously difficult to diagnose, and as many as a third of physician made diagnoses may be wrong [4]. Untreated asthma may certainly be associated with a raised FeNO50. As is well known, there is no definitive asthma diagnostic test. FeNO50 may have an adjunctive role, along with such tests as spirometry and the acute response to inhaled β-2 agonist, home peak flow monitoring and exercise challenge. The bedrock remains a good history and physical examination, combined with simple physiological measurements and a realisation that even the most distinguished professors may get things wrong and constant re-evaluation of diagnostic possibilities is essential in children with asthma in whom treatment appears not to be working. No paediatric study has shown that measuring FeNO50 or any other inflammatory marker improves the diagnostic process.

**Phenotyping asthma:** Although it has been suggested, and seems logical [5], that differentiating eosinophilic from neutrophilic asthma, and determining if there is discordance between inflammation and symptoms, using combinations of invasive and non-invasive measurements will be useful in clinical management, no study has yet demonstrated that this is the case. Studies on, for example, the use of macrolides to treat neutrophilic asthma have been small and short term, and largely in adults, and cannot be used to support a blanket recommendation in clinical practice. Indeed, what is clear is that much so-called therapy resistant asthma is no such thing, and far more valuable than inflammetry is gweeting the diagnosis and basic management right, including identifying co-morbidities. Even in true bill therapy resistant asthma, far more work, involving international collaboration, is needed before inflammetry can be recommended outside a research context.

**Monitoring asthma control and titrating therapies:** Adult studies have suggested that a treatment strategy which normalises sputum eosinophilia as opposed to titrating the dose of inhaled steroids on symptoms, as is advised by conventional guidelines [6,7]. Furthermore, it has been suggested that asthmatics with persistent sputum eosinophilia are prone to severe exacerbations, which are benefited by the anti-IL5 monoclonal mepolizumab [8,9]. However, in our study of 55 children with really severe asthma, there was only a non-significant trend to benefit from the sputum eosinophil strategy [10]. We did show in a post hoc analysis that the sputum strategy led to a reduction in exacerbations in the month after the (3-monthly) measurements, but this needs confirmation. There are no data on mepolizumab in children. So in summary, more data are needed before a sputum eosinophil strategy can be recommended in children.

An alternative to induced sputum eosinophils is FeNO50? The two correlate best in steroid-naive patients [11]; steroid treatment worsens the relationship. The two cannot be used interchangeably; the relationship varies over time even in the same individual [12]. It is also clear that sputum cellular phenotype changes over time. In our year-long study, 42% of children changed cellular phenotype at least once [13]. Although adult studies [6] are based on the assumption that sputum phenotype is stable over time, recent data have cast doubt on this concept even in adults. It also seems clear that there are some people who constitutionally have a raised FeNO50, in one study, asthmatic children with FeNO50 ≥ 200 ppb had a review of inhaler technique, and, if FeNO50 was still high, were given very high dose inhaled steroids, but FeNO50 remained elevated [14]. A viral cold can of itself lead to an elevation in FeNO50 [15]. For sure, an elevated FeNO50 may mean an imbalance between allergic drive (ongoing allergen exposure in the environment) and anti-inflammatory therapy (prescribed dose too low, or poor adherence), but this is not the only possible explanation. To use FeNO50 as a marker of non-adherence is clearly wrong. A year long paediatric study using FeNO50 to titrate ICS dose did show benefit, but only in reduction of BHR, which is difficult to argue is a relevant clinical end-point [16]. A recent meta-analysis [17] concluded that there is insufficient data in children to recommend routine use of monitoring FeNO50 in clinical practice. Indeed, the most detailed study ever performed, using telemonitoring of FeNO50, failed to show any benefit at all! This study, together with another from an inner city area in which when protocolised asthma management was optimised, the addition of FeNO50 measurements led to no additional benefit [18], underscores the lesson that it is more
important to get the basics right before introducing fancy toys for the boys.

**Predicting exacerbations:** Two studies have shown that inflammometry can predict relapse on reducing [19] or stopping [20] treatment with ICS. In the first, if there was no sputum eosinophilia then reduction was always successful; and in the second, a rising FeNO50 after stopping ICS predicted asthma relapse. Another study using FeNO50 to predict the onset of seasonal, pollen sensitive asthma symptoms showed some benefit [21]. A similar study the following year by the same group failed to confirm this (personal communication). This is the area in which there is the best evidence, but the total number of children studied is very small; it would surely be wrong to base a general recommendation on such small studies, which can best be considered as hypothesis generating.

**Conclusion:** What will be the role of inflammometry? This paper has been nihilistic, but clearly with more data, inflammometry will be seen to be important, in the following contexts:

1. It is a part of the picture in routine asthma management. No-one suggests that spirometry is the gold-standard of asthma care, but we all use it, because interpreted with the whole clinical picture, it gives useful information. The same is true for sputum cytology and FeNO50.

2. Genuine severe, therapy resistant asthma is an umbrella for a multiplicity of different pathophysiological subtypes. Sub-phenotyping using biomarkers, including of inflammation, is going to be needed, unless we just elect to try every treatment on everyone in a haphazard order.

3. With the advent of novel cytokine-specific therapies, we must either determine subgroups who will benefit (such as has been done with mepolizumab, above) or give everyone everything, in which case (a) we are unlikely ever to show any benefit in randomised controlled trials, and (b) we will be exposing children to unnecessary risks.

So inflammometry will have a role in the future, but at the moment, cannot be recommended for routine use outside the research arena. What I hope this debate will do is highlight the tantalising possibilities suggested by small studies, and stimulate the need for international collaboration to find out how best to use these potentially powerful tools. In the meantime, getting the basics right is far more important than measuring airway inflammation in routine clinical practice.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FeNO50</th>
<th>Induced sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Easy to maintain and calibrate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Completely non-invasive</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Easy to use, no co-operation needed</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Direct measurement of all relevant aspects of inflammation</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rapid availability of answers</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Evidence of beneficial clinical outcomes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Production in Normal and Asthmatic Children. Am J Respir Crit Care Med. 2006; 174: 260–267.**

**References**


**III.4. Obstructive Lung Disease – Lung diseases in children: immunity, viruses or genes?**

### III.4.1 A primer on immunology for the pulmonologist

L. Kobrynski, Assistant Professor of Pediatrics, Division of Allergy and Immunology, Emory University, USA

Correspondence: Tel.: 404 727 3575. E-mail: lkobryn@emory.edu.

**What are Primary Immune Deficiencies:** Primary Immune Deficiency disorders (PIDD) refer to a group of over 150 distinct defects of the immune system, many of which are due to single gene defects. Congenital defects in various parts of the immune system have been described in humans. Although, the underlying immunologic defects are present at birth, individuals may not become symptomatic until adulthood. Most primary immune deficiencies (PIDDs) are due to single gene defects causing either the absence of a specific protein or a non-functional protein. This distinguishes them from secondary immune defects due to medications, malignancies, or other infections. PIDD can be inherited in an X-linked, autosomal recessive or autosomal dominant fashion. One of the largest clinical phenotypes, Common Variable Immune Deficiency (CVID), has a pattern of variable inheritance, with both AR and AD forms being reported [1] and genetic linkage studies showing a familial predisposition. Despite the differing patterns of disease severity and onset, all patients with PIDD suffer from recurrent infections which cause significant morbidity and mortality.

![Fig. 1. Frequency of various primary immune deficiencies.](image)

The true prevalence of PIDD is not known, but it is estimated that 1:1,200 individuals in the United States has been diagnosed with a PIDD [2]. This number is in contrast to previous minimal estimates of 1:10,000 to 1:500,000 based on data from disease registries [3–9] and suggests that many cases of PIDD remain undiagnosed. PIDD are typically classified by the nature of the immune defect, whether it affects antibody production by B cells (humoral immunity), T cell function (cellular immunity), both T and B cell function (combined immune defect), killing of bacteria by neutrophils (phagocytic defect) or complement. Figure 1 shows the breakdown of PIDD by the underlying defect [10] with the largest proportion resulting in defects of antibody production. About 40% of individuals with PIDD present with infections or other findings of PIDD in the first few years of life. The most severe defects, such as Severe Combined Immune Deficiency (SCID), are fatal in early childhood if not treated. Previously PIDD were thought to be pediatric diseases, but the mean age of diagnosis for CVID is 29 years for males and 33 years for females [11]. Most will have a history of infections for several years prior to diagnosis. In adults the average delay in diagnosis is 5 years. Diagnosis of PIDD, even in the face of symptoms starting early in childhood, may be delayed until adolescence because of a lack of clinical suspicion, underscoring the need for improved awareness of these disorders. Recent results from a UK national audit show that the median delay in diagnosis has decreased from 3.5 years to 1 year [12]. Early diagnosis and treatment has been shown to reduce morbidity and mortality in many PIDD [13] (Buckley SCID BMT). End organ damage, particularly in the lungs, frequently occurs in the first decade of life as a sequela of infection.

**Normal host defenses of the respiratory tract:** The respiratory tract communicates with the outside environment, thus host defenses against respiratory pathogens are critical. Innate immune defenses are the first line responders against pathogens. The components of the innate immune system in the respiratory tract are the mechanical barriers, the mucous membranes, the mucus containing antimicrobial peptides such as defensins and secretory IgA, the cilia, the cellular effector cells, the phagocytes and NK cells which engulf and kill microbes, the matural antimicrobial agents, defensins, lactoferrin, lysozyme and myeloperoxidase, reactive oxygen species, cytokines and chemokines to recruit effector cells to the site of infection.

**Innate immunity:** Innate immune responses are generally the first line of defense against viral, bacterial and fungal pathogens and involve the activation and recruitment of macrophages, neutrophils and Natural Killer cells with release of chemokines, cytokines, or antimicrobial peptides. Clearance of infectious organisms can be accomplished through binding of serum complement facilitating opsonization of microbes, or by phagocytosis and intracellular killing in phagocytes through reactive oxygen or nitrogen molecules.

**Humoral immunity:** The humoral immune system relies on adaptive immunity to produce antigen specific responses against infectious pathogens. Microbial peptides are presented on the surface of antigen presenting cells (dendritic cells, macrophages, B cells) associated with co-stimulatory major histocompatibility class II (MHCII) molecules. Cognate interaction between T cells and B cells by binding of T cell receptor (TCR) with B cell receptor (BCR) complex and binding of secondary signal (CD40-C40L or CD28-CTLA4) results in intracellular signaling to trigger clonal proliferation and maturation of antigen specific cells with immunoglobulin heavy chain isotype switching to produce specific IgG or IgA antibodies.

**Cellular immunity:** Cellular immunity involves the activation and proliferation of naïve T cells in response to an antigen. Macrophages or dendritic cells can express microbial peptides on their cell surface with MHCI or MHCII. Recognition of foreign peptides on the surface of antigen presenting cells (dendritic cells, macrophages, B cells) associated with co-stimulatory molecules of the innate immune system in the respiratory tract can activate infected macrophages. Cytotoxic T cells kill infected cells, or T helper cells (Th1,1) that activate infected macrophages. The majority of patients with antibody deficiencies, up to 80%, and neutrophil defects will have more than one episode of pneumonia prior to diagnosis [11,14,15]. Frequently the pattern of infection or identification of the causative pathogen will serve as an indicator to the nature of the immune defect. Table 1 summarizes clinical characteristics of pulmonary infections in different PIDD.

**Pulmonary disease in primary immunodeficiency:**

| Defects in interferon gamma (IFNγ) and TNFα | IFNγR1, IFNγR2, IL12/IL23 and IL12R are inherited in an AR fashion and activate infected macrophages. |  |
| Defects in interferon gamma (IFNγ) and IL12 axis cause an increased susceptibility to mycobacteria. Defects in IFNγR1, IFNγR2, IL12/IL23 and IL12R are inherited in an AR fashion and affect infected individuals develop disseminated and life threatening infections with mycobacterium, including BCG and nontuberculous mycobacteria |  |
Individuals with cellular immune defects such as Severe Combined Immune Deficiency (SCID) or an absence of the thymus (complete DiGeorge syndrome) present early in life with opportunistic infections, frequently pneumonia due to Pneumocystis jiroveci. Other viral pathogens, parainfluenza 3 and respiratory syncytial virus (RSV), cytomegalovirus (CMV) and Herpes viruses, can cause severe interstitial pneumonitis and may be fatal. Without immune reconstitution, usually achieved by hematopoietic stem cell transplantation in SCID, affected patients will succumb to recurrent viral, fungal and bacterial infections.

Combined immune deficiencies include disorders such as Wiskott-Aldrich Syndrome (WAS), Ataxia-Telangiectasia (AT), and Hyper-IgE syndrome. Recurrent pulmonary infections are a common feature for all these disorders. Pyogenic bacteria are the most frequent pathogen, but pneumocystis and other viral pathogens also cause infections. Bronchiectasis is a common complication of respiratory infections in WAS and AT. Pneumatoceles are characteristic for S. aureus infections in Hyper-IgE.

Individuals with antibody deficiencies typically develop bacterial infections of the sinopulmonary tract after maternal antibodies wane after six months of life. Infants with X-linked agammaglobulinemia have an increased frequency of bacterial pneumonias, along with recurrent otitis media, and chronic diarrhea. While many individuals with selective IgA deficiency are asymptomatic, others have a history of frequent otitis media and sinusitis. Some individuals will also be more susceptible to lower respiratory infections and gastrointestinal infections. Many individuals with CVID do not have a notable history of infections until the 2nd decade of life or later. Infections of the sinopulmonary tract occur more frequently than in the general population, with an increase in severity, and are often associated with other sites of infection. Pyogenic bacteria, such as Staph. aureus, Strept. pneumoniae, Haemophilus influenzae and Moraxella catarrhals, are responsible for the majority of the pulmonary infections, but infections with atypical mycobacterium, and opportunistic organisms may be seen in patients with impaired T cell function and in patients with hyper-IgM syndrome. Other antibody deficiencies (NEMO, AR-HyperIgM, selective antibody deficiency) also predispose affected individuals to upper and lower respiratory tract infections.

Pneumonia associated complications, bronchiectasis, empyemas, granulomatous lung disease, are seen more frequently in patients with antibody deficiencies (except SAD and IgA deficiency) [18]. Bronchiectasis may already be present at the time of diagnosis (Fig. 2) and end-stage lung disease with respiratory insufficiency is the most frequent cause of death in CVID [11]. Frequently progression of lung disease occurs despite replacement of serum IgG with gammaglobulins [19].

In Chronic Granulomatous Disease (CGD), infections with catalase positive organisms (S. aureus, Pseudomonas sp., Aspergillus, Nocardia, Serratia, Klebsiella) can involve multiple sites. The majority of patients will present with a history of pneumonia [14]. The hallmark of the respiratory infections in patients with CGD is the unusually invasive nature of infections with Pseudomonas or Aspergillus, the propensity for abscess formation and the development of noncaseating granulomas. Bronchiectasis is seen less frequently in patient with CGD compared to individuals with antibody deficiency, but can develop after recurrent S. aureus infections. Necrotizing pneumonias due to Pseudomonas species may necessitate lobectomy.

In addition to bronchiectasis, other chronic lung changes occur in PIDD. Hilar and mediastinal adenopathy is frequently seen. Bronchiolitis obliterans may develop, or involvement of the airways and the parenchyma can lead to pulmonary fibrosis and pulmonary hypertension. Subsequent to opportunistic viral or fungal infections, persistent focal ground-glass opacities may be seen on CT scan. Interstitial lung disease occurs in patients over 40 years of age with antibody deficiencies [20]. Multiple pulmonary noncaseating granulomas, sometimes calcified can be seen in patients with CGD and CVID. In both disorders, intracellular pathogens (PJP, mycobacterium) can sometimes be identified in the granulomas (Fig. 3). In CVID these granulomas have been termed “sarcoid-like” [21]. Benign lymphoid hyperplasia involving the lung and gastrointestinal tract occur in as many as 30% of patients with CVID [22]. Non-Hodgkin lymphomas are more prevalent in patients with CVID [11,23]. Thoracic lymphomas may present with enlarged mediastinal nodes, or an anterior mediastinal mass which may compress the airway or blood vessels. The presence of an anterior mediastinal mass in a patient with hypogammaglobulinemia and low or absent B cells is characteristic of Good syndrome [24]. In these cases the development of a thymoma carries a poor prognosis.

**Evaluation of the patient with suspected primary immunodeficiency:** Any patient with a history of recurrent, unusually severe pneumonias, or infection with atypical or opportunistic pathogens should undergo evaluation to identify a possible immune deficiency. The types of infections, their frequency, severity, pathogens involved and the age of onset may suggest the clinical phenotype and can be used to direct the laboratory evaluation. In addition to the history of infections, clinicians should inquire about associated problems and a family history of PIDD. Clinical algorithms have been suggested to help identify individuals with possible PIDD (Fig. 4: JMF 10WS). Laboratory testing can then be used to delineate the immune defect. The pattern of infection is the most useful element to discriminate the different immunologic defects. Table 1 shows the pathogens typically associated with defects in different arms of the immune system. Figure 5 shows a testing algorithm for screening patients for a PIDD [25]. It is worth noting that some tests are available only in specialized laboratories.


Increased risk of infections among persons with asthma

T.V. Hartert. Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Center for Asthma & Environmental Sciences Research, 6107 MCE, Nashville, TN 37232–8300, USA

Correspondence: Tina V. Hartert, M.D., M.P.H. Division of Allergy, Pulmonary and Critical Care Medicine, Center for Asthma & Environmental Sciences Research, 6107 MCE, Vanderbilt University School of Medicine, Nashville, TN 37232–8300, USA. Phone: +1 615 322 3412; fax: +1 615 936 1269. E-mail: tina.hartert@vanderbilt.edu

Keywords: Asthma, Infection, Pneumococcal disease

Are persons with asthma at an increased risk for infections? One of the problems in answering this question is that historically studies of infections and asthma have centered on the impact of respiratory infections on asthma exacerbations, a respiratory disease, rather than focusing on infection susceptibility or infections outside of the respiratory tract. Recent investigations provide biologically plausible explanations for an increased susceptibility to certain viral and bacterial infections among persons with asthma, however, the exact mechanisms for this increased risk are not known. While we know that persons with asthma have a disturbed airway epithelial physical barrier, increased and aberrant mucous production, and other alterations in innate and adaptive immunity, whether these are the mechanisms through which asthmatics have an increased risk or more severe infections is not known. In addition, the medications used to treat asthma may also be immunosuppressive, or could possibly even enhance immune responses specifically among persons with asthma who are prescribed and compliant with their medications. Thus what we do not know, is whether the increased association of infections and infection severity in asthma is an epiphenomenon due to enhanced airway inflammation and/or allergic inflammation resulting in more severe respiratory infections in individuals with a chronic respiratory disease, or whether these differences among persons with asthma truly alter host defenses rendering asthmatics more susceptible to bacterial and viral pathogens. What follows is a summary of our current understanding of the data supporting the association of asthma and serious infections, potential mechanisms of host susceptibility to infections, and preventive implications. The data that support biologic plausibility for persons with asthma being at increased risk for particular infections come from several lines of evidence. The first is that asthmatic inflammation may inhibit or alter host defense rendering asthmatics more susceptible to infections. A second is that innate immunity may be altered in asthma and this alteration may inhibit antimicrobial host defense and/or response to injury and in this way render asthmatics more susceptible to and less able to resist infections. Lastly, in support of link between response to infections and the underlying chronic disease asthma, are the many known genetic factors that impact patterns of immune response to infectious agents, that are also strongly linked with asthma [1–4].

The body of literature that actually supports an increased risk of infection among persons with asthma is relatively small, and can be conceptually grouped into evidence for increased infection-related morbidity, increased infection latency (propensity to persist and cause chronic infection), and increased invasiveness of infections among asthmatics. Importantly, as asthma is a respiratory disease, we need to understand whether infections outside of the respiratory tract are more common or severe among persons with asthma; unfortunately, in this regard there is little data to my knowledge. Persons with asthma have been shown to have increased rates of pneumococcal nasal colonization, as well as hypopharyngeal colonization as neonates before the development of asthma, which provides strong support for a pre-existing defective immune response among persons destined to develop asthma [5,6]. Data also supports latency of infection among persons with asthma; for a number of pathogens, including respiratory syncytial virus, adenovirus, Human rhinovirus, Mycoplasma pneumoniae and Chlamydia pneumoniae. Respiratory-related infection morbidity has also been shown to be higher among persons with asthma. Almirall and colleagues have shown that both asthma and inhaled corticosteroids are risk factors for community-acquired pneumonia in a European population based case-control study among persons age ≥14 years. Asthma has also been shown to be an independent risk factor for influenza-attributable morbidity among children and pregnant women [7–9]. Previously, our group reported that persons with asthma had a greater than 2-fold increased risk of invasive pneumococcal disease, using the Active Bacterial Surveillance Core data from the US Centers for Disease Control and Surveillance, which identified Streptococcus pneumoniae from sterile sites, (blood cultures, cerebrospinal and joint fluid) among both children and adults [10]. A follow-up study by Juhn et al also showed an increased risk of serious pneumococcal disease among persons with asthma [11]. The available evidence from these studies, as is true with nearly all of the investigations looking at the relationship between infections and asthma is that they are based on observational data. While an association between asthma and a subsequent infectious event can reflect causal mechanisms, alternatively, such associations can be the result of other unmeasured factors or characteristics that are closely related to asthma (confounders). However, in both of these investigations of the association of asthma with invasive or serious pneumococcal disease, “asthma” identified those at high-risk, and in both of these studies, the results are strikingly consistent. The consistency of these data suggest that the increased association of clinically significant pneumococcal infection in asthma is not just an epiphenomenon caused by enhanced airway inflammation rendering persons with asthma more clinically symptomatic from pneumococcal respiratory disease, but that allergic inflammation and asthma are associated with or alter host defenses and in this way render persons with asthma more susceptible to pneumococcal disease. The strongest evidence for this true increased susceptibility to pneumococcal disease among persons with asthma lies in the data supporting an increased risk of serious pneumococcal disease that has also been recognized with rhinovirus infections, where persons with asthma are more likely to experience rhinovirus viremia, and this increased susceptibility has been shown to likely relate to defective innate immune responses [11]. The association with increased risk of invasive pneumococcal disease is additionally important, as pneumococcal vaccine is most efficacious for invasive pneumococcal disease. It is important to realize that although these studies have limitations, these observational investigations are likely to be the
extent of the available human evidence to support the association between asthma and an increased risk of serious infectious diseases, as randomized trials of most infections are unethical to conduct for obvious reasons. For these reasons, these data were used by the Advisory Committee on Immunization Practices (ACIP) to make new recommendations for pneumococcal vaccination for persons with asthma [13]. What we still lack is information on the asthmatic response to pneumococcal vaccination, and to determine if the protection that it confers, is as robust as that in non-asthmatic hosts.

Although it is imperative for us to understand the mechanisms underlying why persons with asthma are at increased risk for vaccine preventable diseases in order to identify novel targets for treatment, to further understand the disease, and to advance preventive efforts, we do not need these answers now to put these findings into clinical context. Whether the disease, and/or the medications used to treat the disease put individuals at risk, asthmatics have an increased risk of serious pneumococcal disease, and increased morbidity from a variety of respiratory viral and atypical pathogens. The risk of invasive pneumococcal disease among asthmatics is similar to persons with chronic obstructive pulmonary disease (COPD) in whom pneumococcal vaccination has been recommended; the risk for significantly increased morbidity related to influenza, particularly among pregnant women, and especially those with asthma is well recognized, and both of these findings have led to new vaccine recommendations [13,14].

In sum, the available evidence suggests that asthmatics are at increased risk of enhanced morbidity, latency, and susceptibility to a variety of bacterial and viral pathogens. This recognition has established asthma as a disease in which possibly the aberrant immune response to pathogens leads to suboptimal viral/bacterial clearance and/or host response to infection. These findings have led to vaccine policy changes for selected infections, but a deeper comprehension of why asthmatics are at increased risk for these infections should lead us to a better understanding of asthma, and means to prevent the significant increased morbidity associated with selected viral and bacterial infections among persons with asthma.

References


III.4.3 Genetics of asthma exacerbations

F. Martinez. Tucson, USA

Mounting evidence suggests that asthma is a highly heterogeneous condition, and that an important component of this heterogeneity may be the presence or absence of susceptibility to asthma exacerbations. I support of this contention, it has been reported that the best predictor of a future exacerbation is having had one in the past. This is apparently true even in the framework of randomized and highly controlled clinical trials [1], in which it is unlikely that inappropriate therapy or differential adherence may explain the clustering of asthma exacerbations within groups of individuals. Of great relevance is also the observation that, in similar clinical trials, incidence of exacerbations has been associated with subsequent lung function decline [2]. Based on these observations and also given the large role that exacerbations play in asthma morbidity and costs, determining the potential role of differential gene expression and genetic variants in determining the risk for asthma exacerbations has become an important priority for our labs.

In order to assess the potential role of differential inflammatory responses during acute asthma exacerbations in determining lung function decline in asthma, we characterized gene coexpression networks in induced sputum obtained during an acute exacerbation from asthmatic children with or without chronic airflow limitation [2]. We showed that decreased activation of Th1-like/cytotoxic and interferon (IFN) signaling pathways during acute asthma exacerbations were strongly associated with chronic airway obstruction (i.e., decreased FEV1/FVC ratios). These associations were independent of atopy, the detection of concurrent picornavirus infections, and the use of medications at the onset of the exacerbation. Th2-related pathways were also detected in the exacerbation responses, but variations in these pathways were not related to FEV1/FVC ratios. The patterns of association with lung function observed between acute gene expression and FEV1/FVC ratios at baseline and during convalescence were not observed with FEV1/FVC ratio measured during the acute episode. We speculated that determinants of the severity of the acute obstructive response may be different from those that influence long-term effects on lung function. Finally, bioinformatics analyses of cellular immune signatures enriched within the Th1-like/cytotoxic pathway suggested a role for T cells and iNKT cells in the exacerbation responses, and we showed that the activation of Th1-like/cytotoxic and IFN signaling networks was strongly correlated with a marker of T cells (TRBC2). Markers of iNKT cells (Vα24, Vα11) were also associated with acute exacerbations; although they were not related to airflow obstruction, they were strongly correlated with IL-12A.
and IL-21 responses. These results thus suggest that impairment of acute Th1-like/cytotoxic and IFN signaling responses presumably to viruses and other environmental exposures may have a major role in the development of chronic airflow limitation. These results suggest potential candidate genes for studies of the genetics of asthma exacerbations and for its potential role in lung function decline in asthma.

References


III.5. Obstructive Lung Disease – Asthma epidemiology and treatment

III.5.1 What have we learnt from asthma epidemiology studies from around the world?

D.P. Strachan. Professor of Epidemiology, Division of Population Health Sciences and Education, St George's, University of London, London SW17 0RE, United Kingdom

Correspondence: E-mail: d.strachan@sgul.ac.uk

This presentation will focus on the principal findings relating to asthma arising from the International Study of Asthma and Allergies in Childhood (ISAAC), now in its twentieth year. Fuller information about ISAAC methods, findings and resulting publications can be viewed at http://isaac.auckland.ac.nz/.

ISAAC Phase One was an international multi-centre cross-sectional study involving two age groups of school children, 13–14 year olds (adolescents) and 6–7 year olds (children). Schools were randomly selected from a defined geographical area. Written questionnaires on asthma, rhinitis and eczema symptoms (translated from English) were completed by the adolescents at school, and at home by the parents of the children. An asthma symptoms video questionnaire for the adolescents was optional. Phase One was completed in 156 collaborating centres in 56 countries with a total of 721,601 children participating. In the 13–14 year age group 155 centres from 56 countries participated, of which 99 centres completed a video questionnaire. For the 6–7 year age group there were 91 collaborating centres in 38 countries. ISAAC Phase One demonstrated a large variation in the prevalence of asthma symptoms in children throughout the world including hitherto unstudied populations.

ISAAC Phase Two involved more intensive studies in a smaller number of selected centres, representing a wide range of asthma prevalences. It included a total of 53,383 participants from 30 centres in 22 countries. Children aged 9–11 years were examined for flexural dermatitis, underwent skin prick tests for atopy, bronchial responsiveness to hypertonic saline, blood sampling and storage for serum IgE and genetic analyses, and additional questionnaires were completed by their parents. At the level of individual children, the association of atopy with asthma was stronger in more affluent centres than in less affluent centres. At the level of whole populations (centres), however, the correlation between the prevalence of atopy and the prevalence of asthma symptoms was weak. Thus, international variations in the prevalence of atopy did not explain much of the between-centre variations in disease prevalence. These findings, across diverse study centres worldwide, suggest that much asthma in childhood has a non-allergic basis, especially in developing countries. High rates of bronchial responsiveness to inhaled hypertonic saline challenge (BHR) were not confined to centres with high prevalences of asthma symptoms, nor to affluent countries. At the individual level, the association between wheeze and BHR differed across centres but this heterogeneity could be largely explained by a stronger association with wheeze in atopic children than in non-atopic children.

ISAAC Phase Three, a repeat of Phase One after at least five years, examined time trends of childhood asthma, rhinoconjunctivitis and eczema around the world, and expanded the world maps of these conditions. Additional questions on risk factors were included in many centres. Phase Three was completed in 237 collaborating centres in 98 countries with a total of 1,187,496 children participating. In the 13–14 year age group 233 centres from 97 countries participated. For the 6–7 year age group there were 144 collaborating centres in 61 countries. For 104 centres in 55 countries, comparison with the Phase One results provided information on change in prevalence over a period of 6–8 years. Following reports from English language countries in the 1990s of increases in asthma prevalence from the 1980s, continuing increases in prevalence had been expected. However ISAAC found that in most high prevalence countries, particularly the English language countries, the prevalence of asthma symptoms changed little between Phase One and Phase Three, and even declined in some cases. In contrast, a number of countries that had high or intermediate levels of symptom prevalence in Phase One showed significant increases in prevalence in Phase Three. With the exception of India, all of the countries with very low symptom prevalence rates in Phase One reported increases in prevalence in Phase Three. The increases in asthma symptom prevalence in locations of high population density such as Africa, Latin America and parts of Asia indicate that the global burden of asthma is continuing to rise, and at the same time the global prevalence differences are lessening.

Explaining the international differences: The unique contribution that ISAAC can make is to evaluate which risk factors, if any, explain the large differences in prevalence and severity of asthma symptoms observed between diverse study centres. Only factors which are strongly associated with asthma at the level of individual children, and which vary in prevalence substantially across study centres, can explain the wide variation in occurrence of childhood asthma around the world. Preliminary results from ongoing work that addresses this issue will be presented.

III.5.2 The use of long-acting β-agonists in childhood asthma

F.M. Ducharme. Montreal, Canada

Inhaled corticosteroids (ICS) are the most effective treatment for long-term control of asthma in children at step 2; they are recommended as first line agent in management of childhood asthma in international consensus statements [1]. When ICS are insufficient to achieve control, various step 3 options may be considered, such as increasing the dose of inhaled corticosteroids, [2] or adding a second drug such as a long-acting beta-2 agonist (LABA) or a leukotriene receptor antagonist [3]. In adults with unsatisfactory control, international guidelines clearly favour the addition of LABA over other options. In children, however, recommendations differ markedly across national guidelines, underlying the uncertainty in preferred approach.

The objectives of this presentation are to review the evidence regarding the role of LABA as an adjunct therapy to ICS in the management of children with suboptimal control on ICS. As LABA are bronchodilators, a fair comparison between options must include, in addition to lung function, other endpoints such as exacerbations requiring rescue oral steroids (moderate) or hospital admission (severe) as well as other markers of control.
Is there any gain to adding LABA vs. placebo to ICS? Compared to ICS alone, the addition of LABA to ICS is not associated with a reduction in exacerbations requiring oral steroids, but is superior for improving lung function and preventing withdrawals compared to the same dose of ICS. However, there are no significant improvement in symptom-free days, hospital admission, and use of reliever medication [4].

Is it better to increase the ICS dose or add LABA? Compared to a double dose ICS, the combination of LABA and ICS does not decrease the risk of exacerbations requiring oral steroids, but rather show a trend towards an increased risk of exacerbations and hospital admissions. However, combination therapy is associated with a significantly greater improvement in peak flow and growth than with a high dose of ICS [4].

Is it best to add LABA or LTRA to ICS? There is insufficient evidence to firmly support one option over the other in children [5]. Contrary to the marked improvement observed in adults, there is insufficient evidence to firmly support the use of LABA as adjunct therapy to ICS as a step 3 strategy in children. One must weigh the greater linear growth and modest improvement in PEF against the possible, but unproven, increased risk of increased severity of exacerbations associated with combination therapy. The reasons for the discrepancy in findings between adults and children are unclear but may relate to different disease severity and remodelling.

References


III.5.3 Treatment guidelines for asthma – the individualized approach

D.P. Skoner1,2. 1Director, Division of Allergy, Asthma & Immunology, Department of Pediatrics, Allegheny General Hospital, Pittsburgh, Pennsylvania. 2Professor of Pediatrics, Drexel University College of Medicine, West Virginia University School of Medicine, USA

Introduction: Asthma is a highly prevalent chronic inflammatory disease of the respiratory tract that affects more than 300 million people worldwide. Asthma produces significant morbidity and mortality and health care expenditures. Despite significant advances in understanding the pathophysiology and the treatment of asthma, morbidity has been unchanged and costs remain very high. Moreover, it is well recognized that certain populations are disproportionately affected by asthma morbidity and mortality statistics. Asthma is increasingly recognized as a complex disease with a number of clinical phenotypes in adults and children. Asthma phenotypes differ in a number of ways, including natural history, the factors that trigger symptoms, severity, control, risk of adverse outcomes, and both efficacy and safety responses to therapy. Thus, tremendous heterogeneity exists within and among asthma patients. This heterogeneity makes treatment decisions complex and surely underlies some of the poor outcomes associated with asthma. This conference will identify sources of asthma heterogeneity and illustrate a clinical approach to the asthma patient that takes this heterogeneity into consideration and individualizes therapy by taking into account each patient's need, circumstances, and responsiveness to therapy. Despite significant advances in understanding of the pathophysiology and treatment of asthma, recent surveys have revealed that asthma control and morbidity have not improved. Therefore, these advances have not translated into improvement in outcomes despite their potential to do so. Despite an updated national guideline for asthma, clinicians continue to underestimate asthma severity and control, under-prescribe controller therapies, and patients continue to be non-adherence with medical and non-medical approaches to therapy. More education and behavioral modification of health care professionals is clearly needed. This conference will bring the latest developments in this rapidly changing field to health care professionals practicing, researching and teaching asthma care. Recent research has focused on the heterogeneity among patients with asthma, with regard to variable expression and natural history, as well as response to medications. Many factors underlie the heterogeneity, including environmental factors such as allergens, pollution, tobacco smoke and viruses, demographic and social factors such as low socioeconomic status, obesity and gender, and genetics. Gene-by-environment interactions are also evident.

Asthma: clinical overview and sources of heterogeneity: Asthma is a complex disease with a number of clinical phenotypes in adults and children (Busse 2001). The primary characteristics of asthma include airway inflammation, bronchial hyperresponsiveness, and airflow obstruction. Asthma phenotypes differ in a number of ways, including natural history, severity, risk of adverse outcomes, control, and response to therapy (Luskin 2005). Factors contributing to disease heterogeneity: There is an abundant and growing body of clinical trial evidence in support of the concept of asthma heterogeneity. Clinical trial end points may not correlate closely with symptoms scores or with other measures of treatment efficacy. One possible source of this heterogeneity may be genetic diversity. Evidence for race- and sex-based heterogeneity in asthma also may have its foundations in genetic variation. Other factors that must be considered in addressing asthma variability include obesity, smoking, socioeconomic factors, and seasonality. These variables are receiving attention as contributors to the heterogeneity puzzle.

Factors influencing the development and variability of asthma: Asthma is a complex disease that is caused by a complex interaction of genetic, environmental, and social factors. More than 118 genes have been associated with asthma; however, of the genes that have been studied across multiple racial and ethnic groups, not one has demonstrated a positive association in every group, suggesting that genetic risk factors are influenced by genetic ancestry and race. Environmental factors such as exposure to secondhand smoke, certain infectious agents, and pollutants have been associated with asthma and asthma severity. Moreover, there is interplay between the environmental factors and genetic risk factors. In essence, a particular disease may only manifest in the presence of permissive environmental exposure. Demographic factors such as age, sex, and socioeconomic status, as well as social factors, including language and ethnicity, have been shown to influence environmental exposure levels, thereby contributing to disease development (Drake 2008).

Ethnic differences and associated phenotypes in asthma and allergy: One study compared the heterogeneity of asthma and allergic phenotypes among 628 individuals (314 sibling pairs) from 3 ethnic groups in the multi-center Collaborative Study on the Genetics of Asthma (Lester 2001). This was a limited study done for genetic purposes using a sibling pair ascertainment model. The sibling pairs were from 314 African American, white, and Hispanic families living in urban, suburban, and rural communities. All sibling pairs met the study criteria for asthma. It is not possible to make a generalization from this study to a larger population; however, it provides a simple
illustration of the likelihood of ethnic differences in asthma and allergy phenotype.

The percentage of predicted FEV1 was significantly lower (P = 0.0001) in African American patients (84.9% ± 17.2% [mean ± standard deviation (SD)], n = 256) than in white patients (88.7% ± 16.7%, n = 292) and Hispanic patients (95.6% ± 16.1%, n = 80). Likewise, median immunoglobulin E (IgE) levels were significantly higher (P = 0.0005) in African American patients (335.4 IU/mL) and Hispanic patients (357.3 IU/mL) than in white patients (175.2 IU/mL).

In addition, there were significantly more relatives with asthma among the families of the African American sibling pairs than among the families of the white and Hispanic sibling pairs (P = 0.001).

Sex-influenced differences observed in the Childhood Asthma Management Program (CAMP): methacholine challenge: Differences seen between male and female children aged 5 to 18 years with mild to moderate asthma in the Childhood Asthma Management Program (CAMP) and CAMP Continuation Study (CAMP-CS) indicated a sex-specific difference in the natural history of airway responsiveness in asthma (Tantisira 2008). After statistical correction for confounding variables (clinic type, race, duration and severity of asthma at baseline, and recent ICS usage), PC20 (the concentration of methacholine challenge required to induce a 20% reduction in baseline FEV1) increased in boys with increasing age, but showed minimal change in girls as they aged from 11 to 18 years. These results include 1,041 patients in the CAMP study, 941 of whom continued in the CAMP-CS. With 7,748 methacholine challenges administered during the 2 studies, CAMP/CAMP-CS had greater statistical power than previous studies that did not demonstrate sex-specific differences in airway responsiveness, even after FEV1 correction.

Obesity and asthma variability: lung function: Baseline data from The Study of the Effectiveness of Low Dose Theophylline as Add-On Therapy in Poorly Controlled Asthma (LODO) were analyzed to examine the relationship between lung function and body weight in adult patients with mild to moderate asthma, as diagnosed by physicians. Fifty-five percent of the patients in the study had asthma that was poorly controlled on their current therapy. Normal body weight was defined as a body mass index (BMI) of less than 25; overweight, as a BMI of 25 to 29.9; and obese, as a BMI of 30 kg/m² or greater. Forty-seven percent of the patients were obese. Lung function declined with increasing body weight. The differences in percentage of predicted FEV1 and forced vital capacity (FVC) among the normal weight, overweight, and obese patients were found to be significant by analysis of variance (ANOVA) (P = 0.01 and P < 0.001, respectively). FEV1 decreased by 0.47% and FVC decreased by 0.40% for every unit increase in BMI after correction for sex, age, and study site. FEV1 and FVC were not significantly affected by ICS use and smoking history. BMI was not significantly related to airflow limitation or the response to bronchodilators.

The development of asthma in obese individuals may be due to mechanical factors, such as reduced lung volume and tidal volume as well as inflammatory factors. There is increasing awareness that obesity is associated with chronic systemic inflammation; this inflammation is due to increased levels of inflammatory cytokines, chemokines, and adipocyte-derived factors, such as leptin, adiponectin, and plasminogen activator inhibitor (Lyon 2003, Shore 2005). Although only a few randomized controlled trials have looked at the effect of obesity on asthma, weight loss in adults has been shown to result in improved pulmonary mechanics and improved FEV1 (Stenius-Aarniala 2000).

Asthma prevalence in low socioeconomic populations: Almqvist and colleagues (2005) conducted a survey of families in predetermined areas in Stockholm, Sweden, with children born between 1994 and 1996. A total of 4,089 families answered questionnaires addressing environmental factors, socioeconomic status, and symptoms of allergic disease in children. Blood samples were taken from 2,614 four-year-old children and analyzed for IgE to common airborne and food allergens. The study found a decreasing risk for asthma as socioeconomic status increased. Saha and colleagues (2005) conducted a cross-sectional study of children between ages 5 and 18 years seen within a network of urban primary care clinics in Marion County, Indiana, in 2000. Age, race, sex, and BMI were significant predictors for childhood asthma. Compared with normal-weight girls, overweight girls were 1.8 times more likely to have asthma. Overweight boys were 3.1 times more likely to have asthma than normal-weight girls. Black children were 1.3 times more likely to have ever had asthma than were white children. Boys who were young, black, and overweight were most likely to have asthma.

Claudio and colleagues (2006) assessed the relationship between hospitalization rates and asthma prevalence in New York City children and investigated the role of sociodemographic factors in asthma. The researchers distributed a parent-report questionnaire in 26 randomly selected New York City public elementary schools stratified according to neighborhood hospitalization rates. Children in low socioeconomic communities had a 70% greater risk of asthma vs other communities; this finding was independent of the children’s own ethnicity and family income level. This finding did not hold true for Puerto Rican children, among whom neither school attended nor income affected the high rate of asthma prevalence.

Seasonal allergies and asthma variability: ragweed pollen count and asthma symptoms: Seasonality is another factor that contributes to asthma variability. The effects of pollen count on asthma symptoms were studied in 58 patients (aged 14–43 years) with both ragweed seasonal allergic rhinitis and asthma during the peak of the ragweed season (August 22–September 4). The asthma symptom score was measured as change from baseline. The asthma score was the sum of scores for shortness of breath or chest tightness and wheezing. As shown in this slide, the 14 patients who received a placebo medication for their allergy symptoms reported a 10-fold increase in asthma symptoms during that time. This suggests a link between exposure to allergens and worsening asthma symptoms (Welsh 1987).

Cigarette smoking and asthma variability: reduced response to oral corticosteroids: Although cigarette smoking is common among adults with asthma, there are few data to explain the influence of cigarette smoking on the therapeutic effect of asthma medications. The objective of this randomized, placebo-controlled, crossover study was to assess the effect of cigarette smoking on the therapeutic response to oral corticosteroids (prednisolone 40 mg/day) vs placebo over a 2-week period in smokers, ex-smokers, and never-smokers with chronic stable asthma (Chaudhuri 2003). This study enrolled 59 patients who were randomized. Fifty patients completed the study and were included in the analysis. Smokers were defined as those who had smoked 10 pack-years or more; ex-smokers had smoked 10 pack-years or more but had quit at least 1 year before the study. The study demonstrated a reduced therapeutic response to oral corticosteroids in patients with chronic stable asthma who smoke. Compared with placebo, oral prednisolone significantly improved FEV1 and asthma control scores in never-smokers with asthma. Morning and nighttime PEF also significantly improved in never-smokers and ex-smokers, though not in current smokers. The mechanistic basis for this finding of a reduced response is not clear.

Evidence of gene-by-environment interactions in asthma: The gene encoding the β2-adrenergoreceptor (B2AR) contains several reported single nucleotide polymorphisms (SNPs). One of the most common SNPs (46: guanine/adene) is responsible for amino acid substitution Arg16Gly. Although not implicated in asthma susceptibility, this gene is thought to play a role in asthma-associated phenotypes such as responsiveness to medications, airway hyperresponsiveness, and asthma severity. Metabolites of tobacco smoke are thought to be high-affinity agonists for β-ARs. Zhang and colleagues (2007) investigated the effect of tobacco smoke exposure and B2AR polymorphisms on asthma severity.
this study, 180 children were genotyped for B2AR polymorphisms and followed up to the age of 11 years. Forty-six percent were classified as having had no exposure to secondhand smoke, with 37% receiving “significant” exposure. In cases where the level of exposure was uncertain, breathing tests were not administered. Arg16 was associated with significantly lower adjusted mean FEV1 and FVC in children with significant exposure to tobacco smoke. No association was seen between Arg16 and Gln27 polymorphisms and lung function in children without significant exposure to tobacco smoke. The authors also showed that both the Arg16 and Gln27 polymorphisms were associated with reduced exhaled nitric oxide (NO). This association was more pronounced in children with no exposure to cigarette smoke.

B2AR gene polymorphisms have been shown to be linked with decreased lung function in children significantly exposed to tobacco smoke and decreased levels of exhaled NO in those with no exposure to cigarette smoke.

**Factors contributing to heterogeneity in asthma: summary:** Various genetic, environmental, and physiologic factors contribute to asthma. Evidence for genetic-based differences in asthma severity and progression has been noted in studies of gender and ethnic differences (Lester 2001, Burchard 2004, Tantisira 2008). Physiologic and biologic factors, including obesity, also play a role (Dixon 2006). Environmental factors, including socioeconomic status and seasonal allergens, can lead to increased asthma risk and worsening of symptoms (Almqvist 2005, Welsh 1987, Chaudhuri 2003). Interactions between environmental and genetic factors play a role in asthma heterogeneity (Zhang 2007).

**Pharmacogenetic mechanisms:** Clinically observed heterogeneity in asthma is also documented by the results of clinical trials and the response of patients to different treatment options. Preliminary research suggests that genetics may have a role in individual response to asthma pharmacotherapy (Tantisira 2005).

Genetic variations can alter the response to therapy by affecting drug metabolism, unintended biologic targets (leading to adverse effects), and the therapeutic target itself or pathways that are involved in producing therapeutic effects (Israel 2005).

**Genetic variation in the FCER2 gene and therapy responsiveness:** Tantisira and colleagues (2007) examined the effect of budesonide therapy on severe exacerbations over a 4-year period in individuals possessing variants in the FCER2 gene. FCER2 codes for the low-affinity IgE receptor, CD23, which has been shown to down-regulate the IgE-mediated immune response upon activation. Individuals homozygous for the single nucleotide polymorphism (SNP) T2206C mutation in FCER2 experience a 3- to 4-fold increase in the risk of severe exacerbation, compared with wild-type homozygotes and heterozygotes. In the white subgroup in this study, individuals on budesonide therapy homozygous for the T2206C mutation (orange line) were more likely to experience a severe exacerbation than those on budesonide therapy with heterozygous or homozygous wild-type genotypes (blue line). A statistically significant interaction between genotype and budesonide use was seen in this white subgroup using a time-to-event multivariate analysis, testing proportional hazards assumptions (P = 0.004). There was no significant interaction between genotype and budesonide use for African American subjects, although this may be the result of sample size. The authors proposed one mechanistic explanation: that homozygous mutant (CC) individuals exhibit decreased CD23 expression and resultant CD23 actions. In addition, IgE levels in blood and sputum increased through the use of oral and inhaled corticosteroids. The combined result may lead to increased risk of severe exacerbations in these children and provides an example of gene-environment interaction in asthma. The results of this study demonstrate that FCER2 was a pharmacogenetic predictor associated with marked increased risk of emergency visits and hospitalizations in children on budesonide therapy.

**Genetic variation in leukotriene pathway genes and LTRA responsiveness:** Responsiveness to leukotriene receptor antagonists (LTRAs) is also variable among patients. One possible explanation would be genetic variation. Lima and colleagues (2006) identified 5 polymorphisms in leukotriene pathway-candidate genes that were associated with changes in FEV1 and the risk of exacerbation while receiving montelukast sodium. Two hundred fifty-two participants were genotyped: 69% were white and 26% were African American. Racial disparities were discovered in 17 of the 28 SNPs investigated; therefore, association analysis was carried out only in white participants (n = 61). This study detailed the effect of 2 SNPs in the leukotriene pathway-candidate genes on the percent predicted FEV1 after 6 months of montelukast sodium treatment compared with baseline. Both genes encode key proteins in leukotriene physiology: Patients with GG homozygotes for the ALOX5 SNP had a higher response to montelukast sodium at 6 months of treatment compared with patients with AA homozygotes and AG heterozygotes. Patients with heterozygotes for the MRPI SNP had a significantly higher FEV1 response to montelukast sodium compared with those with CC homozygotes. No significant associations were seen between these SNPs and percent predicted FEV1 in participants assigned to placebo.

Additional data collected in this study (Lima 2006) examined the influence of LT pathway polymorphisms on the risk of having at least 1 severe asthma exacerbation in participants receiving montelukast sodium. Individuals in this study carrying a variant number of repeats (2, 3, 4, 6, or 7) in the ALOX5 promoter on 1 allele had a significant reduction in the risk of having at least 1 severe asthma exacerbation compared with those with homozygotes for the 5-repeat alleles receiving montelukast sodium (P = 0.045). For the LTC4S A-444C SNP, heterozygotic individuals in this study experienced a significantly reduced risk of having an asthma exacerbation compared with those with AA homozygotes (P = 0.023).

**Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial:** The objective of the Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial was first to analyze biomarkers and characteristics of asthma that predict a patient’s response to short-term ICS treatment administered for 6 weeks. After responders and nonresponders to ICS treatment were identified, the second objective was to then evaluate whether a short-term response, or lack of response, to an ICS can predict long-term asthma control. The study examined the variability of response in 83 adults with asthma (Martin 2007). After a 2-week characterization period, subjects were started on single-blind ICS hydrofluorokalium-beclometasone propionate 160 mcg twice daily by inhalation. Biomarkers assessed at baseline and at 6 weeks included (12-agonist response, fraction of exhaled nitric oxide (FeNO), sputum eosinophils, lung function, and bronchial hyperresponsiveness (methacholine PC20). Characteristics evaluated included length of asthma history, age, sex, height, weight, and ethnicity.

Seventy-two patients completed the 6-week phase of the trial. On the basis of their FEV1 response to ICS at the end of 6 weeks, “responders” were identified as those with a greater than 5% improvement, and “nonresponders” were identified as those with a 5% or less change from baseline. Subjects were then randomized to a double-blind, placebo-controlled 16-week trial to evaluate asthma control using the Asthma Control Questionnaire (ACQ). Of the 72 patients who completed the 6-week phase of the trial, 54% were determined to be responders to ICS treatment and 46% were categorized as nonresponders. The bar graph on this slide describes the distribution of patients, with 33% of the group on ICS treatment for 6 weeks. The majority experienced a less than 10% change in FEV1. The responders had a significantly lower percent predicted FEV1 and FEV1/FVC (forced vital capacity) ratio at baseline than the nonresponders. Sputum eosinophils and FeNO were not statistically different between the groups.

For subjects who were labeled responders during the 6-week trial, results at the end of 16 weeks indicated that those who remained on ICS treatment maintained good asthma control. Responders
randomized to placebo for 16 weeks had worse asthma control as measured by the ACQ. Nonresponders did not have variable responses to ICS treatment during the 16-week trial. It did not matter whether patients continued ICS treatment or were switched to placebo. The ACQ results did not differ between the 2 treatment groups within the nonresponder category.

In summary, the PRICE trial found that short-acting β2-agonist response, a low percent predicted FEV1, and FEV1/FVC at baseline were all strong predictive biomarkers of ICS response. Response was confirmed by the mini ACQ, which was administered every 4 weeks to assess control. Nonresponse, or FEV1 improvement of 5% or less, indicated that these patients may not need an ICS in their treatment program. However, these results need further confirmation in larger, longer-term studies than this 16-week trial. If such studies confirm the results of this trial, different therapeutic strategies may need to be considered for ICS nonresponders.

**Variability in treatment response: distribution of individual responses for FEV1:** This study (Malmstrom 1999) demonstrates the clinical challenge posed by a variable disease such as asthma and describes the distribution of individual responses for forced expiratory volume in 1 second (FEV1) in patients taking montelukast sodium and beclomethasone. In this 12-week clinical study, the average percent change from baseline in FEV1 was 13.1% with beclomethasone, 7.4% with montelukast sodium, and 0.7% with placebo (P < 0.001 for each active treatment compared with placebo; P < 0.01 for beclomethasone compared with montelukast sodium). The distribution of individual patient responses for FEV1 was a unimodal, bell-shaped curve that was generally similar and largely overlapping for both montelukast sodium and beclomethasone. There was a variability of response to treatment ranging from excellent response, to partial response, to poor or no response. The mean percentage of asthma control days, defined as a day with no asthma attacks, no nighttime awakenings, and 2 or fewer puffs of β-agonist, was 46% for montelukast sodium and 49% for beclomethasone, a difference that is not statistically significant (P = 0.10).

**CLIC: characterizing response to a leukotriene receptor antagonist and an inhaled corticosteroid:** The objective of the Characterizing Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC) study was to determine whether patient responses to an ICS (fluticasone) and an LTRA (montelukast sodium) are concordant. The study examined the variability of response in 144 children aged 6 to 17 years with mild to moderate persistent asthma. The primary outcome variable was percentage change in prebronchodilator FEV1 from baseline to the end of each treatment period. Responses were also assessed for relationships to baseline asthma phenotype-associated biomarkers. After a 5- to 10-day characterization period, subjects were randomized to 1 of 2 crossover treatment sequences, with an 8-week period of either fluticasone propionate 100 mcg twice daily, or montelukast sodium, 1 tablet at night. In this study, there was no placebo control, which is important to note in the context of interpreting the results. An FEV1 of 75% or greater was predefined as the effect size that represented a clinically meaningful response. The results demonstrated an agreement in responses to the 2 medications at the end of the 8-week treatment periods, with a concordance correlation of 0.55, but with substantial variability among participants. As assessed by FEV1, 17% of participants responded to both treatments, 23% responded only to fluticasone alone, 5% responded to montelukast sodium alone, and 55% responded to neither treatment. The finding of substantial within-subject variability in the primary CLIC outcome of FEV1 response underscored a need for more outcome data on which to base recommendations for controller asthma medications for school-aged children (Szefler 2005, Zeiger 2006).

Accordingly, Zeiger and colleagues (2006) undertook an analysis to further characterize interpatient and intrapatient profiles and responses to fluticasone and montelukast sodium using CLIC subjects with mild to moderate childhood asthma. They examined the difference in asthma control days per week between fluticasone propionate and montelukast sodium (fluticasone minus montelukast sodium) for individual participants. In a comparison of individual responses, 29.3% of subjects achieved at least 1 more asthma control day per week with fluticasone than montelukast sodium, and 12.2% achieved at least 1 more asthma control day per week with montelukast sodium than fluticasone. Participants who experienced more than 1 day of improvement were balanced in terms of sequence and time period with both fluticasone and montelukast sodium treatment.

**Variability of response to pharmacologic therapy in outcomes measured:** summary: Patients with asthma may respond differently to different pharmacologic therapies (Martin 2007). Genetics may play a role in individual asthma response to asthma controller medications (Tantisira 2005, Tantisira 2007, Lima 2006). Intertreatment variability was observed in 2 studies of montelukast sodium versus beclomethasone (Baumgartner 2003, Israel 2002). Intertreatment and intrapatient variability was observed in response to fluticasone and montelukast sodium in children with mild to moderate asthma (Zeiger 2006).

**Clinical management of a heterogeneous disease:** from severity to asthma control: change in focus: The diversity of asthma – its heterogeneity in disease expression as well as response to treatment – is well documented and remains the subject of intense study. Meanwhile, current clinical guidelines and research offer methods of individualizing assessment and treatment. Both the 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) guidelines and the 2006 Global Initiative for Asthma (GINA) guidelines are based on controlling asthma rather than treating asthma based on the severity of symptoms (GINA 2007, NHLBI 2007). The rationale for the new focus on asthma control rather than asthma severity is based on several observations: 1) Asthma severity may change over months or years (GINA 2007, Bouquet 2007); 2) Asthma severity classifications provide an incomplete picture of the burden of the disease (Kwok 2006); and 3) There is a heterogeneous response to asthma treatment, even among patients with asthma of similar severity (Bouquet 2007).

In the EPR-3, severity is used to describe the intrinsic intensity of disease, during the patient's initial presentation, before initiation of long-term controller therapy. Asthma severity is assessed to guide clinical decisions about initiating the appropriate medication. Once the patient has started taking long-term control medication, the focus switches to control, the degree to which the manifestations of asthma (symptoms, functional impairment, and risk of possible adverse events) are minimized and the goals of therapy are met. The level of asthma control will guide decisions to either maintain or adjust therapy (NHLBI 2007).

**Rationale for choice of treatments for patients with asthma:** Different types of treatments are needed to control asthma because (Jones 2006): 1) Individual patients can vary in their response to different controller medications; 2) Patients may not respond to a particular controller medication, and their asthma symptoms may even worsen; and 3) It is not currently possible to predict a patient's response to a particular asthma medication. Effective asthma management involves ongoing education and a partnership between health care professionals and patients, as well as regular review of asthma control and treatment. As part of the importance of choosing the right medication for each patient, the NAEPP guidelines identify preferred and alternative treatments for each of the various steps (NHLBI 2007).

**Challenges in treating a heterogeneous disease: summary:** Asthma is a complex syndrome characterized by many clinical phenotypes and variable responses in outcomes measured. Genetic, environmental, and other factors can influence the degree of expression of asthma symptoms and the response to therapy. Clinical trials have demonstrated that variability of response is broad and is seen across
multiple therapeutic interventions. The increasing focus on asthma control is reflected in the evolving treatment guidelines, which recognize that asthma is not a static condition and successful control of symptoms may require the adjustment of therapy over time. Asthma therapy must be individualized by taking into account each patient’s need, circumstances, and responsiveness to therapy.

**Asthma treatment guidelines:** Asthma treatment guidelines provide an age-based framework for initiating therapy, and for stepping up and stepping down therapy using an evidence-based approach. The guidelines are definitely helpful and provide guidance on treatment decisions, but, if followed too rigidly, can result in the exact opposite of an individualized approach.

Asthma guidelines for children provide three equally preferred step-up options when children are uncontrolled by low dose inhaled corticosteroids. Until recently, the relative risks and benefits of those options were unknown. A recent New England Journal of Medicine article (Lemanske 2010) compared these options and provided supportive evidence. The investigators randomly assigned 182 children (6 to 17 years of age), who had uncontrolled asthma while receiving 100 mcg of fluticasone twice daily, to receive each of three blinded step-up therapies in random order for 16 weeks: 250 mcg of fluticasone twice daily (ICS step-up), 100 mcg of fluticasone plus 50 mcg of a long-acting beta-agonist twice daily (LABA step-up), or 100 mcg of fluticasone twice daily plus 5 or 10 mcg of a leukotriene-receptor antagonist daily (LTRA step-up). They used a triple-crossover design and a composite of three outcomes (exacerbations, asthma-control days, and the forced expiratory volume in 1 second) to determine whether the frequency of a differential response to the step-up regimens was more than 25%. A differential response occurred in 161 of 165 patients who were evaluated (P < 0.001). The response to LABA step-up therapy was most likely to be the best response, as compared with responses to LTRA step-up (relative probability, 1.6; P = 0.004) and ICS step-up (relative probability, 1.7; P = 0.002). Higher scores on the Asthma Control Test before randomization (indicating better control at baseline) predicted a better response to LABA step-up (P = 0.009). White race predicted a better response to LABA step-up, whereas black patients were least likely to have a best response to LTRA step-up (P = 0.005). In conclusion, nearly all the children had a differential response to each step-up therapy. LABA step-up was significantly more likely to provide the best response than either ICS or LTRA step-up. However, many children had a best response to ICS or LTRA step-up therapy, highlighting the need to regularly monitor and appropriately adjust each child’s asthma therapy.

Until recently, a lack of response to asthma medications was viewed as rare. Now, significant variation in treatment response for all asthma medications is expected. However, very little information has been available about methods to predict favorable treatment responses. Research conducted by the National Heart, Lung, and Blood Institute’s Asthma Clinical Research Network and Childhood Asthma Research and Education Network verified the variability in response to several long-term control medications, including inhaled corticosteroids and leukotriene receptor antagonists, in adults and children, with mild-to-moderate persistent asthma (Szefler 2010). The networks also identified potential methods to use patients’ characteristics, such as age and allergic status, and biomarkers, such as bronchodilator response, exhaled nitric oxide, and urinary leukotrienes, to help predict responses to inhaled corticosteroids and leukotriene receptor antagonists and to determine which of the two treatments might be more effective in individual patients. This information is now available to assist the clinician in personalizing asthma treatment at the time of initiating long-term control therapy.

Concerns about the function of the hypothalamic-pituitary-adrenal axis and the growth of children using corticosteroids continue to influence adherence with guideline treatment recommendations. Some children treated with inhaled corticosteroids grow well and some grow poorly when treated with inhaled corticosteroids, illustrating heterogeneity. Recently published studies continue to support a small one-year growth effect from the use of inhaled corticosteroids and have overturned the long-held notion that there is no long-term effect. In that regard, a study published last year showed that children who were short as a result of treatment for 5 years with inhaled corticosteroids did not regain that lost height during a multi-year follow-up period (Strunk 2009). Another recent study showed the dose-response effect of inhaled corticosteroids on the hypothalamic-pituitary-adrenal axis in children (Skoner 2010).

**References**


Luskin AT. What the asthma end points we know and love do and do not tell us. *J Allergy Clin Immunol.* 2005; 115:5330–545.


Martin RJ, Szefler SJ, King TS, et al.; for National Heart, Lung, and Blood Institute’s Asthma Clinical Research Center. The Predicting Response to
IV. Infection, Inflammation & Other Topics

IV.1. Infection, Inflammation & Other Topics – Gastroesophageal reflux

IV.1.1 The clinical manifestations of GER in children
M. Ghezzi, O. Sacco, D. Girosi, N. Ullmann, G.A. Rossi, Pulmonary and Allergy Units, Giannina Gaslini Institute, Genoa, Italy

Gastroesophageal reflux (GER) is a physiological process occurring with different frequency and characteristics in healthy infants, children and adults, most episodes being brief and asymptomatic. In contrast, GER disease (GERD) occurs when this normal event results in the occurrence of symptoms/signs or complications [1]. The most common clinical manifestations of GERD caused by gastric contents reflux include “typical symptoms”, related to the upper portion of the gastrointestinal tract, and “atypical supraesophageal” respiratory symptoms, affecting the respiratory tract [1,2]. Typical symptoms include regurgitation, vomiting, abdominal or retrosternal pain, dysphagia and hematemesis. Upper respiratory tract symptoms comprise, chronic sinusitis, laryngitis, hoarseness, vocal cord nodules, granulomas and ulcers, feeding-related choking, pharyngonasal reflux and/or cyanosis, recurrent cough/spasmodic cough, stridor, “pseudolaryngomalacia”, subglottic stenosis, posterior glottic erythema and oedema [1–3]. Involvement of the lower respiratory tract may be associated with apnoea, ALTE, recurrent aspiration pneumonia, persistent and/or nocturnal cough, wheezy bronchitis and “difficult-to-treat” asthma. Less commonly recognized presentation of GERD include Sandifer’s syndrome and unexplained “feeding problems”. One difficult task in managing reflux is to determine to what extent it is physiologic or constitutes a pathological condition. Indeed, some nocturnal aspirations of gastric reflux occur periodically also in normal healthy subjects, but clearly may result in recurrent and/or progressive lung disease in others. An association between GER and respiratory symptoms has been well documented, but a causal relationship between GER and respiratory symptoms is difficult to determine in an individual child since there are no gold-standard diagnostic tests [4]. Currently, the diagnosis of aspiration is made clinically with some supporting diagnostic evaluations. During the past 2 decades, GER has been recognized more frequently because of an increased awareness of the condition and also because of the more sophisticated diagnostic techniques that have been developed for both identifying and quantifying the disorder and to relate acid and weakly acid GER events with respiratory symptoms [5].

References
for pH monitoring. In other words: pH 4.0 may be an appropriate cut-off for heartburn, but it has not been validated in patients with respiratory symptoms caused by GER. Esophageal pH monitoring is often considered as an investigation technique studying esophageal motility, which it obviously does not. In fact, esophageal pH metry does even not measure GER. The technique simply measures changes in esophageal pH, not GER. The commercialization of esophageal pH monitoring devices in the 1980s changed the work-up of GER substantially. It took many years to discover advantages, but also pitfalls of pH monitoring. The first clinical tests were performed in the early 1960s by Miller [4]. Electronic technology has profoundly changed the practice of medicine, principally through its ability to monitor, record and analyze large volumes of data. The introduction of computers has provided physicians with powerful tools to identify elusive and intermittent disorders, such as GER disease (GERD). As a consequence of this technical evolution, measurement of the impedance in the esophagus has become possible. The basic principle of impedance recording is identical to pH-monitoring: registration of esophageal events with a probe placed transnasally and connected to a recorder. Impedance allows the detection of the frequency, the esophageal height and duration of reflux episodes, independent of the pH of the refluxate. The term “multiple intraluminal impedance monitoring” is preferred because of the concurrent measurement of impedance from multiple intraluminal recording segments. The method allows detection of GER based on changes in electrical resistance to electrical current flow between two electrodes, when a liquid and/or gas bolus moves between them (Fig. 1, Table 1). GER as measured by intraluminal impedance monitoring, Impedance detects GER if there is a sequential orally progressing drop in impedance to less than 50% of baseline values starting distally (3 cm above the lower esophageal sphincter) and propagating retrogradely to at least the next two more proximal measuring segments. According to the corresponding pH change, impedance-detected reflux can be classified as acid if the pH falls below 4 for at least 4 seconds or, if pH was already below 4, as a decrease of at least 1 pH unit sustained for more than 4 seconds. Weakly acidic reflux is defined as a pH drop of at least 1 pH unit sustained for more than 4 seconds with basal pH remaining between 7 and 4. Reflux is considered to be weakly alkaline when there is impedance evidence of reflux but the pH does not drop below 7 [5,6]. In many studies, weakly alkaline and weakly acidic reflux are grouped together as “non-acid reflux”. Intraluminal air (which has a very low electrical conductivity) provokes a rapid and pronounced rise in impedance [5].

The main indications for esophageal pH monitoring are (1) clinical and laboratory research, (2) clinical procedure to diagnose acid reflux, especially in children presenting with atypical GER manifestations and (3) the evaluation of the efficacy of treatment of GERD on the frequency and duration on the presence of acid in the esophagus [7,8]. Multichannel intraluminal impedance (measuring flux of ions) will measure more events than measurements of drops in esophageal pH, since not all reflux is acid.

**Hardware and software: pediatric needs:**

The **Device**: Purchase costs, system abilities, costs in use, number of measurements and durability of the material are factors to consider before purchasing equipment. Impedance equipment is considerably more expensive than pH metry devices. Of importance for pediatric use is a time indication on the display of the recording device (i.e., the number of data recorded, the real time and duration of the investigation) and the protection of event marker(s) to avoid erroneous use by the child [8]. A system should refuse to work if it has not been calibrated properly. There is no difference between a device for pH or impedance recording: it is a “box” that stores data in memory; at the end of the recording, the device needs to be connected to a computer to read-out the stored data. One of the advantages of pH and impedance monitoring is the possibility of obtaining an ambulatory recording, even in young children. The device should be as small and light as possible. For pH metry, devices no larger than a credit card, although of course a little thicker, are now commercially available. The utility of wireless technology for GER diagnosis has been validated in several studies, with improvements over catheter-based pH monitoring in tolerability, accuracy and sensitivity, as well as the ability to record periods both off and on therapy with proton pump inhibitors in a single study [9]. The major advantage of the wireless capsule is the possibility to allow prolonged pH recording in more physiologic conditions. The capsule sloughs off the wall of the esophagus in 7 to 10 days and passes out of the body naturally. However, data in children are currently limited [10].

**The pH and impedance electrode:** pH sensors or “electrodes” exist in several forms, of which the two most popular are glass and antimony. Ion-sensitive field effect pH electrodes are modified field effect transistors. Clinical studies require a pH sensor that is both affordable and reliable. Glass electrodes with an internal reference are “the best”, but are expensive and have a rather large diameter (3.0–4.5 mm) [11,12]. Although the passage of such an electrode through the nostrils of a baby is, most of the time, technically possible, it does not mean that it is well tolerated and that it is the best option. Owe to their smaller diameter, antimony (2.1 mm) or glass microelectrodes (1.2 mm) are preferable in infants. Antimony electrodes also exist with a diameter of about 1.5 mm for use in premature babies; these electrodes are too flexible for use in older babies. Glass electrodes have only one pH sensor. Antimony electrodes with multiple pH sensors may help to detect alkaline reflux episodes, although measurement of esophageal pH is not recommended to detect alkaline reflux [13]. Antimony electrodes with two sensors can also be helpful to evaluate the therapeutic efficacy of acid-reducing medication: the esophageal sensor measures the incidence of acid reflux, while the gastric sensor measures efficacy of the medication. Antimony is only poorly resistant to gastric acid, but the fact that acid should be reduced or minimized in these patients reduces the impact of this shortcoming. Thus, “Bilitec” (a technique measuring the presence of bile in the refluxed material) and non-PH dependent techniques such as impedance offer much more benefits to measure non-acid reflux compared with using pH-electrodes with multiple electrodes.

Glass microelectrodes and, historically also antimony electrodes need an external cutaneous reference electrode, which may cause erroneous measurement resulting from transmucosal potential differences. If the environmental temperature is high or the patient

---

**Table 1: Definition of types of gastro-esophageal reflux (GER) detected by intraluminal impedance**

<table>
<thead>
<tr>
<th>Type of GER</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid GER</td>
<td>pH falls below 4 for at least 4 seconds, or, if pH was already below 4, decreases by at least 1 pH unit sustained for more than 4 seconds.</td>
</tr>
<tr>
<td>Non-acid reflux</td>
<td>Weakly acidic and weakly alkaline GER</td>
</tr>
<tr>
<td>Weakly acidic reflux</td>
<td>pH drop of at least 1 pH unit sustained for more than 4 seconds with basal pH remaining between 7 and 4</td>
</tr>
<tr>
<td>Weakly alkaline</td>
<td>pH does not drop below 7</td>
</tr>
<tr>
<td>Gas reflux</td>
<td>Rapid and pronounced rise in impedance</td>
</tr>
</tbody>
</table>

**Fig. 1. Representation of impedance changes observed during bolus transit over a single pair of measurement rings.**
necessitates a manual analysis, the relevant question remains what can be attributed to reflux. Although impedance-interpretation shown the pitfalls of an arbitrary cut-off limit such as pH 4.0. Impedance: the technique is considered one of the advantages of impedance. Impedance-sensors, since the esophageal height of reflux episodes is, by consensus, positioned 5cm above the proximal border of the LES by means of a standard stationary esophageal manometry procedure. Ideally, as in adults, the electrode should be sited in the LES, whereas the other pH antimony sensor measures esophageal pH. Location of the electrode: The exact esophageal location of the electrode is of critical importance regarding the number and duration of acid reflux episodes recorded. The closer the electrode is to the lower esophageal sphincter (LES), the more acid reflux episodes will be detected [15,16]. In adults, the electrode is, by consensus, positioned 5 cm above the proximal border of the LES. Also in adults, determination of the position of the LES can be performed with a standard stationary esophageal manometry procedure. Study is generally regarded as the optimum method for pH probe localization [12]. In children, several other methods have been proposed to determine the location of the electrode: fluoroscopy, calculation of the esophageal length according to Strobel’s formula (distance from the nose to the cardia’s upper border measured from the tracheal bifurcation in cm), and fluoroscopy, ideally, as in adults, the electrode should be sited in reference to the manometrically determined LES. However, this has several inconveniences: (1) manometry in infants and children is time consuming, rather invasive, or at least unpleasant and (2) this method has the inconvenience that the electrode is located at a fixed distance to the LES; whereas the length of the esophagus increases from less than 10 cm in a newborn to over 25 cm in an adult. Moreover, manometry cannot be performed in all centers. Therefore, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Working Group recommended the use of fluoroscopy to locate the electrode [8]. The radiation involved is minimal, and the method can be applied in every center. As the tip of the electrode moves with and during respiration, the tip should be positioned in such a way that it overlies the third vertebral body above the diaphragm throughout the respiration cycle. Dislocation by a curled electrode is also prevented with fluoroscopy. If the pH device is exposed to x-rays, the data and calibration may be erased. For impedance it is also relevant to know the location of the impedance-sensors, since the esophageal height of reflux episodes is considered one of the advantages of impedance. Impedance: the technique: Experience with pH-monitoring has shown the pitfalls of an arbitrary cut-off limit such as pH 4.0. A similar comment can be made for impedance: the automated analysis considers only a drop of impedance of 50% or more as a reflux episode. However, it is likely that a drop of 49% also can be attributed to reflux. Although impedance-interpretation necessitates a manual analysis, the relevant question remains what level of decrease in impedance is needed to be considered as a reflux episode? A drop in impedance is not related to the volume of the refluxate. The multiple impedance rings allow the height of the reflux episode to be identified. If pH-monitoring is performed with a probe with multiple pH sensors, it is also possible to determine the height of the refluxate. The major difference between both techniques is restricted to the detection of non-acid reflux. As a consequence, another fundamental question arises: what is the clinical relevance of non-acid or weakly-acid and alkaline reflux? Patient preparation: Other than fasting, no special patient preparation is required for pH monitoring. The patient should fast for at least 3 to 5 hours before the study, depending on the age, to avoid nausea and vomiting. If the child is able to communicate, it is important to reassure the child at the beginning of the study and explain what will happen. The child should understand that the passage of the catheter through nostrils and pharynx is uncomfortable, but after the first few swallows, it will feel better. To facilitate insertion, a spray containing silicone can be placed on the electrode (but not on the pH sensor!) and/or the mucosa of the nostrils can be sprayed with a topical anesthetic. Sedation should not be used because the sedative interferes with swallowing and influence LES-pressure. Histamine, (H2) blockers and proton pump inhibitors should be stopped at least 3 or 7 days, respectively, before a diagnostic pH monitoring (except when the investigation is performed to evaluate the acid-blocking effect of the drug). Antacids are permitted up to 6 hours prior to the start of the recording. Prokinetics should be stopped at least 48 hours before the pH monitoring [15]. Whether acid suppressing medications decrease reflux events or only change the pH of the reflux events has been insufficiently validated with impedance. This issue is one of the priority areas for research with impedance. It is best not to start a pH meter study the same day that an upper gastrointestinal tract endoscopy is performed because the sedation, fasting and inflated air may be confounders. It is best to start pH meter at least 3 hours after a barium swallow or radionuclide gastric or esophageal studies. Patient-related influencing factors: recording conditions: Feeding, position and physical activity are examples of patient-related factors influencing reflux events. Patient-related factors can possibly influence the results of reflux investigations remain a controversial topic [8,15]. The answer to the fundamental question regarding whether patient-related factors should be minimized and standardized is difficult and necessarily ambiguous. If the reflux investigation is performed as part of a diagnostic workup in a patient, it is interesting to undertake the study during normal daily life. On the other hand, if the reflux investigation is performed as part of a clinical research project, recording conditions should be standardized. Standardization of recording conditions inevitably causes a loss of patient-specific information. Duration of the recording: The duration of the recording should be as close as possible to 24 hours and at least 18 hours, including a day and a night period both for pH and impedance measurements [8,17,18]. If pH monitoring is performed for diagnostic purpose, there is no indication for short-duration pH tests (eg, Tuttle and Bernstein tests, 3-hour postprandial recording). The first reports on the clinical use of pH monitoring concerned esophageal tests of short duration. Tuttle and Grossman developed the “standard acid reflux test” [19]. This test was modified by Sklar et al. and Brophy et al. and colleagues, demonstrating that pH tests can contribute to define abnormal GER. The Tuttle-test was reported to have a sensitivity of 70% [22]. However, after great initial enthusiasm for this test, criticism was overwhelming. The test is unphysiologic in requiring intragastric instillation of acid and various artificial maneuvers to raise intragastric pressure. In the early 1980s, it was reported that the false-positive rate might be as high as 20% and false-negative rates as high as 40% [23–25]. Bernstein and Baker demonstrated, in 1958,
that heartburn could be provoked by infusing diluted hydrochloric acid into the esophagus in susceptible individuals [26]. This test was reported to be 100% positive in heartburn patients [27]. A modified Bernstein test was used to illustrate the relationship between GER and apnea and stridor and between nonspecific chest pain and GER [28,29]. Provocative testing can be used in particular conditions to demonstrate the relationship between GER and specific symptoms such as bradycardia in relation to the presence of acid in the distal esophagus. However, provocative testing has the inconvenience that the investigation conditions are unphysiologic, which likely explains discrepancies reported in the literature. For instance, Ramet and colleagues showed prolongation of the R-R interval on ECGs in infants during provocative testing with instillation of acid in the esophagus, [30] whereas other investigators could not reproduce these findings in 24-hour recordings under more physiologic conditions [31,32].

There is now substantial evidence that both in controls and in the majority of infants and children with classic symptoms of GERD, esophageal acid exposure is highest during the day, probably because of provocation of GER by food ingestion and physical activity. Controls have more reflux upright than supine and more reflux awake than asleep [33]. The relationship between esophagitis and nocturnal acid reflux is far from clear [34–36]. Limited experience with impedance confirms knowledge for pH monitoring: more reflux during the day (during activity) than at night (during sleep), more acid reflux during fasting and more non-acid reflux during feeding.

The reproducibility of impedance-pH recording on 2 consecutive days is rather poor, especially for non-acid reflux [32]. The variability between the number of acid and non-acid reflux episodes with a second recording performed two days after a first recording have a high variation: 0.2–5.3 and 0.04–8.6 times the value obtained at day 1, respectively [37]. However, reproducibility of pH-monitoring on 2 consecutive days is reported to have high correlation coefficients, ranging from 0.88 to 0.98 [38]. Applying a similar study design, Nielsen and coworkers reported an overall reproducibility of 70% for impedance [39]. The reflux index at day 2 was 0.2–3.3 times the initially obtained value at day 1 [39]. Intraluminal impedance monitoring data can be read manually or analysed automatically using commercially available software. Over 95% of reflux events detected by automatic impedances pH analysis were confirmed by two independent investigators, although they added about 33% acid, weakly acid and non-acid reflux episodes [40]. The agreement between investigators for reflux episodes detected by manual reading of 24 hours impedance-pH tracing was only about 50% [40]. Inter-observer variability was reported much better in impedance recordings obtained in neonates during a period of 6 hours [41].

The discrepancy between automatic analysis and manual reading is influenced by the pre-set definitions of the automatic reading: the software indicates as acid reflux only those episodes in which the impedance falls below 50% of baseline in two consecutive channels simultaneously with a drop in pH below 4. This means that the reflux (or “drop in impedance”) should reach at least 5–7 cm above the pH channel to be detected as “acidic impedance reflux”. Most pediatric centres choose to register all reflux episodes detected with the pH channels independently from the impedance reflux events. More data are needed regarding the comparison between automatic and manual reading. It is clear that more reflux episodes and more non-acid reflux are detected by manual reading; however, there is some evidence that more reflux detected equates to better diagnosis. Moreover, manual reading induces human bias in the interpretation of the results. In general, “pH-reflux” does last longer than “impedance-reflux”, or in other words, acid exposure lasts longer than bolus exposure. This observation is likely to be related to a difference in clearance time between acid and bolus exposure.

**Feeding:** Feeding during pH monitoring is an area of controversy. On the one hand, it seems logical to forbid the intake of acidic foods and drinks. However, many popular foods and beverages have a pH of <5.0 (eg, cola drinks, fruit juice, tea, soup), resulting in a quite restricted diet. A too restricted diet might alter the patient’s normal dietary habits in such a way that the investigation is no longer performed in physiologic conditions. Electrodes are temperature sensitive; therefore, very hot and ice cold beverages and foods (eg, coffee, tea, ice cream) should be avoided [8]. Chewing gum or hard candy should be withheld because these increase saliva production and thereby induce swallowing and esophageal peristalsis, tending to normalize test results. This is also true for impedance recording: during periods of increased saliva production and swallowing, less reflux will occur. In older children, alcohol intake and smoking should be recorded on the diary.

In infants, it has been suggested to replace one or several feedings during pH monitoring with apple juice [42]. This solves the problem of gastric acidity after a milk feeding. Apple juice has a pH of about 4.0, a very rapid gastric emptying and is not part of normal infant feeding. Although the ingestion of acid, such as a cola drink, might simulate a reflux episode, the duration of ingestion is limited to a few minutes and most of the time irrelevant in relation to 24-hour data. It is also possible to eliminate these false reflux episodes with the help of a diary. Impedance (in combination with pH) tracing allows much better determination of the bolus-movement: from proximal to distal, as happens after a swallow, or from distal to proximal, as happens during GER.

The influence of a particular food on the frequency of acid GER episodes detected by pH monitoring might be opposite to its influence on the incidence of reflux episodes: for instance, a high fat meal provokes GER because of delayed gastric emptying [43]. Since the duration of postprandial gastric anacidity after a fat meal is prolonged, a meal with a high fat content will result in delayed gastric emptying and, thus, less acid reflux episodes will be detected by pH monitoring [43,44]. Postprandial GER after feedings varying in fat content is an interesting research topic for impedance. Some drugs that influence gastric emptying have a comparable effect on pH monitoring data: prokinetic drugs enhance gastric emptying, shorten the period of postprandial gastric anacidity, and prolong the periods during which acid GER can be detected. Combined impedance and pH recording may enhance understanding of the effects of various constituents of food on GER.

The impact of postprandial non-acid reflux decreases with age, since the number of feedings decreases, and with it the total duration of postprandial periods and the overall buffering effect of milk [45]. It seems logical that non-acid reflux events decrease with time elapsed from the last meal [46]. While symptom correlation (within a 5 minutes window) is similar between acid and non-acid reflux (25.2% vs 24.6%), reflux events reaching the proximal esophagus are more frequently associated with epigastric pain and burping [45].

**Position:** Different patterns of GER (upright, supine, combined) have been reported in adults and older children [47]. Orenstein and colleagues demonstrated that the prone sleeping position is the preferred position for infants as far as GER is concerned because crying time is decreased if compared with the supine position [48–50]. There is evidence that the prone anti-Trendelenburg 30° sleeping position reduces GER in normal subjects and patients, although the position is difficult to apply and maintain correctly (infants have to be tied up in their bed). Meanwhile, the literature on sudden infant death syndrome (SIDS) shows that infant mortality decreases if infants are put to sleep in supine position at birth [51,52]. The impact of this sleeping position on the diary during reflux monitoring. The impact of position has been analyzed through combined manometry and impedance in 10 healthy preterm infants (35–37 weeks of postmenstrual age): 89 reflux episodes were recorded (74% were liquid, 14% air and 12% with mixed contents) [53]. In the right lateral position, the total number of reflux episodes (as well the total as the liquid episodes) was significantly higher than in the left lateral position despite a faster gastric emptying in the right position. This finding
Interpretation and Parameters: Interpretation starts with a visual appreciation of the tracing, which is subjective and difficult to standardize. Nevertheless, it is one of the outmost importance to look at the tracing. A progressive constant reduction in esophageal pH at the end of a feeding, which continues up to the next feed, may be suggestive for cow’s milk protein allergy [57]. Parameters that are classically analyzed for pH monitoring are the total number of reflux episodes, the number of reflux episodes lasting more than 5 minutes, the duration of the longest reflux episode, and the reflux index (the percentage of time of the entire duration of the investigation during which the pH is less than 4.0). From all classic parameters, the acid exposure time or reflux index is the most relevant. The correlation between all four parameters is good, and they are closely related to the reflux index [58]. Results should also be automatically calculated for periods of interest, such as sleep, wakefulness, feeding, postprandial fasting and body position. A time relation between atypical manifestations (eg, cough, bradycardia, desaturation) and changes in pH (not necessarily a drop in pH below 4.0) should be searched for. The duration of reflux during sleep has been suggested to be a good selection criterion for reflux related to apnea in infancy (the “ZMD-score”) [59]. For unclear reasons, this parameter has been insufficiently validated. However, it should be noted that the response time of an antimony electrode (the time needed to reach 95% of the exact pH) is at least 5 seconds.

The “area below pH 4.0” is a parameter considering the acidity of reflux episodes, [60] which has been shown to correlate better with the presence of reflux esophagitis than with the reflux index in children [61].

Various complex reflux scoring systems (Johnson-Demeester Composite Score, Jolley, Branicki, Kaye, Boix-Ochoa scoring systems) have been developed. The majority of the parameters were developed for assessing reflux esophagitis in adults. Jolley and colleagues proposed a score for children [62]. However, there is abundant literature, both in adults and children, that not one parameter of pH monitoring (except the “area under pH 4.0”) and no single symptom has a high specificity for esophagitis. Endoscopy and histology remain the gold standard to diagnose esophagitis. In marked contrast to these complex scoring systems is the simple recommendation by some investigators that the reflux index or total acid exposure time should be regarded as the most important, if not the only, variable in clinical practice [58,60]. Scores based on symptom indices are not applicable in infants and young children.

A major interfering factor in the interpretation of pH monitoring data is the “yes” or “no” interpretation provided by computer software: a pH of 4.01 is regarded as normal, whereas a pH of 3.99 will be considered as acid reflux. Minimal changes in esophageal pH around pH 4.0 can be at the origin of different software interpretations, although without difference in clinical meaning. The oscillatory index, a parameter measuring the time pH oscillates around pH 4.0, was developed to evaluate this risk for erroneous computer interpretation [63].

A similar comment can be made regarding impedance: a drop in impedance of 50% is postulated to be a GER-episode. However, it is very unlikely that a drop in impedance of 49, 50 or 51% has a different meaning. Although impedance allows or more often requires a manual analysis, the relevant question that remains is: what is the decrease in impedance needed to be considered as a reflux episode? The drop in impedance is not related to the volume of the refluxate. If pH monitoring were to be performed with a probe with multiple pH sensors, it would be possible to determine also the height of the refluxate. The major difference between pH and impedance-pH monitoring is restricted to the detection of weakly acid reflux.

Normal ranges: As for any measurement, normal ranges are mandatory. However, because there is a continuum between physiologic GER and pathologic GERD, normal ranges should be regarded as a guideline for interpretation. Reproducibility has been shown for various parameters. Intrasubject reproducibility supports the diagnostic use of continuous pH monitoring. In general, a reflux index above 7% is considered as abnormal, a reflux index below 3% as normal, and a reflux index between 3 and 7% as indeterminate. However, normal ranges were developed to separate patients at risk for esophagitis from those not at risk, which is not the major indication of the procedure. Normal ranges proposed by one group can be used by another group only if the investigations are performed and interpreted in a comparable way. This means that materials and methodology should be identical. For some individuals and in some clinical situations, it may be more important to relate “events” (eg, coughing, wheezing, apnea) to recorded events rather than to know if the data are within the normal range. There are no normal ranges currently available for impedance. Significantly fewer acid reflux episodes are detected using pH monitoring combined with impedance when compared to pH monitoring alone [64]. Estimates of esophageal acid exposure using pH monitoring alone were two-fold higher than estimates derived using pH and impedance techniques. Of the total acid reflux episodes detected by pH monitoring alone, almost 3/4th could not be confirmed by combined pH and impedance [65]. Detection of significant numbers of “pH-only” episodes raises concerns regarding possible over-estimations of acid exposure that may occur when estimates are based solely on esophageal pH monitoring.

Weakly acidic reflux: Weakly acidic reflux was previously called non-acid reflux. The distribution of numbers of acid and non-acid reflux detected by impedance is listed in Table 2. Up to now, there has been general consensus that investigations measuring reflux during the postprandial period (ultrasound, radiology, scintigraphy) are of limited value in the diagnosis of GER-disease because of the high prevalence of GER in the postprandial period. The pH of reflux during a postprandial period is mostly above pH 4 (thus regarded as non-acid based on pH-monitoring criteria). However, based on experience obtained with impedance, there is general consensus that it is preferable to consider this type of reflux as “weakly acidic” reflux.

If a naso-gastric tube passes the cardia, impedance shows an increase in postprandial reflux (from 72 to 122 episodes) in preterm infants [65]. Del Buono confirmed these findings in neurologically impaired children: more than half of the reflux events are nonacidic and would therefore go undetected by conventional pH meter [66]. The number of reflux episodes, both acid and nonacid, and the median height of reflux events was increased in the subgroup that was followed through a premature subgroup (n=7) compared to another subgroup [47]. However, the difference in GER-events may well be explained by the difference in neurologic impairment between groups. In a small group of 7 healthy preterm newborns receiving nasogastric milk feeding, the mean prevalence of non-acid reflux (29 episodes/24 hours) was more than two-times the prevalence of acid reflux (12 episodes/24 hours) and about 80% of these reflux episodes reach the proximal esophagus [46]. The same group reported in a larger series of 21 healthy premature neonates a
much higher incidence of approximately 70 reflux events in 24 hours; of the reflux episodes, 25% were acid, 73% weakly acidic, 2% weakly alkaline [67]. In preterm infants, weakly acidic reflux is more prevalent than acid reflux, particularly during the feeding periods [67]. In contrast, similar to healthy adults, weakly alkaline reflux was uncommon. Most reflux events are pure liquid during both fasting and during postprandial periods; gas reflux is very rare. The majority of reflux events in asymptomatic preterms reaches the proximal esophagus or pharynx. The acid exposure related to reflux events and detected by impedance is significantly lower than the total acid exposure during 24 hours [60]. Increased acid exposure could be attributable to pH-only reflux events or, less frequently, to slow drifts of pH from baselines at approximately 5 to 6.5% [67]. Conversely, Condino et al. report in a group of 34 infants, aged between 2 and 11 months, that the distribution or acid and non-acid reflux is almost equal: 47% of the reflux episodes were acid and 53% non-acid [45].

Table 2. Number of reflux episodes (total and weakly acid) recorded by impedance in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>No. of children</th>
<th>No. of pH reflux</th>
<th>No. of pH reflux/imp/patient</th>
<th>% weakly acid reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinelli [93]</td>
<td>Typical and atypical GER</td>
<td>50</td>
<td>2922</td>
<td>58.4</td>
<td>51%</td>
</tr>
<tr>
<td>Peter [65]</td>
<td>Tube feeding</td>
<td>16</td>
<td>1152 (esophageal)</td>
<td>72</td>
<td>5%</td>
</tr>
<tr>
<td>Del Buono [66]</td>
<td>Neurologically impaired</td>
<td>16</td>
<td>425</td>
<td>26.6</td>
<td>56%</td>
</tr>
<tr>
<td>Lopez Alonso [40]</td>
<td>Preterm</td>
<td>7</td>
<td>284</td>
<td>41.0</td>
<td>46%</td>
</tr>
<tr>
<td>Lopez Alonso [67]</td>
<td>Preterm</td>
<td>21</td>
<td>1401</td>
<td>71</td>
<td>7%</td>
</tr>
<tr>
<td>Condino [45]</td>
<td>GER-Deaf</td>
<td>11</td>
<td>1261</td>
<td>115.8</td>
<td>51%</td>
</tr>
<tr>
<td>Condino [76]</td>
<td>Asthma</td>
<td>24</td>
<td>1636</td>
<td>157.3</td>
<td>51%</td>
</tr>
<tr>
<td>Omari [53]</td>
<td>Healthy preterm</td>
<td>10</td>
<td>89</td>
<td>8.9</td>
<td>7%</td>
</tr>
<tr>
<td>Corvaglia [54]</td>
<td>Healthy preterm</td>
<td>10</td>
<td>1054</td>
<td>105.5</td>
<td>56%</td>
</tr>
<tr>
<td>Wenzl [55]</td>
<td>Regurgitation term infants</td>
<td>14</td>
<td>1183</td>
<td>84.5</td>
<td>55%</td>
</tr>
<tr>
<td>Corvaglia [94]</td>
<td>Pathological regurgitation</td>
<td>5</td>
<td>316</td>
<td>63.2</td>
<td>78%</td>
</tr>
<tr>
<td>Del Buono [56]</td>
<td>Effect Gaviscon®</td>
<td>20</td>
<td>747</td>
<td>37.3</td>
<td>69%</td>
</tr>
<tr>
<td>Wenzl [66,70,71]</td>
<td>Physiological aspiration</td>
<td>22</td>
<td>364</td>
<td>16.5</td>
<td>89%</td>
</tr>
<tr>
<td>Peter [72]</td>
<td>Pathological aspiration</td>
<td>21</td>
<td>524</td>
<td>24.9</td>
<td>78%</td>
</tr>
<tr>
<td>Mousa [73]</td>
<td>Atelectasis</td>
<td>25</td>
<td>1211</td>
<td>48.4</td>
<td>49%</td>
</tr>
<tr>
<td>Rosen [74]</td>
<td>CBD</td>
<td>28</td>
<td>1822</td>
<td>65.2</td>
<td>45%</td>
</tr>
<tr>
<td>Thilmany [75]</td>
<td>CBD</td>
<td>25</td>
<td>3235</td>
<td>129.2</td>
<td>49%</td>
</tr>
</tbody>
</table>

With pH-monitoring, impedance is a technique that will allow a more accurate determination whether apnea of short duration is a physiologic phenomenon occurring frequently in relation to an episode of GER [69]. In a group of 22 infants, 364 episodes of GER were detected with impedance [70,71]. Visual validation records confirmed 165 apneas. Of these events; 49 (30%) were associated with GER and 38 (77.6%) were exclusively recorded by impedance [70,71]. A decrease of oxygen saturation >10% was observed in 19 reflux events recorded with impedance, of which only 3 (15.8%) episodes were acid (pH <4.0) [70,71]. Nineteen preterm infants (gestational age 30 weeks) presenting with apnea were studied at a mean age of 26 days (13–93 days): 2,039 episodes of apnea (median: 67; range: 10–346), 188 oxygen desaturations (median 6; range 0–25), 44 bradycardias (median 0; range 0–24) and 524 episodes of GER (median 25; range 8–62) were detected [72]. The frequency of apnea in a 20 second period before and after an episode of GER was not different than the frequency of apnea not related to a reflux-episode (0.19/min [0.00–0.85] versus 0.25/min [0.00–1.15]) [72]. The analysis and conclusions were identical for oxygen desaturations and bradycardias [72]. Mousa analyzed the temporal relationship between apnea and GER in a group of 25 infants presenting with an Apparent Life-Threatening Event (ALTE) or pathologic apnea [73]. A time interval as long as 5 minutes between apnea and reflux was considered acceptable to demonstrate a “temporal link” between the two phenomena [73]. In total, 527 apnea episodes were recorded but only 80 (15.2%) were temporally linked to a reflux episode. Of these 80 episodes, 37 (7.0%) of the total episodes of apneas were related to acid reflux and 43 (8.2%) to non-acid reflux. Thus, even when considering a time interval as long as 5 minutes, one can conclude that a relationship between reflux and apnea is uncommon [73].

Chronic respiratory symptoms such as chronic bronchitis, wheezing, chronic cough and infant apnea have been related to GER. A strong relationship between acid and non-acid GER and respiratory abnormalities was suggested by Wenzl et al.: in a group of 22 children presenting with repetitive regurgitation and chronic respiratory symptoms, impedance recorded 364 reflux events, of which only 11.4% were acid [68]. Three hundred and twelve (85%) of these reflux episodes, of which 12% were acid, were associated with irregular breathing [61]. In a minority of these episodes (n:19), oxygen desaturations of more than 10% occurred (3/19 or 19% of such episodes were acid). Analysis of the polysomnographic recording showed 165 episodes of apnea, of which 30% were associated with a reflux episode; again the majority (78%) of reflux episodes were detected with impedance only [68]. However, an association between pathologic proximal or mixed apnea and GER has not been convincingly demonstrated but has also not yet been well studied. Clear cut-off values discriminating normal from pathological children still need to be determined. The number of reflux events per hour (2 to 3 events per hour) is slightly lower in normal healthy preterm infants than in premature neonates with cardiorespiratory events (4 per hour) [67]. When compared with pH-monitoring, impedance is a technique that will allow a more accurate determination whether apnea of short duration is a physiologic phenomenon occurring frequently in relation to an episode of GER [69]. In a group of 22 infants, 364 episodes of GER were detected with impedance [70,71].

Chronic respiratory manifestations, such as coughing and wheezing, are reported to occur in older children with reflux. Rosen and coworkers reported their experience in 28 children (mean age: 6.5±5.6 years) with chronic respiratory disease under treatment with antacid medications [74]. A total of 1,822 episodes of reflux were measured with MII-pH; 45% of them were non-acid. Multivariate analysis showed a stronger association between respiratory symptoms and non-acid reflux episodes than with acid reflux episodes [74]. Also the height of the refluxate in the esophagus was related to respiratory symptoms: the higher the reflux, the stronger the association [74]. The association score between symptoms and episodes of reflux detected with impedance and pH-monitoring was 35.7±28.5 and 14.6±18.9 (p=0.002), respectively [74]. However, it is not too surprising that pH-monitoring detects less reflux during antacid treatment. In a series of 25 children (age 6 months to 15 years) with unexplained chronic cough, wheeze or spurtum production, data support a relation between acid GER and chronic pulmonary symptoms, but do not support a role of non-acid reflux in children with respiratory symptoms not on antacid medication [75]. Condino et al studied 24 children with recurrent asthma and concluded that both acid and nonacid reflux occur with equal frequency in children and that most symptoms occur in the absence of a reflux event [76]. In a selected group of 22 adults, a relation between chronic cough and GER was studied by combined manometry and MII-pH [5]. Using a time-frame of 2 minutes and symptom association probability, 69.4% of coughing episodes were considered independent of a reflux episode. When a “reflux-cough” sequence occurred, the reflux in 65% of cases was acid, in 29% weakly acid and in 6% weakly alkaline [5]. Contradictions in the literature on the role of acid and nonacid GER in children with
chronic respiratory symptoms may, in part, be explained to the fact that these studies have not considered whether reflux is primary (motility disorder) or secondary (to infection, allergy, respiratory efforts, etc.) in nature.

The use of pH alone for the detection of acid reflux is very sensitive but lacks specificity compared with MII-pH. pH alone may overdiagnose abnormal acid reflux. Also, the use of pH for the detection of weakly acid reflux has poor sensitivity [77].

**pH monitoring and other investigations:** Many different techniques to evaluate GER exist, focusing on different aspects, such as postprandial reflux (scintiscan, barium swallow, ultrasonography), histologic abnormalities (endoscopy), continuous measurements that are pH dependent (pH monitoring) or not (Bilitec, impedance), and pathophysiology by measuring the relaxations of the LES (manometry). Recent evidence in adults reveals the clinical utility of Bilitec monitoring showing a possible role for duodenogastrolesophageal reflux in a subset of patients who continue to report reflux symptoms in the setting of normalized esophageal acid exposure on high dose proton pump inhibitor [9]. However, bile reflux can also be detected by impedance. Bilirubin is as toxic to the esophageal mucosa as acid, but the number of patients with esophagitis and only pathologic alkaline or non-acid reflux and normal acid reflux is small [78,79]. In specific situations other techniques might be of interest such as lipid laden macrophages, pepsin and lactose in bronchial secretions. Abnormal pH monitoring does not accurately predict the risk for esophagitis [80,81]. In a group of reflux patients with esophagitis, the sensitivity of pHmetry is 88% and of scintigraphy is 36% [82]. In a group of patients with abnormal scintigraphy, the sensitivity of pH monitoring is 82%, endoscopy 64%, and manometry of the LES 33% [82]. Nonacid reflux may be inoffensive (simple postprandial) reflux at a neutral pH, but may also contain bile, which is toxic for the esophageal mucosa [83]. There is limited experience with esophageal bile monitoring in children. The overall correlation between scintiscanning and pH monitoring is acceptable (r = 0.78) [84]. However, during simultaneous pH recording and scintiscanning, only 6 of 123 reflux episodes were recorded simultaneously [85]. There is no correlation between the number of reflux episodes detected using scintigraphy and pH monitoring [86]. Barium studies seem to have a much lower sensitivity to detect reflux episodes if pH monitoring is regarded as the gold standard [84]. According to many authors, there is a high frequency of both false-positive and false-negative results with barium studies that relates to the short investigation time on the other hand and the intensity of reflux-provoking maneuvers on the other hand. Fifteen-minute postprandial period color Doppler ultrasonography was compared with 24-hour pH monitoring, showing agreement in 81.5% [87]. However, if pH monitoring was considered the gold standard, the specificity of the color Doppler ultrasonography was as low as 11%, and there was no correlation between the incidence of reflux episodes measured with both techniques [87]. A far higher number of reflux episodes is detected with impedance in comparison with pH monitoring because only 14.9% of all reflux episodes are acid [88]. However, only 57% of acid reflux episodes are detected with impedance [88].

**Conclusion:** The miniaturization of devices and electrodes has made pH monitoring a procedure that is easy to perform, even in the youngest children. Patient-related factors, such as feeding and physical activity, influence the results of pH monitoring. Impedance monitoring is the preferred method in children because it can be recommended in clinical practice. Hardware- and software-related factors, as well as patient-related factors and recording conditions, determine the results of both pH and impedance recordings. In clinical practice, pH monitoring is of interest in a subset of patients in whom GERD is suspected but who present without clear regurgitation or emesis and to measure the efficacy of treatment such as acid suppression and/or prokinetics. Impedance has theoretical benefits over pH monitoring, but the technique still needs clinical validation. Impedance is a costly and time consuming technique, which allows for the detection of all reflux events. The diagnostic sensitivity of MII may correspond to that of the pH probe in untreated patients, but superior to the pH probe in patients treated with anti-acid medications [89]. Episodes detected only by pH monitoring are numerous in children; therefore, pH monitoring should be included in pH-MII analyses [90].

Day-to-day variability of the number of non-acid reflux episodes is considerable [1] and the detection of non-acid reflux episodes has a high inter-observer variability [3]. Although impedance clearly records more GER-events than pH-monitoring, the advantage and the relevance of recording more episodes of GER in daily clinical practice needs to be demonstrated. Thus, impedance still needs to be considered as a clinical research tool. The clinical relevance of the detection of weakly acid and non-acid reflux is also still a matter of research, because current data are inconclusive and specific treatment is not available. Symptom-correlation analysis, especially for extra-esophageal symptoms, is likely to be more convincing with impedance than with pH-monitoring.

Since pH-monitoring is part of an impedance recording, it is likely that impedance will become more frequently performed in routine practice [91,92]. From the data presented in the chapter, it emerges that it is currently difficult to draw conclusions on the precise advantages of the application of MII-pH in children to detect GER-events. The heterogeneity in the studies (in terms of populations recruited and technical criteria such as time and symptoms association), and the lack of normative data and of outcome measures. More homogeneous inclusion criteria and analysis associated with a complete baseline and prospective clinical features are mandatory. Impedance is a new, promising technical development offering unexplored possibilities to investigate GER [91,92]. Although many papers suggest a degree of usefulness, the technique is still in a phase where the added value to other techniques in the routine work-up of patients needs to be evaluated and demonstrated without scientific rigor.

**References**


IV.1.3 The role of bronchoscopy in GER: from bench to clinical application

M. Kazachkov. Maimonides Infants and Children’s Hospital of Brooklyn, USA

Introduction: The association between gastroesophageal reflux (GER) and respiratory symptoms in children is well-recognized. The incidence of GER is dramatically increased in children with asthma and upper airway obstruction syndromes, but the causal relationship between GER and respiratory symptoms remains poorly understood. Multiple animal and human studies were conducted in the attempt to provide better understanding of the pathophysiologic link between GER and respiratory disorders. However, their results, although suggested presence of the link between two conditions but in general failed to explain the nature of this relationship. The goal of this lecture is to give an overview of experimental studies on the role of GER in respiratory disorders and to explain the role of flexible bronchoscopy in both research and clinical work related to the subject.

History of the subject: The “classic” animal studies of 1930–40s showed major negative impact of aspiration of acid and gastric content on morphology and physiology of lower airway. It raised interest in the phenomenon of GER as a potential contributor to airway morbidity. In 1981 Mansfield et al reported a significant fall in respiratory conductance during intraesophageal hydrochloric acid challenge in dogs. In the second phase of the study the vagus nerve was interrupted and intraesophageal hydrochloric acid instillation no
Impact of GER on upper airway:

more prominent after laryngeal and tracheal acidification than after provided more convincing changes in respiratory mechanics in Summarizing the above, experimental esophageal acidification not associated with any changes in lung function. Of notice, acid reflux without aspiration were related to significant acute changes in peak expiratory flow of total lung resistance, which was not evident during esophageal Tracheal effusion of little amount of HCL caused severe increase in the more sensitive and less specific spirometric, flow-volume loop and airway resistance parameters; the finding are unlikely to be clinically significant”. Laryngeal and tracheal exposure to gastric acid has been shown to cause more prominent changes in pulmonary function than esophageal acid exposure. Significant spasm of smooth muscles of the trachea occurs with laryngeal acidification of experimental animals but not with acidification of their esophageal mucosa. Tracheal effusion of little amount of HCL caused severe increase of total lung resistance, which was not evident during esophageal acidification. Spontaneous episodes of tracheal micro-aspiration were related to significant acute changes in peak expiratory flow in asthmatic patients. Of notice, acid reflux without aspiration was not associated with any changes in lung function. Summarizing the above, experimental esophageal acidification provided more convincing changes in respiratory mechanics in animals than in humans and bronchoconstriction was significantly more prominent after laryngeal and tracheal acidification than after esophageal acidification in both animals and humans.

Impact of GER on upper airway: At various times it was shown or speculated that GER has an effect on obstructive sleep apnea, chronic cough, hoarseness, recurrent croup, and upper airway obstruction (UAO). The causal relationship between GER and UAO is most likely bi-directional. It was suggested that UAO may cause GER due to presence of wide negative intrathoracic pressure swings, which could create an abdomino-thoracic pressure gradient sufficient to overcome the barrier of the lower esophageal sphincter. The animal model of acid-induced laryngitis was successfully created in the past. It histologically proved that heavy exposure of proximal esophagus and larynx to gastric acid ends up with ulcerative esophagitis and laryngitis. The symptoms of laryngitis associated with acid exposure known as posterior laryngitis or laryngopharyngeal reflux (LPR) are well-defined in adult medicine. They include chronic cough, “globe sensation” and hoarseness. However, extrapolation of this concept to pediatric medicine does not work every time. There is some evidence of causal relationship between LPR and hoarseness in children, but the attempts to link chronic cough in children to GER are not based on strong research grounds. Airway endoscopy remains to serve as a main tool in diagnostics of LPR. The Reflux Finding Score (RFS) was established for quantitative characteristics of LPR. It includes assessment of such endoscopic phenomena as laryngeal edema, vocal cord glaucoma, ventricular obliteration, posterior comissure thickening, subglottic edema, etc. RFS was validated in adult studies but, once again, its validity in pediatrics has never been established. The experimental research had added certain controversy to the subject – severity of acid reflux to proximal esophagus did not correlate with RFS in dogs. Overall, existence of LPR and validity of RFS for its assessment is accepted by adult medicine but the degree of impact of GER on upper airway diseases in children remains unclear.

GER and lower airway disease: There is a large body of literature dedicated to relationship of GER to lower airway disease. The “GER-asthma connection” keeps providing controversy to the research world and cannot be adequately discussed in the format of this lecture. There are two main principles suggested as an explanation for impact of GER on lower airway. First principle is based on the concept of “bronchospasm theory” and was discussed in this lecture earlier. Second principle suggests “secondary aspiration” of gastric content into lower airways and deserves our full attention. The result of aspiration of gastric acid, mixture of gastric acid and food, and even non-acidic gastric content (the latter may happen after aggressive use of acid reducing medications) is harmful for respiratory system to say the least. Major inflammatory changes, bronchoconstriction, chronic infection and bronchiectasis formation were proven to result from aspiration. GER-related aspiration into lower airway may be promoted by neurological disorder, muscle weakness and muscle discoordination. Upper airway obstruction syndromes may facilitate GER and related aspiration. There is a suggestion that this type of aspiration may occur even in children with no underlying abnormalities. Early detection and prevention of GER-related aspiration into lower airway becomes essential for airway health. That is why the concept of establishing of reliable “gold standard of aspiration” became very practically attractive. There are several biomarkers of aspiration suggested previously and widely used practically. Their detection in bronchoalveolar lavage (BAL) serves as a “proof of aspiration” in minds of many practitioners. However, the very fact of presence of biomarkers of aspiration in BAL has to be interpreted with caution. Lipid laden macrophages detection in BAL fluid was suggested as a sensitive diagnostic test for diagnosis of aspiration. It is known that certain amount of lipids is present in the cytoplasm of alveolar macrophages. These “endogenous” lipids are thought to originate from products of turnover of surfactant and cell membrane materials, which are engulfed by alveolar macrophages. There is substantial difference in amount of phospholipids in BAL fluid obtained from different animal species. For example, diving mammals have higher concentration of phospholipids in BAL fluid compared with humans and pigs. The dogs were found to have much higher amount of lipids in their cytoplasm than humans and some other animal species. The analysis of lipid composition of lung washings and BAL fluid of dog lung showed presence of “white layer” with a very high content of phospholipids, which was not described in other species. Accumulation of lipids in the cytoplasm of alveolar macrophages is observed in wide variety of pathologic conditions. They include aspiration, acute chest syndrome in sickle cell anemia, use of inhibitors of lysosomal phospholipase or treatment with intravenous fat emulsions. Relatively high amount of lipids was found in alveolar macrophages of children with cystic fibrosis and some other pulmonary diseases. In order to quantify the level of lipids in alveolar macrophages, the alveolar fluid is collected by BAL and the number of macrophages containing lipids along with the amount of lipids present in the macrophages is determined to calculate the lipid laden macrophage index (LLMI). Proven aspiration to lower airways is strongly associated with high LLMI. However, for the reasons mentioned above, the sensitivity of LLMI for detection of aspiration in children with pulmonary disorders is not high. Pepsin is a digestive protease, released by the chief cells in the stomach. The inability of the pulmonary and bronchial tissue to produce pepsin makes its presence in BAL an indicator of gastric content aspiration – the concept highly attractive to the diagnosis of GER-related aspiration.
Animal studies provided strong background for using pepsin assay in diagnosis of GER-related aspiration. Pepsin was reliably detected in BAL and tracheal aspirates of experimental animals after forced installation of gastric juice in their airway. No peptic activity was detected in control groups, which underwent installation of normal saline in the airway.

Pepsin was detected in increased amount in BAL of children with proven GER-related aspiration and its concentration correlated with presence of reflux of gastric acid to proximal esophagus. Children with GER and respiratory symptoms have significantly higher concentrations of pepsin in BAL than asymptomatic controls. Finally, enteral feeding was associated with a higher level of pepsin in neonates with chronic lung disease of prematurity.

Limitations of use of pepsin detection as biomarker of aspiration includes absence of reliable “gold standard” control as well as wide variability of pepsin concentration in BAL, which depends on dilution and timing of sampling after aspiration event. Overall, high reproducibility of animal and human studies make pepsin the most reliable biomarker of aspiration available now.

Present research studies address the validity of various biomarkers of inflammation in differential diagnosis of infection and aspiration.

**Conclusions:** GER-related respiratory disorders in children are a controversial topic for researchers and pediatric pulmonary practitioners. The experimental studies provided valuable data, which suggested several potential mechanisms of impact of GER on respiratory system. The theory of direct gastric content exposure and subsequent damage to upper and lower airway seems to be more solid than “bronchospasm theory”.

Although the impact of GER on upper airway is well-known and endoscopic evidence of GER-related upper airway disorders is validated in adult medicine, it still remains to be the area of controversy for the pediatricians. LLMi do not carry sufficient sensitivity to serve as a “gold standard” for aspiration into lower airway. The current research supports the promising role of pepsin as a reliable biomarker of GER-related aspiration in children.

**Suggested reference**


**IV.2.1 Aerosol antibiotics – not just for CF**

**B.K. Rubin. Jessie Ball duPont Distinguished Professor and Chairman, Virginia Commonwealth University Department of Pediatrics, Physician in Chief, Children's Hospital of Richmond, Richmond, VA, USA**

**Abbreviations:**

CF: cystic fibrosis  
CRS: chronic rhinosinusitis  
FEV1: forced expiratory volume in the first second of exhalation  
TSL: tobramycin solution for inhalation (TOBI)  
VAP: ventilator associated pneumonia

**Introduction:** Aerosols can deliver high concentrations of antibiotics to the airway with low systemic bioavailability, thus reducing toxicity. This approach is of particular value in patients with cystic fibrosis (CF), who require frequent courses of antibiotic therapy. In the phase 3 registration study, 468 patients with CF were enrolled in a 6-month masked, placebo-controlled trial of preservative-free, non pyogenic tobramycin solution for inhalation (TSL) 300mg, alternating between 4-week courses of tobramycin and placebo. The forced expiratory volume in 1 second (FEV1) increased by more than 11% by the end of 6 months, with a 36% reduction in the mean number of hospital days and a 10-fold reduction in sputum bacterial density. Other antibiotics being prepared for aerosol delivery include colistin, gentamicin, ciprofloxacin, levofloxacin, amikacin, and aztreonam. Although aerosolized antibiotics may find a role in the therapy of patients with diseases other than CF, the emergence of bacterial resistance to these antibiotics is a risk, thus efficacy must be clearly demonstrated for a favorable cost benefit.

**Non-CF bronchiectasis:** Bronchiectasis is caused by reoccurring or continuous presence of bacteria in association with airway obstruction. Although CF is the most common cause of childhood bronchiectasis, there are many other causes. Secretions in the bronchiectasis airway are similar to the pus found in the CF airway, and pulmonary complications and progression of disease in non-CF bronchiectasis is similar to CF bronchiectasis, thus many centers treat patients with bronchiectasis using aerosolized antibiotics. There have been only a few small studies of aerosolized antibiotics to treat pseudomonas infection in adults with non-CF bronchiectasis. Reported studies have been underpowered for long term outcomes of interest such as time to exacerbations, hospitalization, or frequency of exacerbation. Although there is a reduction in sputum bacterial density while patients are receiving TSL if Pseudomonas is the primary pathogen, this has not been associated with improved quality of life, decreased need for additional antibiotics, or improvement in pulmonary function. Dyspnea and wheezing appear to occur more commonly in adult patients with non-CF bronchiectasis than in CF patients who receive TSI and there is a concerning deterioration in airflow (FEV1) among patients with non-CF bronchiectasis who receive TSI when compared to those who receive placebo aerosol. It is unknown if other inhaled antibiotics such as colistin or aztreonam will be tolerated or have better long term outcome for the treatment of non-CF bronchiectasis.

It is important when conducting studies not only to ensure that they have sufficient power to detect clinically significant outcomes, but that the study population is fairly homogeneous. For example, aerosolized antibiotics may not be the most effective or efficient way to deliver antibiotics to a patient with isolated lobar bronchiectasis resulting from a severe respiratory infection or retained foreign body. As well patients with weakness, poor cough, underlying immunodeficiency, or other systemic causes of bronchiectasis are at high risk of disease recurrence unless the underlying cause of the bronchiectasis is treated along with treating the infection itself. Although the use of aerosol antibiotics for patients with non-CF...
IV.2.2 Management of infants newly diagnosed by neonatal screening

J. Sermet-Gaudelus, K. Southern. 1 CRCM, U 845, Université René Descartes, Paris, France; 2 Institute of Child Health, University of Liverpool, Liverpool, UK.

The successful expansion of newborn screening for cystic fibrosis (CF) across Europe has highlighted the need for clear guidance on the management of screen-positive infants, based on the best available evidence. In response to current varied practice, the ECFS Neonatal Screening Working Group developed Evidence based guidelines on the management during the first year of life of infants with CF diagnosed through newborn screening.

General statements focus on the necessity of a paediatric multidisciplinary team of CF specialists (physician, nurse specialist, physiotherapist, dietician, psychologist, and social worker) in a centre with appropriate equipment and resources to facilitate a level of care according to the guidelines. Measures must be in place to prevent cross-infection. Infants must be reviewed in clinic by the team every 4–8 weeks, and more frequently after diagnosis or if there are any clinical concerns. Education of the families must be implemented from diagnosis. Parents should be encouraged to ensure their infant receives standard childhood immunisations, according to national guidelines including Anti-influenza vaccination.

Monitoring nutrition and growth on a growth chart with age specific percentiles is mandatory. Growth targets should reflect genetic potential, sibling height and local population demographics. At diagnosis, infants must have pancreatic function assessed clinically and by measuring stool fecal elastase and repeated if necessary. Preventive nutritional care includes encouragement of breast-feeding, pancreatic enzyme replacement therapy (PERT) and fat-soluble vitamins supplementation in infants with pancreatic insufficiency (PI). Energy intake should be adapted to achieve normal growth. Higher intake (up to 150% of the dietary reference values for age) may be necessary. There is no evidence to support the routine use of hydrolysed formula, however, it may be of value for infants with non-CF malabsorption (short bowel syndrome, post-infectious lactase deficiency, cholestatic liver disease, and cow’s milk protein intolerance). Sodium chloride supplementation (2 mmol kg \(^{-1} \text{day}^{-1}\)) should be considered for all CF infants, and increased during periods of hot weather and with other causes of high salt loss. In infants with nutritional concern, dietetic increase calorie intake, review of PERT, and possibly interventions to reduce gastric acidity should be considered. If poor weight gain persists despite optimal PERT, other causes of poor growth/malabsorption should be excluded.

Monitoring pulmonary status includes respiratory cultures at each visit, according to best local practice. Techniques to facilitate airway clearance should be undertaken on a regular basis. Debate exists as to the best strategy in asymptomatic infants. Evidence of respiratory infection (cough, wheeze, increased work of breathing, and added sounds on auscultation) must prompt respiratory culture and additional antibiotic treatment. Bronchoalveolar lavage (flexible bronchoscopy) should be considered in symptomatic infants not responding to standard therapies if routine cultures are non-contributive. Antibiotic treatment must be initiated following recognition of Pseudomonas aeruginosa, even in the asymptomatic infant with a protocol aimed at eradication. Intravenous antibiotics should be considered if the infant remains symptomatic despite initial therapy or if respiratory cultures remain positive. If the infant remains symptomatic with persistently negative respiratory cultures, other causes, especially Gastro-Oesophageal Reflux, should be excluded.

The quantity and quality of published trials on the early management of infants with CF are poor. There is an urgent need for large randomised controlled trials of interventions in this screened population. Future trials may target: Anti-staphylococcal antibiotic...
CF-related complications. Treatment at a specialized CF center by and outside CF centers and prompt identification and treatment of exacerbations, implementation of effective hygienic measures in inflammatory therapy as soon as possible, early treatment of acute inflammation, improved mucous drainage, initiation of antimicrobial and anti-inflammatory therapy, augmentation of MCC and strategies that increase the life expectancy and quality of life of the patients.

The improved clinical status of the patients is mainly the result of a better understanding of the natural course of infection and inflammation in the progression of lung disease in CF. The survival of patients with cystic fibrosis (CF) is progressively improving. The discovery and cloning of the CFTR gene over 21 years ago led to the identification of the structure and function of the CFTR chloride channel. New therapies are expected to further increase life expectancy of the patients.

Currently, there are a number of potential drugs for treatment of CF lung disease in clinical trials. These therapies are targeted at all points in the pathogenesis of lung disease, from gene transfer to drugs that treat mucus, infection and inflammation in the airways. An exciting development is that of modulation of the abnormal protein that causes CF, the cystic fibrosis transmembrane conductance regulator (CFTR), where drugs are targeted at specific defects in CFTR transcription, processing or functioning. Inhaled therapies are being developed to augment airway surface liquid height, either by modulating the abnormal ion channel function in the airway epithelial cell or by rebalancing with osmotic agents. Anti-inflammatory therapy is also of great interest in CF and there are several candidate drugs in clinical trials. A number of antibacterial agents formulated for inhalation are at various stages of study or newly approved, which should improve options for chronic management of airway infection. Hopefully, many of these potential therapies will come to market and will further extend the life expectancy of people with CF.

Pneumonia is still one of the most important causes of mortality in children, especially among those under the age of 5 years. This is most significant in developing countries, where incidence rates are up to 10 times greater than in developed countries [1]. Almost 2 million children died from acute respiratory infections in the year 2000, most from pneumonia. More than half of such children were living in Africa and Southeast Asia [2]. It is estimated that more than 150 million episodes of pneumonia occur every year among children under five in developing countries, accounting for more than 95 percent of all new cases worldwide. Between 11 to 20 million children with pneumonia will require hospitalization, and almost 2 million will die from the disease. The incidence of pneumonia among children decreases with age. Data on the pathogen-specific causes of pneumonia are limited, and available information is often difficult to interpret. It is known that Strepococcus pneumoniae is the leading cause of severe pneumonia among children in developing countries. Bacteria also contribute to non-severe pneumonia cases, but to a lesser extent, and more cases are probably of viral origin. Another major cause is Haemophilus influenzae type b (Hib). Other pathogens include important viruses, less common bacteria and fungi. However, more specific information for the aetiology of childhood pneumonia is not available especially in the developing world.

UNICEF and WHO have published guidelines for diagnosing and treating pneumonia in community setting in the developing world.
The approach is proven, affordable and relatively straightforward to implement [3]. Amoxicillin is effective drugs against bacterial pathogens and are often used to treat children with pneumonia in developing countries. There is concern that many of these children may be caused by viral in origin and are receiving antibiotics unnecessarily. This could increase antibiotic resistance in the community. Infants under two months with signs of pneumonia/sepsis are at risk of severe illness and death more quickly than older children, and should be referred to a hospital immediately [4]. Preventing children from developing pneumonia in the first place is essential for reducing child deaths. Key prevention measures include promoting adequate nutrition (including breastfeeding and zinc intake), raising immunization rate of three vaccines which have the potential to save millions of children’s lives by reducing deaths from pneumonia (pneumococcal conjugate vaccine, Hib vaccine, and measles vaccine) and reducing indoor air pollution. HIV-positive children are less likely to develop HIV-related pneumonia if they are given a daily dose of cotrimoxazole. Recent research also suggest that hand washing may play a role in reducing the incidence of pneumonia.

Conclusion: Pneumonia is still nowadays a disease associated with social and economic burden, affecting a large number of children worldwide. The WHO criteria for diagnosing pneumonia in communities with few resources has had a positive impact record on mortality in the past decades but concomitantly it introduced a practice associated with the overuse of antibiotics due to criteria that have far greater sensitivity than specificity for children under the age of 5 years. There is a need for new, rapid, and inexpensive tests able to differentiate viral from bacterial pneumonia and to continue investing in the development of more efficient vaccines for organisms associated with pneumonia.

References

IV.3.2
Respiratory disease, tuberculosis and HIV in African children
E. Maleche-Obimbo, University of Nairobi, Kenya

Respiratory disease is the number one cause of hospitalization and death in African children, with an estimated 35 million cases and 1 million deaths annually (compare industrialized countries 1.6 million cases with one death annually). Out of every 2 children that die in the world from pneumonia, 1 is an African child. Factors that contribute to this include poverty, over-crowding, indoor pollution, high prevalence of malnutrition and Human Immunodeficiency Virus (HIV) disease. The major identified aetiological agents are bacteria (S. pneumoniae, H. influenzae type B, Staphylococcus, M. tuberculosis [TB]) and viral (Respiratory syncytial virus). In addition HIV infected infants commonly have gram negative bacterial pneumonia, TB and opportunistic organisms such as Pneumocystis and cytomegalovirus, sometimes with polymicrobial infection. The increasing antimicrobial resistance observed in HIV infected children is of concern. HIV infected children in Africa experience a higher incidence of pneumonia and TB, poorer response to treatment, and higher mortality from pneumonia and TB than HIV uninfected children. Although improved access to antiretroviral therapy (ART) has markedly reduced this morbidity and mortality, <50% of those who need it currently access ART, and even on ART it appears that they continue to experience more respiratory morbidity than HIV negative children.

Diagnosis of TB in children in Africa is frequently delayed due to the similarity between its clinical presentation and other common (frequently concurrent) diseases such as malnutrition and HIV, the paucibacillary nature of the disease and inability of young children to produce sputum, often coupled with low availability of mantoux test, radiography and rapid diagnostic tests. The clinical spectrum of TB seen in African children, and the challenges experienced in managing HIV-TB co-infection are discussed. Key high impact preventive strategies to reduce respiratory disease mortality in Africa include disease specific vaccinations, optimizing nutrition, prevention and early treatment of childhood HIV, chemoprophyaxis, and use of locally adapted standardized case specific management guidelines for acute respiratory infection and TB.

References

IV.3.3
Pollution/biomass fuel exposure and respiratory illness in children
L. Gochicoa-Rangel, L. Torre-Bouscoulet. Department of Pulmonary Physiology. Instituto Nacional de Enfermedades Respiratorias, México, D.F., Mexico
Correspondence: Dr. Laura G. Gochicoa. Department of Physiology, Instituto Nacional de Enfermedades Respiratorias, Talpan 4502, México D.F. 14080. E-mail: gochis@drt.com

Introduction: Environmental pollution is a global public health problem that affects all living beings. Air pollution can occur in open urban spaces (outdoor) or in enclosed spaces (indoor). Contaminated air contains gasses, dust, odors and smoke. There are two types of contaminants [1]:
1. primary: those that are expelled directly into the air as a result of combustion processes, including sulfur dioxide (SO2), carbon monoxide (CO), vapors from fuels and solvents, lead (Pb) and suspended particles; and
2. secondary: once in the air, some primary contaminants react with other compounds to form contaminants that are equally or even more toxic, such as ozone (O3), nitrogen dioxide (NO2) and some particles. These contaminants can be originated by industrial activities, services and transport, and also by natural sources like volcanic eruptions or fires. Resources used as fuels could be solids (charcoal, firewood, dung, animal and vegetable residues), or non-solids (kerosene, liquid gas from petroleum, gas, electricity).

One of the principal sources of indoor air pollution in developing countries is the smoke produced by the utilization of biomass fuels in poorly-ventilated homes. Such fuels are used for cooking or producing light and heat and these include any plant or animal material that is deliberately burned by humans for use as a combustible [2,3].
Epidemiology: According to the WHO, in the year 2000 it became clear that cooking is a dangerous activity and that the indoor air pollution produced by burning solid fuels is one of the ten major health risks in the world; since that year and for the first time, indoor air pollution was considered an international health problem; but even though remarkable efforts have been done to combat this threat, the results are scarce and poverty has made that more people use this energy source [2]. It has been estimated that almost one-half of the world’s population (three billion people) use these energy sources on a daily basis for cooking, illumination and heating. Of these, 2.4 billion lives in houses where the energy source for cooking and heating consists of solid biomass fuels (wood, charcoal, dung and residues from animals and dried vegetable matter) and that 0.6 billion uses charcoal as their energy source [4]. Calculations suggest that some two billion kilograms of biomass are burned every day in developing countries. Estimates indicate that in some areas of China, India and sub-Saharan countries in Africa as much as 90% of inhabitants are exposed to biomass smoke. In developed countries there are also some communities exposed to biomass smoke due to their use of wood as a source of heat. The constant increases in the cost of other energy sources encourage the use of biomass as an energy source, even in developed nations, particularly Canada and Australia. In addition to the above, exposure to biomass smoke produced by forest fires must also be considered [5]. Estimates suggest that in developing countries, constant exposure to biomass smoke is responsible for 1.5 to 2 million deaths per year, most of which (approximately 1 million) correspond to children below 5 years of age [4,5].

Biomass smoke: The way people cooks in these places is very diverse, either using three big rocks (Fig. 1), an U-shaped hole in a wall, or as charcoal, holes in the ground, or malfunctioning earth or metal stoves. Much of the time, the combustion in this kind of devices is incomplete and leads to discharge of smoke formed by fine particulate matter which fills the living area, and since there is poor ventilation in such homes, they achieve high levels of indoor pollution [6].

The most important substances in biomass are the particulate matter less than 10 μm and 2.5 μm (PM10 and PM2.5), carbon monoxide (CO), nitrogen and sulfur oxides (NO2, SO2), aldehydes, aromatic hydrocarbons and free radicals, among others. Many of these substances act as irritants or as carcinogenic or co-carcinogenic compounds [5]. The PM2.5 are particularly more harmful, as they penetrate deeply into the lungs. The most widely used solid contaminant is wood, either in its natural state or as charcoal. Wood smoke is a complex mixture of various particles and volatile substances that contribute different organic and inorganic compounds. More than 200 chemical compounds have been identified in wood smoke and more than 90% of them can be inhaled because of the diameter of such particles is less than PM2.5 [5,6].

To gain an idea of this problem, guidelines published by the WHO recommend that good air quality requires concentrations of PM10 below 50 μg/m3 and levels of PM2.5 below 2.5 μg/m3. A household that cooks with firewood may have 24-hour mean PM2.5 levels in the range of 300 to 3,000 μg/cm2, or as high as 30,000 μg/m3, during cooking [7]. On the other hand, the Environmental Protection Agency of the United States recommends an average of 9 ppm CO or 10 mg/m3, in 8 hrs; in places where people use biomass as a fuel, CO reaches levels of 2 to 50 ppm, but getting to be up to 500 ppm [7]. As mentioned above, the degree of exposure depends on the ventilation, the type of stove and the time that a person remains inside the home. There is evidence that women and children are most affected by time-consuming in-house tasks, and in the case of children, the most affected are those who are carried by their mothers on the back, exposing them to large quantities of smoke [5].

Pathogenicity of biomass smoke in the respiratory system: The exposure to pollutants during childhood leads to several pulmonary diseases during adulthood. This is explained by the decrease of lung growth due to air pollution in childhood, because there may be common cellular and molecular mechanisms that impaired innate host defenses, increasing the susceptibility to respiratory infections, and also because lung damage initiated in childhood may contribute to an emerging global health issue, namely, COPD due to biomass smoke exposure [9]. There is some uncertainty about the mechanisms whereby smoke causes airway disease, but it is though that oxidative stress may be a component, as oxidizing radicals are present in biomass smoke and are released by inflammatory cells [6]. The constituents of biomass smoke produce deleterious effects on the airways that can be acute or chronic. They cause damage in the defense mechanisms of the respiratory apparatus. Acute effects of exposure include: necrosis of the tracheobronchial epithelium, inflammatory responses by the tracheobronchial epithelium, mucociliary dysfunction, dysfunction of the alveolar macrophages, airway hyperreactivity, reduced pulmonary compliance, and a reduced ventilatory response. Chronic damage includes: peeling of the epithelium of the airways, pulmonary edema, peribronchial and perivascular infiltration by neutrophils, bronchiolitis, lymphoid follicle hyperplasia, eosinophilia and reduction of bacterial elimination (Fig. 2). These effects could explain the association between exposure to biomass smoke and excessive respiratory morbidity and mortality that occur in places of high prevalence [5], where people die as a consequence of acute respiratory infections.

![Fig. 1. Indoor air pollution. Contaminants and biomass fuels.](image1)

![Fig. 2. Acute and chronic biomass damage.](image2)
This association increases in children who are carried on their mother’s back during cooking (OR, 3.1: 95% CI 1.8–5.3) [5].

A recently published meta-analysis showed that children exposed to biomass smoke are three times more likely to develop acute respiratory diseases than those whose major source of fuel is kerosene or LP gas; and that those who survive have a high risk of developing pulmonary illnesses as adults, including COPD, chronic bronchitis, asthma and tuberculosis [4]. Thus, exposure of children to PM adversely affects lung growth and increases their vulnerability to infection [9].

A study conducted in Mexico demonstrated that children exposed to biomass smoke had significantly higher values of 1-hydroxy pyrene (which is a biomarker used to monitor the presence of polycyclic aromatic hydrocarbons) than children exposed to highways with heavy sanitary landfill and brick kiln communities [10].

Several studies in children have established an association between values of pulmonary function or airflow obstruction and chronic exposure to biomass smoke. Children exposed to outdoor pollution show carbon particles in alveolar macrophages, which are directly related to the amount of PM exposure [11] and inversely related to pulmonary function measured by FEV₁ [12]. A study in China demonstrated that children exposed to coal smoke (when this substance is used for cooking) manifest a significant reduction of FEV₁, FVC and PEF. In India, a study was conducted comparing patients exposed to biomass and those who cooked with LP gas and found a significant decrease in pulmonary function in children exposed to biomass; similar results were also demonstrated in Turkey and Jordan [13]. It has also been reported that in 5-to-14-year-old children there is an association between exposure to solid biomass smoke and exacerbations of asthma, with a relative risk of 1.6 (95% CI 1.0–2.5). Nonetheless, the relationship between indoor pollution and development of asthma is controversial. Longitudinal studies are needed to demonstrate these associations [5].

Prevention: The ideal way to prevent damage is the total or partial reduction of exposure through the implementation of strategies designed to modify the fuel sources used for cooking and heating. It has been shown that simple actions like ventilating the dwelling (opening doors and windows, installing chimneys or bonnets) can reduce the number of deaths among children associated with this problem by 83–85%. But this is not an easy task because it depends on many factors, including cultural and economic aspects, degrees of development, resources, technical capacity and the domestic needs of each individual and the population [5]; thus, the long-term results of these interventions are yet unknown.

Outdoor and indoor pollution are risk factors that are completely preventable. It is important that physicians and governments of different countries join forces to intervene and reduce the exposure and, hence, the health risk. Many nations have developed programs to improve air quality, with special emphasis on small particles. However, there are still many regions in the world where concentrations of environmental pollutants remain very high with no regulations related to air quality.

Whatever the case, the most important program for improving indoor and outdoor air quality is educating children, as they are the only ones who can make our world a better home.

Acknowledgements: We would like to thank Diego Alejandro García Hernández for provide us with the photograph from a small community in San Pablo Isayoc Texcoco, Estado de México, México.

References

IV.3.4 Managing CF in resource poor settings
M. Shamaly, Gaza, Palestine

Introduction: Cystic fibrosis (CF) is one of the most life shorting genetic diseases in the Caucasian population. It also occurs among other ethnic groups with variable though lesser frequency. The major clinical manifestations of the disease are pancreatic insufficiency resulting in malabsorption, and chronic pulmonary infection due to host defense defects in the airway mucous membranes and associated high salt concentration in airway secretions. When CF was first identified over 50 years ago, the average age of survival was approximately 10 years. Modern and aggressive therapies at specialized CF centers increased the average age of survival to 16 years in 1980’s until today where the mean age of survival is in the mid thirties. The quality of life has similarly improved over this period. However, some of these therapies are expensive and remain unaffordable to patients living in resource poor areas and countries. The aim of this presentation is to highlight our experience in treating patients with CF in the Gaza strip.

Reasons to establish a CF center in Gaza: Currently, 1.8 million people live in Gaza. Cystic fibrosis is the in the West bank and Gaza strip has never been studied and the prevalence of CF in the Palestinian population is unknown. Notably, children that have been diagnosed and hospitalized with CF in Gaza have deteriorated quickly due to lack of appropriate therapies. Until recently, no specialized CF center with trained personnel existed in Gaza and patients have been cared for at CF centers in Israel. Under the Hamas government, few efforts have been made to educate health care personnel in the care of children with CF. The Ministry of Health staff know little about this disease, patients are managed by physicians who are not specialized in this field, and there are no protocols or regimens that have been adapted to treat patients with CF. Additionally, there have been no specialized CF clinics or CF medications available to treat patients with CF that require hospitalization. System inefficiencies have allowed for only a limited amount of medications to be delivered to a small number of patients.

Aim of the project: Parents of CF patients in Gaza funded a CF organization and sent an international call for help to build a
CF center in Gaza. The establishment of a CF center located in a hospital in Gaza should provide the full spectrum of health services for CF patients including diagnostic capabilities, appropriate consultative services and treatment modalities, and the ability to provide psychosocial support. Establishment of such a CF center would open new opportunities for physicians, nurses and other health care personnel to train in CF centers outside of Gaza in order to obtain expertise and specialization with this disease.

Methods: The CF center team at Hadassah Hebrew University Medical Center, Jerusalem, Israel was the only program that answered this international plea for help. The CF center at Hadassah established a 1-year training program funded by the Peres Center for Peace to train a team of 3 physicians, a nurse and physiotherapist from Gaza that volunteered to participate in this project. The training took place at Hadassah Hospital in Jerusalem, Israel with trainees living in Jerusalem during the week and commuting home to Gaza during the weekends.

Results: After the year-long training period, a CF center was opened in Gaza. A database was established to register all known CF patients. We are currently aware of 80 patients with CF in the Gaza strip. Based on population projections, it is estimated that there are between 140–300 patients with CF in Gaza, a large number of which have not been diagnosed and others whom have died of CF complications without an established diagnosis. Limited resources under the current Hamas government continue to be problematic. Medications are still in short supply and are available mainly by private donations. Prior to the arrival of the trained CF team, the medical staff frequently dosed those medications that were available such as pancreatic enzymes incorrectly. Trained personnel are still unable to provide physiotherapy to many patients. Appropriate and effective inhalation machines are not available and have been replaced by cheaper, less efficient units. Hypertonic Saline is the standard mucolytic/secretion clearance treatment. Families are preparing this at home by mixing 15% Hypertonic Saline with 0.9% Normal Saline. Inhaled antibiotics such as TOBI are not available and are replaced by inhalation of intravenous solutions such as Gentamicin. Nutritional supplements are rarely available and again, only by private donation. Food enrichment is done by families by mixing cereal with oil. Appropriate next steps in the evolution of the CF program in Gaza are to work with health authorities to understand the importance of providing basic therapies to patients.

Conclusions: In resource poor countries, treatment of CF patients should begin with the establishment of a center with dedicated and specialized team members. Creative and less expensive therapies can be used including saline mixtures and inhalation of intravenous antibiotics. Likewise, appropriately trained family members can provide physiotherapy. Lobbying governments unwilling to dedicate appropriate resources to treat patients is not always effective.

IV.4. Infection, Inflammation & Other Topics – Childhood respiratory infections: the new frontiers

IV.4.1 Pneumococcal conjugate vaccines as a probe for better understanding pneumococcal respiratory infections

R. Dagan, Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Respiratory infections are the leading cause of morbidity and mortality in young infants and young children globally. Streptococcus pneumoniae (Pnc) is the leading bacterial pathogen in respiratory infections and a major cause of deaths in children <5 years of age (~11% of all deaths in this age group [1]). Around 14.5 million episodes of serious pneumococcal disease occurred in the year 2000 in children <5 years with ~825,000 estimated deaths, due to serious pneumococcal disease. 95% of these serious pneumococcal disease cases and mortality were attributed to pneumonia [1]. Most serious diseases caused by pneumococcal respiratory disease occur in only 10 countries in Africa and Asia, but pneumococcal respiratory infections are a serious problem globally [1]. Thus it is clear that preventing pneumococcal severe respiratory infections is one of the main global goals [2]. However, what is pneumococcal respiratory disease? The tradition wisdom that pneumococcal pneumonia presenting as alveolar (or lobar) pneumonia is shown to be wrong, although this entity is definitely enriched with bacterial pathogens in general and Pnc in particular.

Using any diagnostics tools detects a bacterial pathogen in only a low proportion of LRI and pneumonia. On the other hand, series of efficacy studies with pneumococcal conjugate vaccine in the US, South Africa, the Gambia and the Philippines showed that the use of pneumococcal conjugate vaccines (PCVs) reduced alveolar pneumonia by ~33%, pointing clearly to an important role of Pnc in alveolar pneumonia [3]. However, other endpoints, such as any severe pneumonia (efficacy of 21%) and any clinical pneumonia (efficacy of 8%) were all affected by PCVs, suggesting that Pnc has a role even in the less “classical” pneumonia. Furthermore, the less specific entities were far more common than the classical alveolar pneumonia endpoints, thus a smaller percentage of efficacy in the “non-specific” pneumococcal cases led to a much higher vaccine attributable reduction (VAR) of disease. Thus, for each episode of culture-proven pneumococcal pneumonia, 7 radiologically-proven pneumococcal pneumonia episodes and 19 “clinical pneumonia” episodes could be prevented [3].

Even more surprising findings were that PCVs could reduce what was considered until recently as “pure” viral infections. The first work was from Israel, where a PCV could reduce 20% of bronchiolitis episodes in daycare center toddlers attendees [4]. Later, in a series of studies, Madhi and Klugman showed in South Africa that hospitalization due to virus-positive pneumonia including RSV, human metapneumovirus, parainfluenza 1–3 and influenza A and B, were significantly reduced by a PCV [5]. This was the proof of the concept that viral infections often represent in fact a common viral-bacterial co-infection was proven. By reducing the pneumococcal component, severity of the viral infections can be reduced, resulting in a significant reduction in the proportion of the children ending up being hospitalized.

After the introduction of the 7-valent PCV (PCV7) to various countries, a reduction in overall outcomes in respiratory infections could be observed. In the US, <30% of hospitalizations due to all-cause pneumonia was seen in the post PCV7 in children <2 years of age. However, at the same time, a 20% reduction of hospitalization due to non-pneumonia LRIs was seen [6] showing that for each case of invasive pneumococcal disease prevented, hospitalization of 14 cases of respiratory infections was prevented by PCV7. The series of studies reviewed above contributed on the one hand to our understanding of the role of pneumococci in respiratory tract infections, but on the other hand showed that the use of PCV was associated with much greater than expected reduction in respiratory disease. The insights acquired on pneumococcal role in the overall respiratory disease burden and the insights acquired on the PCV role in the reduction of such disease lead to the term “vaccine probe” which means that the use of vaccine can show us its unexpected benefit and teach us about pathogens and epidemiology.

We also learned that some serotypes not included in the PCV7 are important, especially the atypical pneumococcal serotypes, namely pneumoencephalitis (or empyema). The most important serotypes are 1, 3, 5, 7F, 14 and 19A, of which only serotype 14 is included in the PCV7. Thus, no one should be surprised that empyema was not reduced after the introduction of PCV7, especially given the fact that another non-Pnc pathogen responsible for this complex entity was MRSA. In fact, an increase in this entity was observed worldwide regardless of PCV7 administration. On the other hand, the new generation PCV10 and PCV13 vaccines...
contain the “empyema serotypes” and thus after switching from PCV7 to PCV13, we are expecting reduction of empyema. However, the effectiveness of the new PCVs has still to be proven, following vaccine implementation.

In summary, the vaccine probe studies has taught us how important PCVs are and that the widespread use of these vaccines can reduce mortality and morbidity. Much more can be learned if additional high quality surveillance programs are set up in countries adopting the vaccine.

References

IV.4.2 How to manage complicated pneumonia
I.M. Balfour-Lynn. Royal Brompton Hospital, London, UK
Correspondence: i.balfourlynn@ic.ac.uk

In previously healthy children, community-acquired pneumonia is normally treated easily and without complications using intravenous or oral antibiotics [1]. However sometimes complications may be encountered which require tertiary respiratory care:

• Parapneumonic effusion / empyema  
• Lung abscess  
• Necrotising pneumonia  
• Pneumatocoeles  
• Pneumothorax  
• Atelectasis  

Another complications is failure to improve in the usual timeframe, and this may require further investigations such as bronchoscopy, CT chest scan etc.  

The mainstay of treatment is administration of intravenous antibiotics and it is important to pick the right one(s), especially in the absence of microbial isolation. Supportive therapy may also be necessary, for example oxygen, intravenous fluids or even ventilatory support.  

Further intervention may be required for example an intercostal chest drain for fluid or air. Management options for an empyema are well described [2]. However where possible it is best to stay out of the chest cavity especially in the presence of necrotising pneumonia, a lung abscess or pneumatoceles.  

Follow up is also important to exclude an underlying cause such as a congenital thoracic malformation or immunodefiency. Prognosis and long term outcomes are usually excellent.

References
IV.5. Infection, Inflammation & Other Topics – What happens to the child with lung disease as a young adult?

IV.5.1 Sequelae of pneumonia and future abnormal spirometry in adulthood: the chicken or the egg?

A. Bush, Paediatric Respiriology, Imperial School of Medicine at National Heart and Lung Institute; and Honorary Consultant Paediatric Chest Physician, Royal Brompton Hospital, London, UK

Introduction: It is essential to realise that the consequences of early life events last until death. The seminal observation by David Barker was that over a wide range of geographical locations and environments, there was a close and direct correlation between infant mortality from bronchitis and pneumonia, and standardised mortality rates from bronchitis fifty years later [1]. Thus any understanding of COPD that does not take into account childhood events is bound to be flawed.

General principles: Firstly, we know that devastating attacks of necrotising pneumonia may occur in apparently totally fit children, and, despite extensive cavitational, radiological and clinical recovery is complete. However, we also know that there may be devastating long term sequelae, for example after adenovirus lower respiratory tract infection. However, the vast majority of respiratory infections are trivial, and any sequelae subclinical.

Most importantly, we know that if the question posed in the title is to be answered rigorously, only a prospective study is adequate. This is illustrated by a major prospective cohort study, in which information about (amongst other things) childhood pneumonia were collected [2]. When the children were adults, their recall was tested. Only 106/193 (55%) correctly remembered having pneumonia as a child, whereas 53/159 (33%) reported having pneumonia were collected [2]. When the children were adults, their recall was tested. Only 106/193 (55%) correctly remembered having pneumonia as a child, whereas 53/159 (33%) reported having pneumonia as a child, whereas 53/159 (33%) reported having pneumonia.

Recent evidence has shown that pathological data fit very nicely with the epidemiological studies. Two cross-sectional studies have established that infants with severe cough and wheeze at a median of twelve months of age have essentially normal lung function, with no evidence of eosinophilic inflammation or reticular basement membrane (rBM) thickening but by a median age of three years, both features are present, although rBM thickening is not to the same degree as in severe paediatric or adult asthmatics [8,9].

What does the data actually show? As stated above, the definitive study has not been done, nor is it likely to be. All the data are flawed in various ways. In the prospective study alluded to above [2], a history of childhood pertussis infection was associated with a non-significant decrement in adult FEV₁, (−41±70 ml, p = 0.25) and a trivial but statistically significant decrement in FVC (−81±76 ml, p = 0.04). For pneumonia, the corresponding decrements were FEV₁, −102±73, p = 0.006, and FVC, −173±70 ml, p = 0.001. The effects were more marked if there was no history of wheeze, and especially if the pneumonia was early on (age 0–2 vs. 2–7 yr olds). This last suggests that the pneumonia caused the damage in the crucial period of lung growth, but this is more than hypothesis generating. However, problems with the study are that although there was prospective recording of infection, not of lung function was only measured in the previous persistent asthmatics [10], putting them in a high risk group for COPD. Whether this is because of a ‘single hit’ in utero, or multiple effects of the gene developmentally, has yet t be determined. Intriguingly, other studies have shown that early life influences come back to cause trouble after a mid-life symptom free honeymoon period. The prospective Aberdeen studies have shown that young children who had ‘wheezy bronchitis’ (which today would be termed ‘episodic, viral wheeze’) attained normal spirometry aged 45–50 years, unlike those with persistent asthma; but had the same accelerated rate of decline lung function as the previous persistent asthmatics [10], putting them in a high risk group for COPD.
again, no pre-morbid measurements [12]. The number followed up was very small, and two technical points need to be remembered. Firstly, spirometry is not a sensitive technique for very distal airway function; and secondly, the normal range is wide, and quite extensive falls in individual lung function, within the normal range, are perfectly possible and will not be appreciated without pre-morbid measurements.

Another good prospective study, unfortunately also without pre-morbid measurements, followed up 62 children with ‘bronchiolitis’, 29 with pneumonia, and no wheeze, and 52 control children [13]. They were re-assessed age 8–9 with spirometry, including mid-expiratory flows, and a methacholine challenge test. At follow up, 15% of the bronchiolitis group, 7% the pneumonia group, and 2% controls had been given a diagnosis of asthma. Bronchial hyper-responsiveness was seen in 62% bronchiolitis children, and 45% of the pneumonia group; and decreased mid-exp flows in 29% bronchiolitis and 21% pneumonia children.

A superb study in the Gambia recruited 190 children hospitalised for pneumonia 1992–4; they could subsequently traced 83 of the group, of whom 69 were still alive, and all but one participated in the study [14]. 67 controls were randomly recruited, although not in a formalised randomised manner. Both groups underwent spirometry, a questionnaire, and anthropometry. Asthma was diagnosed in 9 cases, and 3 controls; and 'lung disease' in 13% cases, 4% controls. There was a nearly 3-fold risk of post-pneumonia chronic lung disease. Conducting such a study was a brilliant feat under the circumstances. Problems include that there was no pre-morbid data, of whom 69 were still alive, and all but one participated in the study. This entity accounts for all children. If polysomnographic evaluations are performed in these snoring children, approximately 25% will be diagnosed with obstructive sleep apnea.

In recent years, epidemiological and pre-post surgical treatment analyses have identified substantial morbidities that primarily affect cardiovascular and neurobehavioral systems, causing pulmonary as well as systemic hypertension, nocturnal enuresis, reduced somatic growth, severe cognitive and behavioral problems that resemble attention deficit-hyperactivity disorder in young children, and sleepiness in older children. The overall morbidity is associated with marked increases in healthcare-related costs. It is agreed that if timely diagnosis and intervention are not implemented, some of these morbid complications may not be completely reversible, leading to long-lasting residual consequences.

It is known that among adolescents with neurobehavioral problems there is a large proportion of children who snored during childhood. SDB during middle- to late-childhood is related to abnormal daytime performance, especially inattention and learning difficulties, that may result in significant functional impairment at school. It is also known that when compared to a matched group, children that underwent surgical removal of the obstruction improved in terms of school grades on 1 year follow up. Moreover, the increasing prevalence of obesity in children has revealed a clinical picture of OSA that is markedly suggestive of the typical presentation of OSA in adults, and remarkably differs from the presentation of OSA in children. This entity accounts nowadays for almost 50% of all cases seen in pediatric sleep clinics, mostly in adolescents. The “changing faces” of OSA patients from childhood to young adulthood will be discussed, critically reviewing

References

IV.5.2

The snoring child, implications for adulthood

A. Goldbart, Department of Pediatrics, Sleep-Wake Disorders Unit, Saban Pediatric Center, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Frequent and loud snoring is a very common condition affecting approximately 10% of all children. If polysomnographic evaluations are performed in these snoring children, approximately 25% will be diagnosed with obstructive sleep apnea.

In recent years, epidemiological and pre-post surgical treatment analyses have identified substantial morbidities that primarily affect cardiovascular and neurobehavioral systems, causing pulmonary as well as systemic hypertension, nocturnal enuresis, reduced somatic growth, severe cognitive and behavioral problems that resemble attention deficit-hyperactivity disorder in young children, and sleepiness in older children. The overall morbidity is associated with marked increases in healthcare-related costs. It is agreed that if timely diagnosis and intervention are not implemented, some of these morbid complications may not be completely reversible, leading to long-lasting residual consequences.

It is known that among adolescents with neurobehavioral problems there is a large proportion of children who snored during childhood. SDB during middle- to late-childhood is related to abnormal daytime performance, especially inattention and learning difficulties, that may result in significant functional impairment at school. It is also known that when compared to a matched group, children that underwent surgical removal of the obstruction improved in terms of school grades on 1 year follow up. Moreover, the increasing prevalence of obesity in children has revealed a clinical picture of OSA that is markedly suggestive of the typical presentation of OSA in adults, and remarkably differs from the presentation of OSA in children. This entity accounts nowadays for almost 50% of all cases seen in pediatric sleep clinics, mostly in adolescents. The “changing faces” of OSA patients from childhood to young adulthood will be discussed, critically reviewing
Bronchiectasis is a morphological term used to describe irreversible dilatation of the airways, often with thickened wall, associated with frequent bacterial infections and inflammatory destruction of the surrounding tissue. Since Laennec's first description of ectatic bronchi in pathological specimens in 1819, the term has been used more to define both clinical and radiological disease. Bronchiectasis not caused by cystic fibrosis (CF) is perceived to be rare in western societies, thus been named an ‘orphan’ disease while the condition remains an important cause of chronic suppurrative lung disease in the developing countries. A decline in hospital admission rates for in the United Kingdom has been noted since the 1950s, with improved sanitation, nutrition, vaccination mainly against pertussis, measles, and use of early antibiotics. Two national bronchiectasis prevalence reports has estimated at 0.5 per 100,000 children under 15 years in age per year and 3.9 per 100,000 per year overall in Finland and at 52:100,000 overall in the United States. However recent reports of high prevalence, morbidity, and mortality within certain communities like native Alaskan children, Pacific Islanders, and New Zealand Maori:A prospective national study of bronchiectasis occurrence requiring both clinical and CT evidence of disease, described a high incidence in New Zealand children (3.7 per 100,000 under 15 years old per year) with significant regional and ethnic disparity.

Improved ability to recognize bronchiectasis on the basis of high resolution computed tomographic scanning, may change previously reported incidences even in developed countries. Bronchiectasis is characterized by airway inflammation. The inflammation appears to arise from obstruction of airway passage, immune deficiency and persistent infection. This inflammatory process predominantly of lymphocytes, which may lead to progressive pulmonary damage. However, there are no established animal models of bronchiectasis or studies performed in the early stages of the disease. A study that investigates clinical, radiological and laboratory features of children with non-cystic fibrosis bronchiectasis showed significant correlation between HRCT severity scores and symptoms, FEV1, sputum IL-8 and TNF-alpha levels which proved ongoing inflammation. Most of the pathological descriptions were made between 1930–1960 when vast numbers of operative and postmortem lung specimens were available. Reid categorized bronchiectasis as having three main phenotypes; (1) tubular: smooth dilation; (2) varicose: dilated with multiple indentations; (3) cystic: dilated bronchi with blind ending sacs [5]. This definition can only tell us the progression of the disease without giving any hints about the pathophysiology or etiology.

Bronchiectasis is a heterogeneous condition and can be considered the end result of a variety of different factors. Previous studies have reported that an underlying cause for bronchiectasis can not be determined in about 30% of patients. However with improving diagnostic techniques the proportion of idiopathic patients have changed, especially with recognition of more subtle immunological abnormalities and improving facilities for the assessment of primary ciliary dyskinesia. The prevalence of idiopathic cases in different series varies from 17–40 % depending on the facilities. Among the identified etiologies, post-infection (post measles, pertussis, adenovirus, tuberculosis) have a decreasing frequency in developed countries, whereas genetic diseases, primary ciliary dyskinesia, alpha 1-trypsin (AAT) deficiency, atypical cystic fibrosis, immune deficiencies have been increasingly recognized. Untreated asthma, undiagnosed foreign body aspirations may represent missed opportunities, but commonly reported. Aspiration and gastroesophageal reflux, collagen vascular disorders and other conditions such as sarcoidosis, Young syndrome, Mounier-Kuhn syndrome, Ehler-Danlos syndrome, Marfan syndrome, yellow nail syndrome are less frequently reported etiologies.

Bronchiectasis establishes when inflammatory and infectious damage to the bronchial and bronchiolar walls leads to a vicious cycle of airway injury, which is enhanced with on going inflammation, documented increased concentrations of elastase, interleukin-8, tumor necrosis factor, and prostanoids in sputum analyses and bronchial mucosal biopsy specimens. Bronchiectasis should be suspected in children who present with chronic productive cough, airway obstruction, and recurrent infections. The diagnosis is made by high-resolution CT scans. There is no evidence based consensus on the treatment of non-CF bronchiectasis. Some beneficial effect on lung functions were reported of long-term, oral, low-dose azithromycin use. Azithromycin also reduced bronchoalveolar lavage neutrophilia and interleukin-8 mRNA.

The management of non-CF bronchiectasis still proves to be difficult in developing countries. Prompt and effective antibiotic use is essential in acute infectious exacerbations. Antibiotic therapy should be prescribed based on bacterial cultures and sensitivity. The use of inhaled steroids remains controversial, however cessation of inhaled steroids with bronchial hyperreactivity were reported to have an increase in bronchial hyperresponsiveness and a decrease in neutrophil apoptosis. Surgery is performed in fewer cases, and there are few data about long-term results of medical and surgical treatment in these countries. Comparing surgery and medical treatment does not seem to be appropriate, as the patients will benefit from either one or the combination of these treatment modalities.

Long term consequences of childhood bronchiectasis have been recently documented. Many reports regardless of analysis strategy have shown that children with bronchiectasis have significant airway obstruction which deteriorates over time. Patients with bronchiectasis have found to have disturbed sleep associated with severity of disease. Night-time symptoms and hypoxemia during sleep may affect sleep quality in children with bronchiectasis. Poor sleep quality may impair growth, learning, and emotional development of children. Patients with bronchiectasis who snored had poorer sleep quality and patients with wheezing had significantly higher rate of snoring.

Other long term outcomes of childhood bronchiectasis include impaired left ventricular diastolic functions and osteopenia. Osteopenia is reported to be more common in children with non-CF bronchiectasis compared to controls and the risk of osteoporosis and osteopenia increases with age.
References


V. Pearls

V.1. Pearls – The art and science of bronchoscopy

V.1.1 How, where and when to perform a bronchial biopsy? Clinical applications

P. Pohnen1, K. Urbanová1, T. Svobodová1, J. Uhlík2, L. Hornofová2.

1Division of Pediatric Pulmonology, Pediatric Department, 2Department of Histology and Embryology, 3Department of Pathology and Molecular Medicine, Charles University, 2nd Faculty of Medicine, University Hospital Motol, Prague Czech Republic

Correspondence: Prof. Petr Pohnen MD PhD FCCP, Pediatric Department, University Hospital Motol, V Úvalu 84, 15006 Praha, Czech Republic. E-mail: petr.pohnen@LFMotol.cuni.cz

Introduction: Sampling of tissue during bronchoscopy has been a long term established method of obtaining information about pathological lesions and processes in the bronchial mucosa. Main role of this technique is in the diagnosis of malignant tumors in adults. In children, bronchoscopic biopsy had been used much less frequently as the indications of bronchocentesis are mostly different to those in adults and tumors of the airsacs are rather rare. However, understanding of the importance of morphological description and confirmation of pathological processes in the bronchial wall in children with chronic bronchial pathologies has brought bronchial biopsy to an attention.

Indications of bronchial biopsy: Flexible bronchoscopy has now been widely used in the diagnostics of respiratory pathologies in children of any age. Assessment of airway patency, excluding of congenital anomalies, stenoses and instability of the airsacs belong to the most frequent indications. These are usually well described using just visual investigation and anatomical evaluation, while morphological evaluation using a mucosal biopsy is not always necessary. Other indications comprise chronic respiratory symptoms, such as persistent or frequently recurrent pulmonary infiltrations, long-term coughing with or without production of sputum, and wheezing. In these cases, anatomical and visual evaluation is usually not sufficient and other methods are required to describe and diagnose the pathology more accurately. Among these usually the bronchoalveolar lavage and mucosal biopsy are very helpful. Targeted biopsy is extremely useful also in evaluation of abnormal intrabronchial structures or masses.

Techniques of bronchial biopsy: Brush biopsy: Brush biopsy is an endobronchial technique whose purpose is to sample superficial cells from the pathological lesions or, in diffuse disease, from the affected mucosa. It has been often used in adults for a diagnosis of malignant lesions, in children the indication is usually to sample material for cytological analysis of inflammation, evaluation of infection (e.g. tuberculosi) or to obtain viable cells for ciliary studies. The technique differs according to the size of used bronchoscope and its working channel. A standard protected brush technique can be used with the bronchoscopes with 2.2 mm channel. Thinner pediatric bronchoscopes (e.g. 3.6 and 2.9 mm scopes) are equipped with the 1.2 mm channel, therefore, only unprotected thin brushes can be used. To prevent losing of the sampled material during the withdrawal of the brush through the channel, the unprotected brushing is usually left as a last procedure during bronchoscopy and after sampling the brush is only just withdrawn into the channel and removed together with the bronchoscope. Then the brush can be pushed out again to remove the sampled material for further processing.

Endobronchial biopsy: Compared to brush biopsy, the aim of bronchial biopsy is to obtain a small piece of tissue that contains all the relevant structures and cells for appropriate histological analysis. In localized pathologies, such as visible endobronchial lesions, nodules or masses, the biopsy must be taken directly from the visible lesion. This may be difficult mainly in lesions that can be approached only with extensive flexion of the instrument or in some mucosal lesions not sufficiently protruding from the mucosa that require a tangential approach. Another technical problem limiting the yield of bronchial biopsy is the size of available forceps. This is not an issue when using bronchoscopes with the 2.2 mm channel. For these instruments, different types of reusable or single-use forceps are available. The most widely used type of forceps for pediatric bronchial biopsy is the fenestrated long oval cup forceps that usually provides sufficiently large sample for an appropriate histological evaluation.

More difficult is to obtain an appropriate bronchial biopsy in smaller children while using a bronchoscope with the channel of 1.2 mm in diameter. Only few models of such thin forceps are available and due to their very small sizes, the biotic samples are often inadequate. Nevertheless, there is a growing number of papers publishing the results of the analysis of sufficient bronchial biopsies in small children what suggests that with proper experience and technique and in a very good co-operation with the histological laboratory, also these small samples can be used for both diagnostic evaluation and research.

The site for bronchial biopsy is derived from the expected pathology and visual assessment. In visible localized pathologies, the biopsy has to be taken directly from the lesion. In general pathologies, the site of biopsy is usually a properly accessible site with a possibility of a good grasp by the forceps. This is mostly any of the interbronchial carinas, where the positioning of the forceps and the embedding into the mucosa is better that anywhere else. To avoid distortion of the histological result by possible secondary changes, it has been recommended to avoid sampling from the main carina or from the origin of the right upper lobe bronchus. It is always better to sample more specimens (usually 3–4) to make sure that at least some will be adequate for analysis.

Processing of the histological specimen: the sequence of processing depends largely on the purpose of the biopsy and expected staining and analysis. For simple morphological analysis, the sampled tissue can be immediately fixed in formaldehyde and transferred to the laboratory for embedding, cutting and staining. For basic evaluation, the standard hematoxylin-eosin staining is usually sufficient; however, some targeted staining protocols can be used for more detailed analysis. Among these, mainly stainings for collagen and other matrix proteins or stainings emphasizing mucus producing elements can be useful. For research analysis, the immunohistochemistry has been frequently used, mainly for analyzing cell populations of special interest or various extracellular or intracellular proteins (tenasci, fibronectin, metalloproteinases, growth factors). The material intended for the immunohistochemical analysis should be fixed by buffered paraformaldehyde rather than standard formaldehyde and the fixation should not be prolonged (optimum 4 hours). In special indications, such as ciliary structural studies, the specimen can be processed for ultrastructural analysis using electron microscopy. In this case, special protocols and fixatives are used.
The yield of bronchial biopsy: Bronchial biopsy is certainly an unique method for evaluation of endobronchial masses and confirming or excluding possible neoplasms. It may help in diagnosing other non-malignant endobronchial pathologies, such as tuberculosis, sarcoidosis, virus-induced lymphoproliferation, granulations etc.

In general non-malignant pathologies, most of the recent studies using bronchial biopsies in children have focused upon asthma and analysis of remodeling of bronchial wall in children with asthma of different severity. These studies have confirmed presence of eosinophilic inflammation, deposition of matrix proteins and increased mass of bronchial smooth muscle and vasculature [1]. Some of these studies confirmed presence of such changes even before the clinical diagnosis of asthma or in children with only intermittent symptoms [2,3]. From purely research approach, this has been now more and more used also in clinical evaluation in differential diagnosis of obstructive symptoms in children. Presence of cellular infiltration and marked signs of remodeling can support the diagnostic and therapeutic decisions in children with atypical symptoms.

Safety of bronchial biopsy in children: Safety concerns were apparently the main reason why routine use of bronchial biopsy was slowly accepted as a possible supplemental method in pediatric flexible bronchoscopy. However, growing experience with this method in children proves that correctly indicated and properly performed endobronchial biopsy does not add any significant risk to that inherent in the bronchoscopy itself. In a large safety study by de Blic analyzing more than 1300 flexible bronchoscopies in children, the authors encountered one pneumothorax associated with endobronchial biopsy, which was not reported in another rather large study that analyzed safety of 170 bronchial biopsies in children aged 2.5 to 16 years with chronic respiratory symptoms [5]. In this study the authors did not report any significant complication, such as pneumothorax, bleeding or subsequent fever. The possibility of adverse effect of such procedure should, however, be always on one’s mind. Especially in situations with expected increased fragility and increased vascularization, the risk of bleeding or bronchial perforation might be theoretically higher. On the other hand, performing a routine coagulation screen in patients without clinically apparent bleeding disorders was proven unnecessary when endobronchial biopsy was planned. Taking bronchial biopsy has been shown to prolong flexible bronchoscopy by about 5 minutes; this might be relevant in children with impaired ventilation.


References


V.1.2 Histological analysis of lung biopsies and airway smooth muscle cell culture

M. Fayon1,2. 1Université de Bordeaux, Centre de recherche Cardio-Thoracique de Bordeaux, INSERM U1045; 2CHU de Bordeaux, Paediatrics Department, Centre d’Investigation Clinique (INSERM CIT 0005), F-33076 Bordeaux, France

Correspondence: Pr Michael Fayon, Service de Pneumologie Pédiatrique, Hôpital Pellegrin-Enfants, Place Amélie Raba Léon, 33076 Bordeaux Cedex, France. Tel.: +33 5 56 79 56 43; fax: +33 5 56 79 61 13; E-mail: michael.fayon@chu-bordeaux.fr

Introduction: Airway remodeling is observed in a variety of pediatric conditions such as asthma [1–6], bronchopulmonary dysplasia [7], cystic fibrosis [8,9] and COPD [2,7]. It includes a number of structural changes, such as epithelial detachment, basement membrane (BM) thickening, smooth muscle hypertrophy, and new vessel formation. These changes contribute to thickening of airway walls and, consequently, to irreversible airway narrowing, bronchial hyper-responsiveness, airway edema and mucous hypersecretion. Airway remodeling is associated with poor clinical outcomes among asthmatic patients [9]. Early diagnosis and prevention of airway remodeling has the potential to decrease disease severity, improve control and prevent disease expression [9].

We hereby summarize means currently used for the assessment of airway remodeling, which may further our understanding of the relationship between structural changes and clinical and functional abnormalities.

Techniques for the assessment of remodeling in tissue: The usual assessment of remodeling is by histological examination of bronchial tissues. Tissue processing, visualisation and quantification have been well described [10]. Airway remodeling is evaluated after histochemical and immunohistochemical staining. In general, the assessment of tissue structure is performed with haematoxylin and eosin staining on paraffin tissues. Sirius red, van Gieson or Masson-Trichrome stain the total collagen. Periodic-acid shift staining is used to visualise the mucus glands. Immunohistochemistry allows detection of specific proteins such as ECM proteins. Specific primary antibodies directed against a variety of cytokines are available. After staining, the slides are analyzed under light microscopy [2].

Reticular basement membrane thickness (RBM): Increased bronchial epithelial RBM thickness has been proposed as one of the main features of airway remodeling [1,3–6]. Measurements of RBM thickness in individuals follows a log-normal distribution. For a precision of approximately ±15%, 31–45 measurements are required in adults. It is recommended that RBM be measured at 20 mm intervals over a 1 mm reticular basement membrane length [11]. This methodology has been successfully applied in preschool and school-age children [12].

Inflammatory and structural cells counts: It is recommended that a zone beneath the RBM of at least 5 mm of RBM should be included for counts of inflammatory cells [12]. The results are usually expressed as the number of cells per area [2].

Increased airway smooth muscle mass is present in fatal and non-fatal asthma. The study of the cellular mechanism (i.e., hyperplasia vs. hypertrophy) may add useful information regarding the functional consequences of airway smooth muscle remodeling [13]. For measurement of myocyte number and mean volume, cell nuclei are counted to enumerate myocytes under the assumption that these cells have only one nucleus. The volume of ASM may be measured using point and line intersection counts as previously described [8,10].

Epithelial integrity: Epithelial integrity is expressed as a percentage of length of the RBM with intact epithelium on 2 biopsies, if possible [14].
Tissue density quantification:
- Surface area. A simple stereologic technique of point counting may be used to determine surface area and structural composition (i.e., the percentage of the biopsy specimen composed of epithelium, RBM, subepithelial stroma, smooth muscle, submucosal glands, and other features) [10,15]. A grid with points is superimposed on the tissue section, and the number of points overlying the tissue of interest and other subepithelial tissue (for normalization) is recorded. The results are usually expressed as the area occupied by the tissue of interest on the area of the chosen subepithelial tissue within the same biopsy specimen. As an example, in one study, the areas of the structures of interest were determined at a magnification of ×200 with the aid of an eyepiece graticule containing 100 points, and the data were expressed as a percentage of the whole biopsy specimen area. The biopsy specimen area was calculated as follows: area (in square millimeters) = number of points counted × 0.0016 [15]. Surface area may also be determined by an automated cell recognition system based on color analysis. Quanecoul software (Quant’Image, 1997; Bordeaux, France) is a tool which calculates three independent criteria, i.e., optic density (OD), hue density (HD), hue (H) from the three primary colours i.e., red, green and blue [16] for its colour recognition.
- RBM–Smooth muscle distance. As airway smooth muscle (ASM) increases in size and ASM cells migrate, the distance between an area stained by ASM bundles and the RBM is reduced. This distance can be determined by at least 10 measurements at 50 μm regular intervals for each section [14].

Overall remodeling scores: Most of the structural changes are not characteristic of one specific airway disease, but are shared by all airway diseases (Table 1 [2]). It may be tempting to adopt an overall semi-quantitative score summarizing the entire remodelling process. However, a specific weight should be attributed to each individual component.

Table 1. Features of airway remodelling in airway diseases [2]

<table>
<thead>
<tr>
<th>Disease</th>
<th>Epithelial alteration</th>
<th>RBM thickness</th>
<th>Subepithelial fibrosis</th>
<th>Mucin gland hyperplasia</th>
<th>Smooth muscle mass</th>
<th>Angiogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>COPD</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CF</td>
<td>Density clumped</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each + represents the degree of association with disease. RBM: reticular basement membrane; COPD: chronic obstructive pulmonary disease; CF: cystic fibrosis.

Smooth muscle cell cultures: In asthmatic airways, recent reports indicate that the increased mass of ASM plays a critical role. ASM is the critical effector cell modulating airway tone – its contraction induces airway narrowing. Increased ASM mass is due to a simultaneous increase in size (hypertrophy) and number (hyperplasia) of ASM cells. Primary ASM cells can successfully be isolated from human airways for cell culture [17–19], thereby providing in vitro remodeling models. It has been shown that adult ASM cells are not only structural cells. They also contribute to bronchial inflammation by secreting a range of inflammatory mediators (secretory phenotype), recruiting and activating inflammatory cells, such as mast cells or T-lymphocytes. Such an increase has been related to a deposition of extracellular matrix proteins [20]. Chemokines have the ability to induce human ASM cells migration to the subepithelial area of the asthmatic airways and to increase their contractility in vitro [21].

ASM cell proliferation (proliferative phenotype) in severe asthma implicates a gallopamil-sensitive calcium influx and the activation of calcium-calmodulin kinase IV leading to enhanced mitochondrial biogenesis through the activation of various transcription factors (PGC-1α, NRF-1 and mt-TFA). The altered expression and function of sarco/endoplasmic reticulum Ca(2+) pump could play a role in ASM remodeling in moderate to severe asthma. Additionally, aberrant communication between an injured airway epithelium and ASM could also contribute to disease severity [22,23].

Studies of ASM cells in children remain extremely scarce. We have shown that stimulated non-asthmatic infant ASM cells may contribute to airway remodeling to a greater extent than adult ASM cells [24]. DNA synthesis in 10% fetal calf serum of infant ASM was significantly enhanced (>5-fold increase vs. ITS control medium) compared to adults (2-fold increase). PDGF-AA induced a response of lesser magnitude: 2.6-fold increase in infants vs. 1.5-fold in adults (p < 0.05). Newer data suggests that a mitochondrial biogenesis related mechanisms may be involved, similar to adult asthmatics. All the above suggests that ASM cells may be prone to non-specific remodeling. Paediatric ASM cells also have the ability to synthesize inflammatory mediators and cytokines. TNFα-stimulated immature ASM produce more LIF (leukemia inhibitory factor (LIF) (an IL-6 family neurotrophic cytokine) mRNA and protein than adult ASM [19]. The secretion of LIF by stimulated immature human ASM cells potentially contributes to neuroimmune airway inflammation and subsequent remodeling. Thus, ASM culture may help us to further understand the mechanisms of airway remodeling, the effect of current asthma treatments on airway remodeling, potential pharmacological targets for the treatment of airway remodeling in asthma, the mechanisms of airway remodeling, the effect of current asthma treatments on airway remodeling and the potential pharmacological targets for the treatment of airway remodeling in asthma [25].

Perspectives: Further studies involving ASM cultures from asthmatic children are warranted. The interaction between ASM cells and other structural (e.g. epithelial) and inflammatory cells should also be explored.

References

B. Cardiovascular effects: Although FFB is not affecting directly the cardiovascular system it may indirectly cause significant hemodynamic changes due to changes in the vascular tone caused by hypoxemia and/or hypercapnia, as well as changes in the intrathoracic pressure (especially during coughing episodes) that may affect the venous return and/or the afterload of the left ventricle.

C. Indications for FFB in the ICU:
1. Diagnostic applications:
   a. Investigation of an infectious process. Bronchoscopy and BAL are commonly used for the identification of pathogens in the lower airways. Although most infections can be documented directly (e.g. from culture of tracheal secretions) or indirectly (from positive PCR in nasal washings), bronchoscopy and BAL become necessary in the following circumstances: a) when it is not clear whether the presence of organisms represents infection or colonization; b) when the infection is caused by organisms that show predilection for the peripheral airways (e.g. Pneumocystis jirovecii); c) when the infection is confined in a particular area of the lung and the involved organisms may not be able to be cultured in routine tracheal secretions (tuberculous and non-tuberculous mycobacteria as well as several fungal and opportunistic organisms belong in this category).
   b. Abnormal breathing sounds. Abnormal breathing sounds include stridor, wheezing (often audible) or a combination of both and are commonly used for the identification of pathogens in the lower airways. Although most infections can be documented directly (e.g. from culture of tracheal secretions) or indirectly (from positive PCR in nasal washings), bronchoscopy and BAL become necessary in the following circumstances: a) when it is not clear whether the presence of organisms represents infection or colonization; b) when the infection is caused by organisms that show predilection for the peripheral airways (e.g. Pneumocystis jirovecii); c) when the infection is confined in a particular area of the lung and the involved organisms may not be able to be cultured in routine tracheal secretions (tuberculous and non-tuberculous mycobacteria as well as several fungal and opportunistic organisms belong in this category).
in older infants and children the causes are often iatrogenic (e.g. subglottic stenosis due to prolonged intubation, injury of the vocal cords or of the recurrent laryngeal nerve causing paresis or paralysis).

c. Evaluation of the nature of abnormalities. Patients in the ICU often present with radiographic findings and/or symptoms of unclear etiology. For example an airway filled with secretions can look radiographically identical to an airway that is completely compressed. In such cases, identifying the exact problem with direct visualization may significantly alter the management.

2. Therapeutic applications of FFB: Compared to the indications for FFB in an outpatient setting, FFB in the ICU has often more therapeutic applications such as the following:

a. Persistent or recurrent atelectasis. Atelectasis is a major cause in the increase of the FiO2 to 1.0 throughout the procedure in order to interventive exists. Some of the “standard” adjustments involve their ventilator settings and specific guidelines for the proper management: Patients with respiratory function of the upper airways

b. Placement of the endotracheal tube. Use of FFB for the placement of the endotracheal tube is reserved for cases in which high precision is required (e.g. placement of the ETT just above the carina in patients with very severe tracheomalacia; or selective intubation of one lung), or when congenital anatomical abnormalities or injuries preclude the proper opening of the jaw for direct laryngoscopy.

D. Practical considerations & precautions: Despite the high potential of problems, most of the potential complications of FFB are predictable and thus preventable if all the necessary precautions are taken.

1. Sedation and pain control: Although not painful, FFB can be anxiety producing, causing significant increases in the heart rate and blood pressure that may be deleterious to a critically ill patient. Thus, it is advisable to give sedatives and/or anxiolytics even to patients who receive round the clock sedation or narcotics.

2. Muscle relaxation. The use of muscle relaxants during the performance of FFB makes the procedure “easier” for the bronchoscopist and safer for the patient because it prevents (a) sudden movements that could result in injury, (b) abnormal labored breathing due to the partial obstruction of the ETT and (c) cough that could potentially raise the intrathoracic and intraluminal pressures to dangerous levels. Muscle relaxation should not be used when the procedure is performed for the evaluation of tracheobronchomalacia.

3. Size of bronchoscope: Although the larger bronchoscopes generally offer superior imaging and/or better suctioning capabilities, it is generally advisable to use the smallest possible bronchoscope for intubated patients in order to minimize the degree of airway obstruction and to increase the maneuverability of the scope. In general there is should be at least a ≥1.3 mm difference between the diameter of the airway and the diameter of the bronchoscope for infants and toddlers, ≥2.0 mm for children and young adolescents and ≥2.5 mm for older adolescents and young adults.

4. Coagulation status: Transfusion of platelets should be considered when the platelet count is <40K/μL and definitely if the platelet count is <20K/μL. It is advisable for the platelets to be transfused shortly before and during the procedure.

5. Ventilation: Patients who are intubated and mechanically ventilated will probably require adjustments in their ventilator settings and specific guidelines for the proper interventions exist. Some of the “standard” adjustments involve the increase of the FiO2 to 1.0 throughout the procedure in order to prevent or minimize the potential of significant desaturation; the increase in respiratory rate in order to compensate for the shallow breathing or apnea that follow the heavy sedation and/or paralysis; the decrease in the positive end-expiratory pressure (PEEP) in order to compensate for the increase in the intraluminal pressure due to the presence of the bronchoscope inside the airway.

Summary: Despite the considerable risks of any invasive procedure performed in critically ill patients, several studies reviewing the rate of complications during and after FFB both in adults and children have shown a rather remarkably low rate of complications.Nevertheless, despite the excellent safety profile of FFB, possible alternatives should be carefully considered. For example, if the main objective of the procedure is to obtain BAL fluid for cultures from patients who have a diffuse disease process, one might consider performing a non-bronchoscopic BAL that allows great return with the use of a small size catheter.

Overall, if all necessary precautions are taken, FFB can be safely performed even in critically ill infants and children.

Selected references


V.2. Pearls – Respiratory physiology and immunology

V.2.1 Respiratory function of the upper airways – from phylogeny and ontogeny to physiology

L-P. Praud. Departments of Pediatrics and Physiology, Université de Sherbrooke, Sherbrooke, Canada

Correspondence: Jean-Paul Praud MD PhD, Departments of Pediatrics and Physiology, Université de Sherbrooke, JIH 5N4, QC Canada. Tel: +1(819) 346 1110, ext. 14851; fax: +1(819) 564 5215; E-mail: Jean-Paul.Praud@USherbrooke.ca

Introduction: The upper airways exert an important influence on breathing. In addition to participating in fetal lung growth, in the successful transition towards air breathing at birth and in the maintenance of optimal lung ventilation thereafter, the larynx is also involved in swallowing and protection of the lower airways. Furthermore, neural immaturity in the newborn is often responsible for reflexes originating from the laryngeal region, the laryngeal chemoreflexes, which are inhibitory to
cardiorespiratory function. This short review will use phylogenetic and ontogenetic background to introduce a few aspects of postnatal upper airway function related to apneas, laryngeal chemoreflexes and swallowing-breathing coordination.

**Phylogeny: upper airways and respiration:**

A pharyngeal pump and a laryngeal closing valve for initial air-breathing in vertebrates: Early lungfishes acquired the ability to use environmental air to fulfill their metabolic requirements more than 370 million years ago. As bimodal breathers, they were capable for the first time of ventilating a primitive lung intermittently, in addition to water breathing. The simultaneous appearance of a closing valve, the primitive larynx, was critical to this evolutionary step to protect the lungs from flooding during feeding and water breathing.

Amphibians were the first to become dependent on air breathing. Air breathing was accomplished by filling the oral cavity with air through the nares by passive recoil of the pharyngeal wall, then forcing air into the lungs by pharyngeal muscle contraction and holding air in the lungs by laryngeal closure, much as the lungfish. With evolution, modern amphibians acquired a well-developed larynx homologous to those of higher vertebrates, with a cartilage skeleton and strong, paired dilator muscles in addition to muscles that close the glottal aperture [1].

**Disappearance of pharyngeal pump mechanism for breathing with vertebrate evolution:** A significant problem with the pharyngeal pump mechanism of filling the lungs is that tidal volume is constrained by the size of the pharynx. Evolution towards vertebrates with large bodies and small heads such as reptiles was only made possible by adding a thoracic respiratory system, i.e., inspiratory thoracic muscles. Contraction of the latter, especially the diaphragm, has remained of crucial importance for lung breathing in mammals. Still, while the pharyngeal contraction phase has disappeared from the breathing cycle, active laryngeal closure remains prominent in today’s vertebrates in certain conditions. Indeed, though absent in most adult terrestrial mammals, active post-inspiratory laryngeal closure remains a basic component of the breathing cycle in many lower vertebrates and in diving mammals, even on land [2]. In addition, active post-inspiratory laryngeal closure represents a mechanism of major importance for early postnatal breathing in terrestrial mammals (see below).

**Ontogeny: from fluid-filled airways to aerial breathing:** While the nasal airway originate from invagination of the ectoderm, the skeleton and muscles of the mouth, pharynx and larynx develop from pharyngeal arches and clefts in the embryo. Following anatomical and functional development, the pharynx and larynx are actively engaged in swallowing and breathing movements in the fetus.

**Respiratory function of the larynx in fetal life:** In the fetal mammal, the larynx is actively closed when fetal breathing movements are absent, reminiscent of the lungfish during diving. Fetal lung growth relies heavily on the high pressure present in the liquid-filled airways generated by this glottal closure, which opposes continuous secretion of lung liquid by the airway epithelium. In addition, coordinated contraction of pharyngeal/laryngeal dilator muscles and diaphragm is observed during bursts of fetal breathing movements [3]. However, these fetal breathing movements do not entrain amniotic liquid into the trachea. Indeed, when necessary, laryngeal constrictor muscles contract to defend the entrance of the trachea against influx of amniotic fluid filled with debris (large larynx in the fetal sheep) [3]. Such laryngeal chemoreflexes are due to laryngeal receptors sensitive to the lower chloride concentration of the amniotic fluid [4]. Finally, breathing-swallowing coordination develops in the fetus, allowing oral feeding around 35 weeks of gestation in the newborn infant born prematurely.

**Respiratory function of the upper airways at birth and in the early postnatal period:** At birth, complete, active glottal closure throughout the very first expirations is vital for establishing an end-expiratory lung volume of air, i.e., the initial functional residual capacity. In the first hours and days after birth, an active post-inspiratory laryngeal closure is frequently observed. By decreasing lung emptying, this expiratory airflow braking mechanism defends functional residual capacity against low lung compliance present at that age [5]. The muscular pharyngeal tube, which is so important for glossoharyngeal respiration in amphibians, however does not retain any respiratory advantage in mammals after birth. On the contrary, its collapsible characteristics render phasic contraction of pharyngeal dilator muscles necessary just before diaphragm inspiratory contraction to prevent unwanted pharyngeal narrowing secondary to decreased intraluminal pressure [6].

Upper airways and apneas: Premature infants born before 27 weeks are virtually all affected by apneas of prematurity, which are responsible for bradycardia and desaturation and carry the potential of neurological sequelae.

- Complete, active laryngeal closure during central apneas in the newborn. Our group has shown that complete, active glottal closure with maintenance of a high apneic lung volume throughout apneas was consistently noted during periodic breathing [7], as well as during most post-sigh apneas in preterm lambs. Such observations were concordant with previous reports in dog pups, newborn opossums and human newborns. Maintenance of a high lung volume during central apneas increases alveolar O2 stores and limits post-apneic arterial O2 desaturation [8]. Such active inspiratory breath-holding has phylogenetic and ontogenetic correlations (see above) and is not related to reflexes originating from laryngeal receptors, e.g., laryngeal chemoreflexes. Of note, while prominent in newborns, closure of the laryngeal valve during central apneas has also been observed in adult humans.

- Passive pharyngeal collapse during central apneas. Loss of central respiratory drive induces passive pharyngeal narrowing during central apneas. Insufficient pharyngeal dilator muscle contraction at breathing resumption can cause pharyngeal closure, i.e., a mixed apnea. The latter is frequently seen in newborns, as well as in older children and adults with obstructive sleep disordered breathing. In fact, pharyngeal lumen size during breathing results from interaction between anatomical and neural mechanisms. Any anatomical imbalance between soft tissue volume (increased with macrognasia, peripherally fat pads, adenotonsillar hypertrophy, ...) and bony enclosure size (decreased with microretrognathia, syndromic malformations, orthodontic anomalies, ...) favors pharyngeal closure. In addition, any neural imbalance between the collapsing force of inspiratory thoracic muscle contraction and dilating force of pharyngeal dilator muscles (decreased by prematurity, REM sleep, sedation, ...) favors pharyngeal closure [9].

**Laryngeal chemoreflexes:** Laryngeal chemoreflexes represent another prominent manifestation of the original, protective valve function of the vertebrate larynx. Laryngeal chemoreflexes (LCR) are triggered by the contact between liquids – especially acid or with low chloride content – and receptors of the laryngeal mucosa in mammals. These lung protective reflexes consist primarily of swallowing, coughing and arousal in mature mammals, thus limiting larynx penetration and tracheal aspiration [4]. However, in the immature, newborn mammal, LCR are composed of both a vagal component, which includes laryngospasm, apnea, oxygen desaturation and bradycardia, and a sympathetic component, which includes systemic reflexes. In fact, chemoreflexes observe a functional flow to vital organs [4]. Clinical relevance of LCR stems from the observation that they are often triggered by gastric reflux, bottle-feeding or oral intake of liquid medications in preterms. In addition, they can be responsible for apparent life-threatening events and probably some cases of sudden infant death syndrome [10]. Abnormal conditions, such as respiratory syncytial virus infection in young infants or laryngopharyngeal reflux during sleep in older children, exacerbate the potentially dangerous cardiopulmonary components of the LCR.
Swallowing and breathing activity: the dangerous liaisons: The pharynx was involved in feeding long before the emergence of air breathing in lungfishes. With air breathing, however, breathing and swallowing became competing functions at the pharyngeal level. Swallowing activity involves the coordinated contraction of more than 25 pairs of upper airway muscles in a sequence designed and coordinated by the brainstem swallowing center. In addition, a precise swallowing-breathing coordination, which includes an obligatory respiratory pause, is a necessity to prevent both prolonged apnea and tracheal aspiration. Thus, while forceful contraction of pharyngeal constrictor muscles propels the food bolus into the esophagus, the tensor and elevator veli palatini and the laryngeal constrictor muscles contract to prevent entry of food into the nasopharynx and the trachea respectively. In humans, phonation modifies upper airway anatomy and adds further complexity to breathing-swallowing interaction. In the newborn, before development of phonation, the larynx is cephalad, and the overlapping epiglottis and soft palate establish a nasal airway for respiration during milk swallowing. This anatomical configuration explains that human infants are preferential nose breathers for the first 6 weeks to 6 months. Postnatal modifications of the upper airways to allow sound production lead to descent of the larynx in the neck and loss of epiglottis-soft palate contact. Increased risks of tracheal aspiration are then prevented by elevation of the larynx during swallowing, by the shape of the epiglottis, which directs food laterally into the pyriform fossa, and by the aryepiglottic folds + arytenoids, which act as ramps to prevent laryngeal penetration. In the meantime, maturation of the swallowing and respiratory centers in the brainstem ensures an optimal swallowing-breathing coordination. Conversely, immaturity, neuromuscular disorders, laryngeal inflammation or upper airways malformations, for example, can be responsible for inadequate swallowing-breathing coordination and tracheal aspiration in children.

Acknowledgments: Jean-Paul Praud is the holder of the Canada Research Chair in Neonatal Respiratory Physiology. His research is supported by the Canadian Institutes for Health Research, the Fonds de la recherche en santé du Québec and the Foundation of Stars.

References

V2.2
Breathing strategies in infancy: Physiology, developmental features and what goes wrong with disease
A. Colin. Miller School of Medicine, University of Miami, Miami, FL, USA

Learning objectives:
1. Analyze anatomic and physiologic features of the respiratory system that are unique to infants and place them at risk.
2. How infants protect themselves against these risks.
3. Clinical implications of these deficiencies and failure of protective mechanisms – The effect of maturation.

Stable functional residual capacity and effectiveness of gas exchange: Maintenance of a stable and adequate functional residual capacity (FRC) is crucial to secure stable gas exchange. FRC is determined by the balance between the opposing forces of the chest wall and lung and is thus a direct function of their respective mechanical properties. This talk will focus on the physiological effects of the transition from a compliant to an elastic chest wall, the changes in lung compliance as it undergoes alveolarization, and how these parallel changes affect the capacity of the developing lung to maintain a stable FRC. However, in early life, before completion of these processes, the lung–chest wall equilibrium results in a mechanically determined FRC that is low relative to older children and adults and is an important determinant of age-related vulnerability to hypoxia. We will describe the leading strategies that infants utilize to actively elevate their FRC. Laryngeal braking, early inspiration before full expiration, and persistence of inspiratory muscle activity into the expiratory phase. The transition from an actively maintained FRC to one that, as in adults and older children, is mechanically determined, occurs in full-term infants late in the first year and into the second year of life. The timing of this transition coincides with the declining compliance ( stiffening) of the chest wall and its gradually increasing contribution to the overall stabilization of the respiratory system. The challenge of maintaining an FRC that permits stable gas exchange is likely compounded in the premature infant by apneic events, which tend to drive the system to critically low lung volumes and result in rapid desaturation.

Airway tethering is a crucial mechanism that secures airway patency and thus adequate maintenance of FRC: tethering couples lung volume changes to airway caliber. This mechanism is also maturation dependent and is less effective in infants in their early alveolarization stages. The process of alveolarization with the associated development of the parenchymal elastic network, as transition occurs from the saccular stage of development to the alveolar stage, is associated with improving airway stability and hence improved maintenance of FRC. The talk will examine how disease conditions that affect airway patency or lung parenchyma disturb this physiology, and the nature of the lung morbidity that evolves from such pathologies in early life.

V2.3
Lung function and bronchial hyperreactivity
N. Beydon. Assistance Publique-Hôpitaux de Paris; Lung Function Test – Physiology Department, Armand Trousseau Hospital, Paris, France

Correspondence: N. Beydon. Armand Trousseau Hospital, 26 Avenue du Docteur Arnold Netter, 75571 Paris Cedex 12, France. Tel.: +33 01 44 73 63 32; fax: +33 01 44 73 63 36. E-mail: nicole.beydon@trsph.aphp.fr

Introduction: Bronchial hyperreactivity (BHR) is commonly measured in children, and thanks to technological advances BHR is now feasible in infants and young children. Asthma is usually defined as a combination of respiratory symptoms often related to allergy, in children with a bronchial disease that encompasses: obstruction, BHR, and inflammation. However, recent findings on airways smooth muscle properties and bronchial structure (anatomical and remodeling) slightly complicate the scheme.
Eventually allergy, inflammation, smooth muscle and structure are involved differently in each individual and are responsible for the occurrence and, sometimes, the persistence of the disease [1–3]. This holistic view of asthma disease in children should help us to interpret new data on the natural course of BHR from infancy to adulthood, and to determine the best way to use BHR measurements in our daily practice.

BHR assessment is performed during bronchial challenge (BC) from which the result must not only be “positive or negative test”, but also include the lung function testing (LFTing) techniques used and the changes measured in the LF indices. Moreover, the decision-making should include the awareness that the use of BC result in an individual is a translation of a knowledge that comes from epidemiological studies conducted in groups of patients.

**Technological aspects:**

*Type of bronchial challenges:* Pharmacological tests are divided into direct tests (methacholine, histamine, carbachol) that primarily stimulate bronchial smooth muscle, and indirect tests (hypertonic saline, Adenosine Mono-Phosphate (AMP), mannitol) of which the response relies on a local cellular reaction. Physical tests (exercise, eucapnic hyperventilation of dry and/or cold air) are also considered as indirect tests, however they do not allow a graded assessment of BHR. Pharmacological tests are more often used because they require minimal cooperation from the child and, therefore, can be implemented in all age groups. Exercise tests are commonly used in children with respiratory complain on exertion.

*Age of the patient:* The LFT techniques used in paediatric population have to be adapted to the child’s age and maturity, which leads to consider cooperative and non cooperative children. The former are explored as adults, whereas the latter are tested using specific techniques. As a result, young children who require a BC should be referred to a Lab that routinely use techniques adapted to the young children and handled by a trained staff.

Children of more than 6 years of age are thought to be able to perform LFT like adults do. But in practice, and particularly for long duration test like BC, before 8 to 10 years of age some children can show a large variability in spirometry results [4] or completely lose interest as the test proceeds, providing no final result. It is the technician’s ability to detect children with short concentration span that warrants the reliability of the test. Indeed, a sub-maximal forced expiration maneuver in the course of a BC must not be interpreted as bronchoconstriction. In that case, additional techniques usually used in children younger than 6 years have to be used (see below). However, in school age children and adolescents, spirometry is the recommended technique to measure BHR, with the same cutoffs than the ones used in adults [5]. The cutoff for a positive response to direct pharmacological tests is a 20% baseline decrease in Forced Expiratory Volume in 1 s (FEV1), and a positive response to indirect tests a 15% baseline decrease in FEV1.

The preschool children are known as the difficult ones, because they have to be tested awake but might be reluctant to participate in the test if not correctly supervised. Once again, trained staff and a welcoming lab (decorating colors, posters, games, adapted furniture …) are mandatory to gain the child’s confidence and collaboration. The techniques used to assess BHR in this age group are direct measurements of bronchial obstruction (resistance measurement, wheezing detection) or measurements of induced ventilation-perfusion mismatch (transcutaneous partial pressure of oxygen [TcPO2] and/or percutaneous oxygen saturation [SpO2]) [6–8]. The cutoff in children with asthma, BC are generally positive because smooth muscle hyperreactivity and bronchial inflammatory cells are present. However, there are some situations such as post-infectious bronchiolitis obliterans, chronic lung disease where only smooth muscle hyperreactivity is present so that direct BC are more likely to be positive than indirect BC [22–24]. Moreover, in groups of asthmatic children equally responsive to methacholine, atopy is the most important predictive factor for AMP responsiveness [25,26]. Finally, asthmatic children are prone to exhibit BHR to methacholine and to exercise challenges (direct and indirect tests), but the methacholine challenge is far more frequently positive than the exercise test, assuming a different pathophysiology of the two tests [27].

In children, most of our knowledge comes from studies on direct pharmacological tests.

**Clinical aspects:** Epidemiological studies on BHR recorded in populations with different health status are helpful to understand the relationship between BHR and respiratory symptoms. However, it might be difficult to implement results from cohort studies in daily practice. The issues that might be worth elucidating are: to which child a BC can be useful? how the result should be interpreted? in which way BC result can interfere with the child’s respiratory symptoms treatment and/or development?

**Cohort studies:** Despite the strong relationship that exists between asthma and BHR in children, BHR is not synonymous to asthma and vice versa. For example, current atopy and early lower respiratory tract illness are good, independent from asthma predictors for BHR in children 11 years of age [28]. However, most children with current asthma exhibit BHR and the usefulness of BHR in asthmatic children must be questioned. Until now, even though the inhaled corticosteroids (ICS) dose-dependent improvement of BHR to methacholine has been suggested [29], there are no recommendations to adapt asthmatic children’s ICS treatment to the BHR levels. Similarly, a 20% or 5% baseline decrease in TcPO2 or in SpO2, respectively, or a SpO2 < 91% during the test or the occurrence of wheezing [9–11]. Concerning resistance techniques, no cutoff has been agreed upon, and a less than 35% increase cannot be considered as a positive response. However, for safety reasons, the use of concomitant alternative techniques (auscultation, assessment of hypoxemia) are recommended when using resistance techniques, because false negative tests can occur [7,12–14]. Spirometry has been used in preschool children with asthma or chronic cough but not in healthy ones [15,16]. A 20% decrease in FEV1 was found a more sensitive endpoint than wheezing occurrence, and a 25% decrease in FEV0.5 which could distinguish between children with asthma and children with chronic cough, was proposed as an even better endpoint. However, studies in healthy preschool children are necessary before stating the diagnosis relevance of these cutoffs [16]. The preschool children can easily be tested during pharmacological tests or physical tests such as cold air challenge [17,18]. Exercise tests are more difficult to conduct in young children, because it is difficult to achieve maximal effort in a number of children [19] and because no studies have established relevant lung function cutoff in this setting.

Infants are tested during induced sleep using pharmacological tests (nebulized drugs) and bronchial reactivity is assessed by TcPO2 and/or maximal expiratory flow decreases. In the absence of consensus, a 15% baseline decrease in TcPO2 has been used to define a positive test, or a 40% baseline decrease in maximal flow at Functional Residual Capacity (VmaxFRC) (20) or a 30% baseline decrease in FEF75 [21].

**Interpretation of the results:** The response to pharmacological direct tests is graded, and the occurrence of BHR for a low dose of pharmacological agent is interpreted as severe BHR. Conversely, most of the indirect pharmacological tests and physical tests give a binary (positive or negative) response.

Results from different types of test are not interchangeable. In children with asthma, BC are generally positive because smooth muscle hyperreactivity and bronchial inflammatory cells are present. However, there are some situations such as post-infectious bronchiolitis obliterans, chronic lung disease where only smooth muscle hyperreactivity is present so that direct BC are more likely to be positive than indirect BC [22–24]. Moreover, in groups of asthmatic children equally responsive to methacholine, atopy is the most important predictive factor for AMP responsiveness [25,26]. Finally, asthmatic children are prone to exhibit BHR to methacholine and to exercise challenges (direct and indirect tests), but the methacholine challenge is far more frequently positive than the exercise test, assuming a different pathophysiology of the two tests [27].
with and without BHR. In another study on early ICS treatment in wheezy infants (IFWIN study), BHR measured during eucapnic hyperventilation challenge at 5 years of age did not differ between ICS and placebo groups, despite a clinical improvement due to ICS use [31]. Therefore, BC might not be helpful in handling asthmatic children’s therapy, but could be more useful to diagnose bronchial disease in children with respiratory symptoms but no asthma or wheeze. The rationale to do so relies on the results of longitudinal studies conducted in children with and without BHR. For example, in a cohort from New Zealand, the presence of asymptomatic BHR at 9 years of age was highly, and increasingly over time, correlated with the occurrence of asthma, wheezing, or atopy markers up to the age of 26 years [32]. After taking into account all outcomes related to symptoms, asymptomatic BHR remained independently associated to asthma, chest tightness, and cough during or after running. Interestingly, cough or phlegm production were not associated with BHR, in line with a previous study in which there was an association between wheeze and BHR at age 7 to 11, but no association between BHR and cough or chest tightness in the absence of wheeze [33]. From these studies, BHR is more related to asthma or wheeze than to non specific respiratory symptoms, and BHR in children is likely to precede asthma symptoms, particularly if it is a long standing bronchial characteristic. But wheeze can occur very early in life, and the relationship between wheeze in infants and subsequent BHR has been studied in a cohort from United-Kingdom (ALSPAC study) [34]. The level of BHR in childhood (7 to 9 years of age) was highest in the children that begun to wheeze after 18 months of age compared to children of other wheezing phenotype groups (particularly early wheezers). However, BHR was related to all wheezing phenotypes compared to the never or infrequent wheeze. The authors concluded that some early environmental influences may play a role in the development of later BHR, wheeze and atopy. The timing of BHR then seems crucial, and as suggested by this study, the later the wheeze during infancy the higher the BHR in childhood. The next step was to explore BR before the occurrence of respiratory symptoms. In 176 unsellected Australian newborns, histamine challenges were performed at 1, 6 and 12 months of age [35]. Wheeze at age 11 years was correlated to a higher level of bronchial reactivity at 12 months of age, but not at 1 or 6 months of age, and asthma or wheeze was never present in children without BHR at both 12 months and 11 years of age. Persistence of BHR beyond infancy was significantly more frequent in children with at least one parent with asthma, or with personal history of lower respiratory tract illness in the first 6 months of life, or with atopy in childhood, but not in those whose mother smoked during pregnancy. Finally, the study children could change bronchial reactivity pattern during the follow-up, and among the 122 children with BHR during infancy, 50% did not display BHR any longer at 11 years of age. Thus, this study confirms the importance of the timing for BHR in infancy for future asthma, and the later the BHR in infancy the higher the risk to wheeze during childhood. The progression of BHR and symptoms entails a loss of BHR in wheezy infants who will grow out of the wheezing disease. In line with these results, the in cohort from Isle of Wright, a similar level of bronchial reactivity at 10 years of age was evidenced between healthy and early transient wheezers on the one hand, and between persistent and late-onset wheezers on the other hand [36]. These cohort studies are in favor of BHR being a marker for asthma/wheeze when present and persisting early in life, under genetic (atopy) and environmental (infection) determinants, with little influence of ICS treatment.

Clinical applications: The use of a BC result in clinical setting requires that the test be performed accordingly to the current knowledge on LFT in children (cf section “technological aspects”). From the previous discussion on BHR and asthma/wheeze symptoms, we suggest that the relevance for BHR measurement in a child is as follows: (1) if a child has current wheezing that responds to asthma medication, then BC test will not add any information on the child’s respiratory disease or treatment, outside the field of research, (2) if a child has non-specific respiratory symptoms beyond infancy, the diagnosis procedure may include a BC. If BHR is detected (and even more if BHR is repeatedly present or present after the preschool years) then the respiratory symptoms can be interpreted as precursors of asthma disease or as a variant to typical asthma symptoms, especially if the child has atopy and/or a history of lower tract illness during early infancy. Anti-asthmatic medication should be considered in the child to cure his/her respiratory symptoms. (3) For wheezy infants, the frequency of respiratory symptoms and of BHR that will not stand beyond this period of life preclude any definitive conclusion from a BC which should, therefore, be performed only in difficult-to-treat infants with uncertain diagnosis and in specialized centers.

Conclusion: In conclusion, BHR can be monitored from birth to childhood for clinical or research purposes. In clinical practice, the result of a BC cannot be interpreted without taking into account the child’s personal and familial history and the clinical presentation of the disease.

References


VI. French Sessions

VI.1 Le plan d’action sur l’asthme combiné à une ordonnance : un outil efficace d’autosuggestion dirigée [The written action plan for asthma combined with a prescription: an effective guided self-management tool]

F.M. Ducharme. Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada

Correspondence: E-mail: francine.m.ducharme@umontreal.ca

Most children with asthma have poor disease control, partly attributable to suboptimal adherence of physicians to guidelines and of patients to medical recommendations. The challenge is to introduce children to guided self-management, that is, asthma education, medical review and the provision of a written action plan.

Written action plan as add-on to management education: There is clear evidence that comprehensive guided self-management improves health outcomes over usual care [1]. However, the independent contribution of a written plan to the overall effect remained to be documented [2].

Written action plan as a unique self-management tool: When comparing guided self-management with and without an action plan, that addition of a plan reduced acute care visits, absenteeism, nocturnal awakenings, and symptoms [3]. Moreover, a Cochrane review concluded that symptom-based plans were superior to peak flow-based plans in children to prevent acute care visits and achieved children’s preference [4].

Incorporating written action plan in clinical practice: Yet, delivery of action plans remains low in part due to the limited time and competing demands during typical medical visits. We develop a written self-management plan based on available scientific evidence and expert opinions that was clear and perceived relevant by children, adolescents, and their parents [5]. Available in French and English, the plans are divided in three control zones identified by symptoms (optional peak flow values) and symbolised by traffic lights. By incorporating the prescription and chart copies in the triplicate format, they were designed to facilitate dispensing by physicians in both the clinic and acute care settings.

Written action plan in the ED setting: Whether providing written action plan is useful when concurrent asthma education and medical review is at best limited, was unclear. In a randomized controlled trial, the provision of the triplicate written action plan significantly increased patient adherence to inhaled and oral corticosteroids and asthma control. Interestingly, it also improved physicians’ recommendation for maintenance fluticasone and medical follow-up, supporting its independent value in the acute-care setting [6].

The best way to achieve guided self-management remains a multifaceted approach. Yet, when other elements of guided self-management cannot be provided concurrently, a written action plan with prescription may be one of the simplest and cheapest effective means to improve guidelines implementation by physicians, patients’ self-management and asthma control.

References


Acute bronchiolitis is the most common lower respiratory tract infection in infants, but no treatment strategy was yet shown to be effective in reducing the severity or duration of symptoms. International guidelines advocate supportive treatment, that is, oxygen therapy when indicated, fractionated meals or fluid management, and avoidance of unnecessary handling. A survey of Swiss pediatricians in 2001 showed a wide variation in the treatment of bronchiolitis, the majority of physicians caring for small children prescribing pharmaceutical agents. Likewise, 42.2% and 47.1% always or sometimes, respectively, prescribed physiotherapy (PT) for inpatients. Interestingly, French speaking physicians prescribed more drugs than their German speaking counterparts, a difference not clearly reported for PT. Following this survey, national guidelines for the management of bronchiolitis were established and thoroughly implemented. This lead to a significant reduction in the prescription of drug treatments and PT, although 58.8% of practitioners still sometimes prescribed PT for hospitalized infants despite lacking evidence for its efficacy, like shown in a 2007 Cochrane review where “conventional chest physiotherapy” (vibration, percussion and postural drainage) brought no reduction in the length of hospital stay, oxygen requirements or clinical severity in infants with acute bronchiolitis.

In Switzerland, techniques using passive expiratory manoeuvres allowing the mobilisation of secretions without airway collapse, have supplanted conventional ones. Nonetheless, the effectiveness of CP using passive acceleration of expiratory flux was not conclusive in reducing the time to clinical stability and the length of hospital stay in infants admitted for acute bronchiolitis, as demonstrated in two recent open randomised trials in France and in Switzerland. Therefore, it seems justified to recommend against the routine prescription of PT, as already proposed by some consensus conferences. This important finding should be included when establishing allocation of resources in the actual cost-containment era. Further work is needed before extending this recommendation to children managed on an outpatient basis.

**VI.2.a**

*Place du kinésithérapeute dans la prise en charge de la bronchiolite aiguë virale – (a) en France [Role of the physiotherapist in the management of acute viral bronchiolitis – (a) France]*

M. Fetouh, Bordeaux, France

Abstract not available at time of publication.

**VI.2.b**

*Place du kinésithérapeute dans la prise en charge de la bronchiolite aiguë virale – (b) en Suisse [Role of the physiotherapist in the management of acute viral bronchiolitis – (b) Switzerland]*

J. Rochat, Lausanne, Switzerland

Acute bronchiolitis is the most common lower respiratory tract infection in infants, but no treatment strategy was yet shown to be effective in reducing the severity or duration of symptoms. International guidelines advocate supportive treatment, that is, oxygen therapy when indicated, fractionated meals or fluid management, and avoidance of unnecessary handling. A survey of Swiss pediatricians in 2001 showed a wide variation in the treatment of bronchiolitis, the majority of physicians caring for small children prescribing pharmaceutical agents. Likewise, 42.2% and 47.1% always or sometimes, respectively, prescribed physiotherapy (PT) for inpatients. Interestingly, French speaking physicians prescribed more drugs than their German speaking counterparts, a difference not clearly reported for PT. Following this survey, national guidelines for the management of bronchiolitis were established and thoroughly implemented. This lead to a significant reduction in the prescription of drug treatments and PT, although 58.8% of practitioners still sometimes prescribed PT for hospitalized infants despite lacking evidence for its efficacy, like shown in a 2007 Cochrane review where “conventional chest physiotherapy” (vibration, percussion and postural drainage) brought no reduction in the length of hospital stay, oxygen requirements or clinical severity in infants with acute bronchiolitis. In Switzerland, techniques using passive expiratory manoeuvres allowing the mobilisation of secretions without airway collapse, have supplanted conventional ones. Nonetheless, the effectiveness of CP using passive acceleration of expiratory flux was not conclusive in reducing the time to clinical stability and the length of hospital stay in infants admitted for acute bronchiolitis, as demonstrated in two recent open randomised trials in France and in Switzerland. Therefore, it seems justified to recommend against the routine prescription of PT, as already proposed by some consensus conferences. This important finding should be included when establishing allocation of resources in the actual cost-containment era. Further work is needed before extending this recommendation to children managed on an outpatient basis.

**VI.3**

*Manifestations pulmonaires de la maladie de Behçet et des maladies apparentées [Pulmonary manifestations of Behçet's and similar diseases]*


Behçet's Disease (BD) is a vasculitis with characteristic features affecting both the skin and mucosa. It is the only primary vasculitis that can affect vessels of all sizes and both the arteries and veins. The presence of these inflammatory episodes and the lack of significant autoanti-bodies has led to its possible classification as an “autoinflammatory disease”. These are a group of diseases characterized by unprovoked inflammatory episodes and the lack of autoantibodies [1]. The prototype of autoinflammatory diseases is Familial Mediterranean Fever [1].

BD is a systemic vasculitis characterized by oral and genital ulcers and uveitis. It most commonly occurs in the Middle East and Far East, with an incidence in Turkey of 30/100,000 and in Japan of 10/100,000 [2]. In France, BD [prevalence 7.1/100,000] is more frequent than polyarteritis nodosa, microscopic polyangiitis and Wegner's granulomatosis [2]. Childhood BD accounts for 1–3% of all cases of BD [3]. Pathologically BD can involve large, medium and small vessels, both arteries and veins [3]. The aorta is the most commonly involved vessel, followed by the pulmonary artery. Other commonly affected large arteries include femoral, iliac, popliteal, subclavian and carotid arteries [3]. Lesions are characterized by perivascular lymphocytic and mononuclear cellular infiltration, with or without fibrin deposition in the vessel wall and surrounding tissue necrosis. Significant neutrophil infiltration is also seen [4]. Large systemic and pulmonary arteritis results in aneurysms, that are often multiple and bilateral. Thrombi often are found in affected vessels, including pulmonary artery aneurysms (PAAs). PAAs may exhibit fibrinoid necrosis. The inflammatory infiltrate consists primarily of lymphocytes, and also has plasma cells, histiocytes and a few eosinophils [4].

The aetiology of BD is unknown. Although it is clear that there is a significant genetic component to susceptibility to Behçet's disease, as it is often associated with HLA-B51, environmental factors also play a role [4]. The disease may be initiated by an immune response against pathogens such as Herpes simplex type I and some strains of streptococci in susceptible people, such as those with HLA-B51 [5]. Cross-reactivity of heat shock protein in microbes and humans may underlie the immune response [6,7].

Behçet's Disease is characterized by periods of exacerbations and remissions. The diagnosis is a clinical one, and although there is no single laboratory test specific for the diagnosis of Behçet's disease, the 1990 classification criteria perform well in a clinical context (International Study Group Criteria for Behçet's Disease) [4,8]. The complete form of BD is less common in children than in adults, delaying the diagnosis [3]. One third of Kone-Paut et al.'s patients failed to fulfil the international criteria [9]. In a Saudi paediatric series, the male-to-female ratio was 1.4:1 and the mean age at onset was 11.5 years (range 7–16 years) and the mean duration of disease was 6.5 years (range 3–13 years) [10]. In other series, the mean age of disease onset was 6.9±3.9yrs, similar in males and females, and BD affected boys and girls equally [9,11].

The clinical spectrum of childhood BD resembled that of adult disease; however, the prevalence of certain manifestations was different between children and adults. Children with BD had significantly less genital ulcers, less vascular thromboses and more non-specific gastrointestinal symptoms, as well as central nervous system involvement and arthralgia [9,11]. Renal involvement in BD is more frequent than has been recognized, although it is most often mild in nature [1]. The prevalence of uveitis differs between the
series but it carries a poor prognosis. Patients who did not fulfill the international criteria had significant less genital aphthosis, less skin lesions or hypersensitivity, and less uveitis [9,11]. In the Saudi series, oral ulcers were present in all patients (100%), genital ulcers in 11 patients (91%), skin manifestations in 10 patients (83%), musculoskeletal symptoms in 9 patients (75%), and central nervous system involvement in 6 patients (50%). One patient had thrombophlebitis and another had pulmonary artery aneurysm. The pathergy test was positive in 3/7 patients. HLA B5 (W51) typing was positive in 5/10 Saudi patients (10).

Erythema nodosum and skin hypersensitivity were common in Turkish patients, whereas neuro-BD was more frequent in French and Saudi Arabian patients [9,11]. Familial cases were particularly frequent (15%) [9,12]. It can be speculated that genetic factors may favor early expression of the disease with severe organ involvement [12]. The mortality rate (3%) was related to large vessel involvement [9].

Pulmonary arteritis, manifested as pulmonary artery aneurysms (PAAs), is diagnosed in 1–10% of patients with BD [3]. PAAs are the most common cause of death in BD [3,13] with 30% of patients with aneurysms dying within 2 years and 50–2 year mortality after the onset of hemoptysis. PAAs are unusual in children with BD. 5–26S children with BD reported in the literature in paucisystemic Behcet's disease [14]. The venous pulmonary aneurysms are often bilateral and predominate in the lower lobes. Their rupture into a bronchus leads to potentially lethal hemoptysis [3]. It has been recognized in adults that PAAs may be the first manifestation of BD [5,13]. Hughes-Stovin syndrome, characterized by PAAs and venous thrombosis, is probably an incomplete form of BD [5,13].

The venous thrombi in BD adhere to the vessel wall and do not result in emboli. Pulmonary embolism is rare despite high frequency of venous thrombosis [13]. However, in situ thrombosis is a feature of BD pulmonary arteritis: underlying diseases in children pulmonary thromboembolism include Behcet's disease [14]. Superior vena cava thrombosis progresses slowly, allowing the development of a prominent collateral circulation. Vascular inflammation can spread to the mediastinum, the pleura and the lungs with diffuse pulmonary haemorrhages, bronchiolitis and organising pneumonia [13,15]. High-resolution tomodensitometry and MRI are the best diagnostic techniques for assessing pulmonary vascular lesions [13,14]. Lung function in adults is either normal or displays an obstructive pattern with high VD/VT and Rrs [16]. Abnormalities in PaO2 and A-a DO2 are also described [16]. End-expiratory high-resolution computed tomography examination shows the presence of air trapping, even if the patient is asymptomatic or has normal pulmonary function tests [17].

Cardiac lesions occur in 7–31% of BD patients and include acute right ventricular thrombi, organizing mural thrombi, particularly right-sided, hypertrophic cardiomyopathy, mitral valve prolapse, pericarditis, myoccardial infarct, left ventricular aneurysm, thickened aortic valve cusps, aortic and mitral vegetations, myoccarditis, and endocardial fibrosis that probably represents organized mural thrombi [3,18].

Recommendations on vascular disease, neurological and gastrointestinal involvement are based largely on expert opinion and uncontrolled evidence from open trials and observational studies. This is especially true for paediatric patients. For the management of acute deep vein thrombosis in BD, immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide or ciclosporine A are recommended. Treatment of pulmonary aneurysms is mainly with immunosuppressives. Surgery carries a high risk of mortality [13]. Early recognition and vigorous use of immunosuppressives with monthly pulses of cyclophosphamide and high dose corticosteroids have changed the prognosis of patients with pulmonary artery aneurysms [13,19]. In emergencies, embolisation has been tried. Pulmonary artery aneurysms in Behcet's disease may become smaller or disappear with medical treatment. Mural thrombotic changes may be observed during the regression of pulmonary artery aneurysms [20]. The venous thrombi in BD adhere to the vessel wall and do not result in emboli. Thus anticoagulants, antiplatelet or antifibrinolytic agents are not recommended. Another reason to avoid these agents is the possibility of a coexisting pulmonary arterial aneurysm, which might result in fatal bleeding [19].

Topical measures (ie, local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers. In Acne-like lesions, topical measures as used in acne vulgaris are sufficient. Colchicine should be preferred when the dominant lesion is erythema nodosum [19]. Current recommendations for treatment of neuro-Behcet's involve the use of azathioprine or methotrexate and corticosteroids as first-line agents, and cyclophosphamide for high risk patients, with anti-tumor necrosis factor therapy only after the failure of standard therapies [21]. Adalimumab, with a mechanism of action similar to infliximab, may comprise an alternative therapy with a s favourable side-effect profile for paediatric patients with acute neuro BD [22]. IFN-α has a potent CS-sparing effect in paediatric BD patients suffering from severe uveitis. However, the possibility of major side-effects with this treatment calls for careful monitoring [23].

The disease is more severe in Mediterranean and Eastern cohorts than in Western populations, and it is generally more severe in males. A 20-year outcome study of 387 Turkish patients revealed an overall mortality of 9.8% in Behcet’s disease [13]. The prognosis of Behcet's disease is generally good after the initial years [13].

References

In children, primary tuberculosis clearly differs from the forms found in adults. Diagnosis and management guidelines should not be extrapolated. Although a key element in the diagnosis, mycobacteriological identification is seldom achieved in children. The younger the patients, the more significant the mediastinal involvement. Substantial airway obstruction sometimes requires specific therapeutic procedures. The flexible bronchoscope (FB) is usually employed for bacteriological sampling purposes and for the assessment and follow-up of endobronchial tuberculosis (ETB). The rigid tube is more suitable for endobronchial debulking maneuvers. Current indications for bronchoscopy in childhood TB remain controversial. They obviously depend on the skills and habits of the endoscopist but also on the institutional environment, available modalities of sedation, paediatric anesthesiologists, dedicated bronchoscopy suite and equipment. Technological advancements in the imaging techniques also tend to balance the indications. FB is useful too when the diagnosis is unclear, as TB can mimic other conditions such as asthma, pneumonia, inflamed foreign bodies, and congenital malformations. More specifically, ETB is an endoscopic differential diagnosis of foreign body inhalation when substantial granuloma formation is generated.

**Mycobacteriological studies:** Mycobacteria detection and isolation can be challenging in children with pulmonary TB. Whatever the specimen collection methods the overall identification rate is poor, partly due to the low density of bacilli but also in relation to the fact that toddlers and preschools have no spontaneous ability to expectorate. Patients with latent forms are usually culture negative. Bacterial sampling is systematically performed in children with a more patent disease (i.e. with clinical or radiological manifestations) in order to:

- apply rapid diagnostic tests: (i) in patients with confusing symptoms; (ii) when resistant strains are suspected in the contamination source
- evaluate the bacillary infectivity (presence of acid-fast bacilli on smears; bacterial density semi-quantitative estimation)
- obtain cultures to identify the strains and to establish an antibiogram (drug resistance?)

Unfortunately, these goals are difficult to achieve. Repeated gastric aspirates have been described as the gold standard for specimen collection since children swallow rather than expectorate sputum. The yield of this method has been demonstrated superior to the one of bronchoalveolar lavage (BAL) [1]. Sputum induction, stimulated by hypertonic saline nebulization, is proposed as an efficient and low-cost alternative to include the youngest patients. Yet some authors counterbalance its advantages with the increased risk of transmission due to induced coughing and the spreading of droplets, requiring respiratory protection measures that may not be available in many resource-limited regions. Other methods include bronchial brushing and transbronchial needle aspiration biopsy (TBNA), but there is quite no data in the pediatric literature. Several studies have compared the performances of selected collection methods but no global analysis is available regarding the advantages vs drawbacks in the whole set. Choosing the most appropriate one depends on various factors including the geographical burden of the disease and economical constraints.

Compared to gastric aspirates and induced sputum, the yield of BAL has been shown to be very low when performed in unselected cases [2]. This is not surprising in paucibacillary latent TB with minimal parenchymal involvement and intact mucosa. Moreover the BAL procedure is usually performed only once and the specimen collection involves a very limited area of the lungs. The sensitivity of BAL is higher in the active forms of the disease and is manifold increased when DNA amplification methods are applied [3]. Although never demonstrated it is clear that BAL sensitivity is maximal when directly performed on visible mucosal changes (ulcerations, caseating lesions) or into large parenchymal infiltrates guided by chest CT-scan. Finally, combining different sampling methods increases the overall detection rate. For instance, gastric aspirates obtain an advantage by being scheduled on the days immediately following bronchoscopy, as the procedure itself improves the bacteriological yield of gastric specimens [4].

In our experience, BAL can demonstrate co-infection with usual microorganisms such as _Haemophilus influenzae_ particularly when ETB lesions are observed. This could explain the fact of why some children with primary TB temporarily improved with non-specific antibiotics, have delayed diagnosis. Although traditionally considered dangerous in toddlers, TBNA is in fact feasible provided it is guided by careful CT study of the mediastinum (Fig. 1). The place of the procedure remains to be specified; it could be an option to a surgical approach when facing mediastinal lymphadenopathy of an unknown nature; or when central necrosis is seen on a chest CT-scan but where cultures are negative. Indications are still very few but probably underestimated.

**Fig. 1.** Intermediate bronchus obstruction in an 18-month-old child with primary tuberculosis: (a) subcarinal enlargement with no contrast enhancement; note the central necrosis into the lymph nodes and the close relationship with the right pulmonary artery (anterior); (b) fine needle puncture through a rigid tube; the child is supine and the right mainstem is right-sided on the picture; the needle is carefully kept away from the anterior wall.

**Endobronchial tuberculosis assessment:** In untreated toddlers, tuberculous mediastinal lymph nodes behave like locally spreading malignant tumors. Dissemination follows the lymphatic ways: the nodes have the potential of invading any adjacent structure with preferential tropism to the central airway. ETB bronchosopic findings can be classified as follows:

- extrinsic compression: mild <50%; severe >50%
- bronchial wall invasion with mucosal inflammatory changes and edema; granuloma formation; mucosal ulceration and perforation (caseating matter emission)
Interventional bronchoscopy: Intractable airway obstruction can produce definitive pulmonary destruction. Surgical adenotomy has been proposed in order to relieve compression but carries the risk of severe postoperative complications. Tuberculous-infected tissues are weak in nature, bleed easily and show a strong tendency to break in the adjacent connective structures (including vessels) with no clear cleavage plane. Impairment of nutritional status often acts as a depressive factor. Therefore, endoscopic debulking should always be attempted first.

FB is not the most appropriate tool for this purpose except for suctioning mucus or caseum plugs. The rigid bronchoscope can be used by itself as a mechanical drill, by rotating and guiding the bevel through the narrowing structure. Various working instruments can be passed through the tube including endoscopic forceps and suctioning mucus or caseum plugs. The rigid bronchoscope can be passed through the tube including endoscopic forceps and suctioning mucus or caseum plugs. The rigid bronchoscope can be passed through the tube including endoscopic forceps and suctioning mucus or caseum plugs.

Cicatricial stenoses can be dilated using long-shape balloon catheters. Tracheobronchial stenting for post-tuberculous bronchomalacia has already been described but only in adult patients.

References

children) was found in children who only had respiratory tract lesions (atopic bronchial asthma).

**The following differences were found:**

- Children who had the first phenotype of bronchial asthma were more often artificially fed (27%) than children with atopic bronchial asthma (11.6%) \(p<0.1\).
- Children with atopic march were born from mothers who smoked during pregnancy 3 times more often (30%) than children with atopic bronchial asthma (11.2%) \(p<0.1\).
- The defective allele of CYP2C19 gene reliably dominated in the first phenotype compared to the second one \(p<0.05\). Similar results were obtained for CYP2D6 gene of the first detoxication phase \(p<0.01\).
- Statistically reliable differences were also found for GSTT1 gene of the second detoxication phase; the defective allele was more often found in children with the atopic march than in children with atopic bronchial asthma (37% and 13% respectively, \(p<0.01\)).

**Conclusion:** The research has found a higher incidence of asthma-provoking factors such as artificial feeding and mother’s smoking during pregnancy in children with the atopic march. Besides, this group had genetic defects of the first and second phases of xenobiotics detoxication system; this is likely to cause differences in clinical presentation of bronchial asthma with phenotypes I and II.

VII.2 Sensitivities of the forced oscillation technique and spirometry in the detection of airway hyperreactivity in asthmatic children


The detection of airway hyperreactivity (AH) following bronchoprovocation tests plays a key role in the diagnosis of asthma. The measurement of lung function by means of spirometry in young children is limited by their inability to cooperate. Alternatively, the forced oscillation technique (FOT) requires minimal patient cooperation and provides direct information on the airway and respiratory tissue mechanisms. The FOT has gained increasing attention for the measurement of lung function in children, but its ability to facilitate the diagnosis of asthma has not been explored. We therefore set out to compare the sensitivities of lung function parameters obtained with the FOT and spirometry in the detection of AH following different airway challenges in asthmatic children. The FOT and spirometry were performed in 20 asthmatic children under baseline conditions and after inhalations of increasing doses of aerosolized histamine and methacholine (0.5–16 mg/mL, for 2 minutes) at an interval of 2 weeks. The respiratory system input impedance was measured by the FOT; the resistance at 6 Hz (R6) and the average resistance between 4 and 24 Hz (R4–24) were extracted from these recordings. Spirometry was used to obtain the volume in the first second of forced expiration (FEV1) and a flow parameter (FEF25–75). Short- and long-term variabilities of the measured indices were also determined.

Following the provocations with both agonists, the FOT detected AH earlier than spirometry \(p<0.001\) at 0.05 mg/mL for R4–24 and R6 and at 1 mg/mL for FEV1 and FEF25–75 after both agonists with significant correlations between the corresponding parameters relating to the central \(R^{2}=0.6\) and 0.48 between R4–24 and FEV1 for methacholine and histamine, respectively and peripheral airways \(R^{2}=0.47\) and 0.50 between R6 and FEF25–75. With regard to the greater variability in the FOT parameters \((R_{4–24}=10.3\%, \ R_{6}=11.3\%\); \(FEV_{1}=4.3\%\); \(FEF_{25–75}=7.1\%\)), the two approaches exhibited similar sensitivities in the assessment of AH, with R4–24 proving to be most sensitive following both challenges. Our findings suggest that the FOT is at least as suitable as spirometry for the detection of AH in asthmatic children. Since the FOT requires less patient cooperation than spirometry, use of the FOT may impose less stress on the children and may lead to a decrease in the age at which AH can be detected. This beneficial feature of the FOT may improve the early diagnosis of asthma in the preschool age range.

VII.3 Cytomegalovirus infection in immunocompetent wheezy infants: diagnostic value of CMV PCR in bronchoalveolar lavage fluid

G. Cinel1, S. Pekcan2, E. Yalcin1, D. Dogru1, U. Ozcelik1, N. Kiper1.
1Hacettepe University, Ihsan Dogramacı Children’s Hospital Pediatric Pulmonology, Ankara, Turkey; 2Selcuk University Pediatric Pulmonology, Konya, Turkey

**Introduction:** Cytomegalovirus (CMV) pneumonitis in immunocompetent hosts is uncommon but is being recognized more frequently, particularly when presenting as severe viral pneumonia. Due to airway caliber and compliance of the lung, infants develop airway obstruction easily during the course of respiratory tract infections. There are only limited numbers of reports about CMV infection associated with prolonged and intractable wheezing in immunocompetent infants.

**Aims:** The aims of our study are to determine lower respiratory tract infections caused by CMV in immunocompetent wheezy infants, using polymerase chain reaction (PCR) in bronchoalveolar lavage fluid (BAL), to compare CMV PCR in BAL and in blood samples for diagnosis, and also to evaluate the benefits of antiviral gancyclovir therapy in these patients.

**Materials and Methods:** We retrospectively investigated the files of patients referred to our hospital between January 2000 and July 2010, with persistent wheezing that could not be explained with any other reason and fiberoptic flexible bronchoscopy (FFB) applied and CMV PCR in BAL fluid performed. Cytostasis was excluded in all patients with sweat chloride measurement, and also known humoral and cellular immunodeficiencies were ruled out with detailed immunologic investigations. FFB was done to all patients with 3.6 mm flexible pediatric bronchoscope (Olympus®). BAL was performed from the right middle lobe bronchus or the most affected bronchial segment and aspirated aliquotes were analyzed for routine bacterial cultures, PCR for respiratory viruses and also CMV PCR. Patients with CMV PCR positivity in BAL fluids were examined for CMV serology (IgM and IgG) and CMV PCR in blood samples.

**Results:** In this 10.5 years period, 102 infants with persistent wheezing with no underlying disease and not responding to any medical therapy, and who had diffuse interstitial infiltration with or without atelectasis on chest radiographs and/or thoracal CT admitted to our hospital. We performed FFB to all to exclude any structural airway abnormality and investigated CMV PCR in BAL fluids with other diagnostic tests. In 51 patients, CMV PCR in BAL fluid were positive. Retrospectively, we could reach to the files of 29 patients (18 males, 11 females; mean age 12.1 months). The mean CMV viral load measured as CMV PCR in BAL fluid of these patients was 27,692.7 copies/mL. We detected a positively directed but weak relation \((r=0.041)\). CMV IgM was positive in 10 patients and CMV IgG was positive in 24 patients.

**Results:** In this 10.5 years period, 102 infants with persistent wheezing with no underlying disease and not responding to any medical therapy, and who had diffuse interstitial infiltration with or without atelectasis on chest radiographs and/or thoracal CT admitted to our hospital. We performed FFB to all to exclude any structural airway abnormality and investigated CMV PCR in BAL fluids with other diagnostic tests. In 51 patients, CMV PCR in BAL fluid were positive. Retrospectively, we could reach to the files of 29 patients (18 males, 11 females; mean age 12.1 months). The mean CMV viral load measured as CMV PCR in BAL fluid of these patients was 27,692.7 copies/mL. We detected a positively directed but weak relation \((r=0.041)\). CMV IgM was positive in 10 patients and CMV IgG was positive in 24 patients.

**Results:** In this 10.5 years period, 102 infants with persistent wheezing with no underlying disease and not responding to any medical therapy, and who had diffuse interstitial infiltration with or without atelectasis on chest radiographs and/or thoracal CT admitted to our hospital. We performed FFB to all to exclude any structural airway abnormality and investigated CMV PCR in BAL fluids with other diagnostic tests. In 51 patients, CMV PCR in BAL fluid were positive. Retrospectively, we could reach to the files of 29 patients (18 males, 11 females; mean age 12.1 months). The mean CMV viral load measured as CMV PCR in BAL fluid of these patients was 27,692.7 copies/mL. We detected a positively directed but weak relation \((r=0.041)\). CMV IgM was positive in 10 patients and CMV IgG was positive in 24 patients.

**Results:** In this 10.5 years period, 102 infants with persistent wheezing with no underlying disease and not responding to any medical therapy, and who had diffuse interstitial infiltration with or without atelectasis on chest radiographs and/or thoracal CT admitted to our hospital. We performed FFB to all to exclude any structural airway abnormality and investigated CMV PCR in BAL fluids with other diagnostic tests. In 51 patients, CMV PCR in BAL fluid were positive. Retrospectively, we could reach to the files of 29 patients (18 males, 11 females; mean age 12.1 months). The mean CMV viral load measured as CMV PCR in BAL fluid of these patients was 27,692.7 copies/mL. We detected a positively directed but weak relation \((r=0.041)\). CMV IgM was positive in 10 patients and CMV IgG was positive in 24 patients.

**Conclusion:** BAL CMV PCR is a valuable test for the diagnosis of lower respiratory tract infections caused by CMV in immunocompetent wheezy infants. Blood CMV PCR and serologic tests are not valuable as BAL CMV PCR in these patients. In selected patients in this group, gancyclovir therapy can be effective.
VII.4 Comparative study of high frequency percussive ventilation, high frequency ventilation by oscillation and conventional ventilation in a piglet model of meconium aspiration

L. Renesme, C. Elleau, P. Nolent, M. Fayon, E. Dumas De La Roque. CHU de Bordeaux, Hôpital Pédiatrique, Néonatologie et réanimation néonatale, INSERM U 885, CIC 0005 (CEDRE), Université de Bordeaux 2, 146 rue Léo Saignant, 33076, Bordeaux, France

Background: Meconium aspiration syndrome (MAS) induces respiratory distress in an infant born through meconium-stained amniotic fluid whose symptoms cannot be explained otherwise. It is a frequent source of morbidity-mortality in term neonates and there is no consensus regarding respiratory support modalities.

Objective: To compare two modes of high frequency ventilation (high frequency oscillation ventilation HFOV and high frequency percussive ventilation HFPV) to a conventional ventilator (CV) in a piglet model of MAS.

Methods: After instillation of a 3ml/kg solution of meconium diluted to 30%, 15 piglets were randomized to one of three groups: HFOV (Sensormedics® 3100A), HFPV (VDR-3c Bird Percussionaire®) and CV (Siemens® Servo-D). We adjusted ventilator settings to maintain the arterial blood gas within a target window during the 6 hours of ventilation. The oxygenation index (fraction of inspired oxygen/mean airway pressure)/(100)/PaO2), mean airway pressure, dynamic lung function, amount of secretions cleared and histological alterations were studied in all groups.

Results: Mean airway pressure was significantly lower in the CV and HFPV groups compared with the HFOV group (p<0.05). The oxygen index was higher during HFOV compared with CV and HFPV (p<0.05). There was no significant difference between groups regarding lung function, amount of secretions and histological alterations.

Conclusion: CV and HFPV devices are as effective as HFOV for the respiratory support in a piglet model of MAS.

VII.5 Comparison of disease expression between patients with primary ciliary dyskinesia (PCD) and patients with CF and pancreatic sufficiency (CF-PS) and insufficiency (CF-PI)

M. Cohen-Cymberknoh1, N. Simonovski1, N. Hiller1, A. Gillees Hillel2, P. Shoseyov2, E. Kerem2, 1CF and PCD Center, 2Department of Pediatrics and Department of Radiology, Hadassah Hebrew-University Medical Center, Jerusalem, Israel

Introduction: In both CF and PCD, pulmonary disease is caused by impaired mucociliary clearance (MCC). In CF it is a result of airway surface liquid depletion and thickened and viscous mucus and in PCD it is a result of defects in the structure and/or function of respiratory cilia. PCD patients do not have PI and are diagnosed at a later age than patients with CF and therefore are expected to have a disease similar to patients with CF-PS who are diagnosed at a later age, have better nutritional status and better survival compared to CF-PI patients who had the most severe structural disease followed by the PCD group and the CF-PS group. In the CF-PI group most of the pathology was situated in the upper lobes, in PCD in the middle and lower lobes and in CF-PS there was no particular pathological distribution within the lungs. In both CF groups we found a strong negative correlation between TBS and FEV1 and, conversely, in the PCD group, this correlation was not found.

Conclusion: In patients with PCD, FEV1 is not associated with age, BMI, rate of PA infection and CT-TBS. Thus, FEV1 is not a reliable variable to predict severity of lung disease in patients with PCD, and other measurements such as CT are needed to evaluate the disease progression. Further longitudinal studies are needed to delineate the pathogenesis and progression of lung disease in PCD.

VII.6 The effect of multiple siblings with cystic fibrosis on disease progression

M. Lavie1, O. Shemer1, G. Sokol1, R. Somech2, O. Efrati1, D. Vilozni1. 1Edmond and Lili Safra Children Hospital, affiliated to the Sackler medical school, Tel Aviv University, Pediatric pulmonary unit and the national center for Cystic Fibrosis, Ramat Gan, Israel; 2Edmond and Lili Safra Children Hospital, affiliated to the Sackler medical school, Tel Aviv University, Pediatrics B north, Ramat Gan, Israel

Introduction: Cystic Fibrosis (CF) is an autosomal recessive genetic disease which can affect several patients in a family. Our aim was to assess the influence of multiple CF patients in one family on disease progression.

Methods: Longitudinal review of medical charts of CF siblings and matched non-siblings between the years 2000 to 2010. Data included demographics, bacterial colonization, associated disease, hospitalization, pulmonary function tests (PFTs), lung transplantation and socio-economic parameters.

Results: The study group included 58 patients; 6 triplets and 20 pairs and the control group included 58 single CF patients matched by age, gender & mutation. Last mean Forced Expiratory Volume in 1 second (FEV1 %pre) was significantly lower for the study group and number of patients with at least one hospitalization per year was significantly higher for the study group compared to the control group [63±20% vs. 77±21% respectively P<0.05 and 25 (43%) vs. 14 (24%) respectively P=0.05]. There were 8 (14%) lung transplants at a mean age of 25.8 years in the study group compared to 5 (9%) in the control group at a mean age of 29.8 years. No statistical differences in socio-economic parameters were found between the groups aside from more religious Jewish patients in the study group. When comparing the singles (n=58), pairs (n=40) and triplets (n=18) we found the triplets group to be younger (16±9 yr vs. 22±1 for singles and 22±8 for pairs P<0.05), last mean FEV1 %pre was lower for the triplets group (58±30% vs. 77±21% for singles P<0.05 and vs. 66±30% for pairs NS). Rate of deterioration of FEV1 %pre was significantly higher for the triplets compared to singles and pairs (−3.5±2.25, −1.32±2.3 and −0.94±2.12 respectively P<0.05). Number of patients with at least one hospitalization per year was significantly higher for triplets and pairs compared to singles [8 (44%), 17 (43%) and 14 (24%) respectively P<0.05]. More patients from the triplets group had lung transplantation and at a younger mean age [4 (22%) at 23.2 yr vs 5 (9%) at 29.8 yr for singles and 4 (11%) at 28.5 yr for pairs P<0.05 for all parameters].

Conclusion: CF patients with one ill sibling or more are expected to have a poorer outcome of pulmonary disease as reflected by a faster and greater deterioration in PFTs, more hospitalizations and more lung transplants at a younger age. This may be attributed to the burden of disease in one family.
VII.7 Endotoxin exposure and childhood asthma: a meta-analysis of observational studies

E. Forno1, A. Mendy2, J. Gasana2, E. Ramos-Vieira3, J. Patel2, P. Kadam2, G. Ramirez2. 1University of Miami Pediatrics, Miami, USA; 2Florida International University Robert Stempel School of Public Health, Miami, USA; 3Florida International University Department of Physical Therapy, Miami, USA

Purpose of the study: Exposure to endotoxin has been widely investigated as a potential factor explaining disparities in asthma incidence between developed and developing countries. However, epidemiological studies have reported conflicting results. We conduct this meta-analysis to examine the effect of endotoxin on wheezing and asthma development in children.

Methods: We performed a comprehensive literature search of epidemiological studies on odds of doctor diagnosed asthma and reported wheeze in children related to endotoxin exposure, using PubMed (MEDLINE), Highwire, CINAHL, and The Cochrane Library search engines. Adjusted odds ratios (OR) and corresponding 95% confidence intervals (95%CI) were retrieved from studies, independently cross-checked, and pooled by means of weighted average to generate summary fixed or random effect sizes, depending on Cochran Q heterogeneity test using STATA 11.1 software.

Results: Eighteen studies were included in the meta-analysis. Endotoxin was found to have a significant protective effect against childhood asthma (fixed meta-OR 0.62, 95%CI 0.41–0.93). However, the exposure to the bacterial component was associated with an increased risk of any wheeze (fixed meta-OR 1.14, 95%CI 1.05–1.23) and recurrent or persistent wheeze after exclusion of one outlier study (fixed meta-OR 1.28, 95%CI 1.04–1.56). In age subgroup analyses, endotoxin-exposed infants (one to twelve months of age) were found to be at high risk for wheeze (OR 1.57, 95%CI 1.20–2.06), while the protective effect of endotoxin against asthma was mainly seen in school-aged children (older than 5) (OR 0.58, 95%CI: 0.42–0.82).

Conclusion: Endotoxin may be a risk factor for wheeze in children, but may protect against the development of asthma later in childhood. The mechanism by which endotoxin could protect against asthma is not fully understood, possible explanations indicate a stimulation of lymphocytes helper 1 which down regulate lymphocytes helper 2 involved in the development of allergic diseases.

Reflections and proposals for action stimulated by the research: The research brings a consensus on the protective effect of endotoxin against the development of childhood asthma, despite its inflammatory properties. It supports the hygiene hypothesis and helps explain the epidemiology of childhood asthma. Reflection can be oriented to the effectiveness of exposing children to bacterial products such as probiotics in preventing asthma and other allergic diseases.

VII.8 Low serum high-density lipoprotein cholesterol in childhood is associated with adolescent asthma

O. Kolokotroni1, P.K. Yioulouros1, S.C. Savva2, B. Behbod1, D. Milton1. 1Cyprus University of Technology Cyprus International Institute for Environmental and Public Health, Limassol, Cyprus; 2Research and Education Institute of Child Health, Nicosia, Cyprus; 3Harvard School of Public Health, Boston, Massachusetts, USA

Background: Whilst emerging evidence from animal and cell experiments has shown high density lipoprotein cholesterol (HDL-C) to have anti-inflammatory effects consistent with a protective role in asthma, human studies investigating the relationship of HDL-C with asthma have produced conflicting results.

Objective: To examine the association between serum lipids at age 11–12 and prevalence of asthma at age 15–17 in Cyprus.

Methods: In 3982 children, we assessed serum lipids, body mass index (BMI) and maximal oxygen consumption (VO2 max) at baseline (2001–2003) and explored associations with respiratory health at follow-up (2007) using multiple logistic regression models.

Results: Adolescents with active asthma had lower HDL-C in childhood than subjects who had no active asthma (56.5 vs. 59.9 mg/dl, p < 0.01), whereas total cholesterol, low density lipoprotein and triglycerides were not significantly different between active and no active asthmatics. After adjusting for potential confounders, the risk for adolescent active asthma was significantly increased in those who at baseline had HDL-C values <40 mg/dl (OR: 2.47, 95% CI: 1.32, 4.63). Further adjustment for BMI and VO2 max at baseline maintained the significant relation of HDL-C <40 mg/dl (OR: 2.02, 95% CI: 1.06, 3.84) with adolescent active asthma. Effect modification by atopic background provided weak evidence (p = 0.15) to suggest that this association might be significant in subjects with atopic background (OR: 2.58, 95% CI: 1.21,5.50) but not in those without atopic background (OR: 1.12, 95% CI: 0.34,3.66).

Conclusion: Low serum HDL-C in childhood is associated with an increased risk for asthma in adolescence mainly in those with familial predisposition for atopy.

VII.9 Quality of life in children with chronic allergic respiratory disease – a population-based child health survey in Hong Kong

S.D. Koo1, S.L. Lee1, T.M. Wong2, W.H.S. Wong2, Y.F. Cheung3, Y.L. Lau2. 1Queen Mary Hospital Paediatrics and Adolescent Medicine, Hong Kong, China; 2LKS Faculty of Medicine, The University of Hong Kong School of Public Health, Hong Kong, China; 3LKS Faculty of Medicine, The University of Hong Kong Paediatrics and Adolescent Medicine, Hong Kong, China

Background: Respiratory health problem is an important public health issue. Allergic rhinitis and asthma are the two commonest chronic allergic respiratory diseases in children. Both impair quality of life but the impact at the population level in Hong Kong has not been studied. These two conditions often coexist but few studies attempted to assess the interaction between them on quality of life impairment.

Objectives: The objectives of this study are (1) to assess the quality of life impairment in children with allergic rhinitis alone, asthma alone, or concomitant asthma and allergic rhinitis; when compared with healthy children and with other diseased group; (2) to assess the impact of either allergic rhinitis or asthma individually; and whether there is an interaction between asthma and allergic rhinitis on quality of life impairment.

Methods: This study was part of a population-based cross-sectional survey of Chinese children aged 14 years or below in Hong Kong. Child Health Questionnaire (CHQ), a generic instrument was adopted for quality of life measurement. Adolescents themselves (aged 11 to 14) and parents (for children aged 6 to 10) were invited to complete CHQ, followed by completing the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Current wheeze was defined by any wheezing in the preceding 12 months. Current rhinitis was defined by sneezing or a runny or a blocked nose without a cold in the preceding 12 months. One-way analysis of variance was used to compare quality of life in children with current rhinitis alone, current wheeze alone, concomitant current wheeze and rhinitis, and healthy children. Children with history of asthma and/or allergic rhinitis but not current symptoms were excluded. Multiple regression was used to assess for any significant interaction between allergic rhinitis and asthma on quality of life impairment, after adjusting for confounders.

Results: 2755 children and 2657 adolescents were included in the current study. The prevalence of current wheeze and current rhinitis was 2.4% and 16.2% respectively. About 2% of participants experienced both current rhinitis and wheeze.
For children aged 6 to 10, significant differences between groups were seen in eight out of twelve CHQ concepts (p < 0.0001) except physical functioning, role/social-physical, self-esteem and family cohesion. Among the eight CHQ concepts where there were significant differences between groups, children with concomitant current rhinitis and wheeze scored the lowest in all of them, except for parental impact. After adjusting for confounders, current rhinitis was independently associated with significant impairment in seven concepts including role/social-emotional behavior, bodily pain, general behavior, mental health, parental impact-emotional, parental impact-time, and family activities (p < 0.01). Current wheeze was associated with lower CHQ scores in general behavior, parental impact-emotional, parental impact-time, and family activities (p < 0.01). Current rhinitis or current wheeze was not associated with significant impairment in “general health” perception but concomitant current rhinitis and current wheeze interacted to result in significant impairment in general health perception (p < 0.01).

For adolescents aged 11 to 14, significant differences between groups were seen in all eleven CHQ concepts (p < 0.005 for all concepts, p < 0.05 for the concept “family cohesion”). and children with concomitant current rhinitis and wheeze scored the lowest in all concepts except family activities. After adjusting for confounders, current rhinitis was independently associated with impairment in all CHQ concepts (p < 0.05) except general health and family cohesion. Current wheeze was independently associated with impairment in all CHQ concepts (p < 0.05) except self-esteem and family cohesion. Concomitant current rhinitis and wheeze did not interact in adolescent to produce extra quality of life impairment.

**Conclusion:** This is the first local population-based study in Hong Kong to show significant quality of life impairment in children with either allergic rhinitis, asthma or with both conditions. In contrast to previous studies, allergic rhinitis in children affects not only the mental but the predominantly physical CHQ concepts, and this effect extends into the adolescent age group. Current rhinitis in adolescent was not associated with a lower general health perception, indicating their poor insight towards allergic rhinitis as a health problem in general. Current wheeze in children was associated with significant impact on children’s behavior and family function. On the other hand, current wheeze in adolescents was associated with impairment in nearly all CHQ concepts including physical and mental concepts. This contradicts a general belief that adolescents with asthma adapt well to the disease. An interesting finding in children is that, while current rhinitis or current wheeze did not lead to poorer general health perception, concomitant current rhinitis and current wheeze had significant interaction resulting in impairment in “parent-rated” general health perception. This suggests that presence of both rhinitis and wheeze would be sufficient to raise parents’ awareness of their children’s general health condition when either one condition alone did not.

With better awareness, improvement in management and effort to reduce common etiologies, quality of life in children with chronic allergic respiratory disease can be promoted.

**VII.10 Surgical correction of mediastinum left displacement improves the imbalance in the pulmonary perfusion and lung volume in children with pectus excavatum**


**Gunma Children’s Medical Center, Shibukawa, Japan; 2Gunma University Graduate School of Medicine Pediatrics, Maebashi, Japan; 3Tokai University School of Medicine, Isehara, Japan**

**Objectives:** The imbalance of pulmonary perfusion and lung volume in patients with pectus excavatum (PE) after the Nuss procedure has not been objectively assessed. Our aim in this study was to investigate the effect of moving the mediastium to its correct position by surgical repair, which may contribute to improving thoracic deformities and pulmonary perfusion.

**Methods:** Sixty-two consecutive patients with PE who, from August 1999 to November 2007, underwent Nuss procedure at Gunma Children’s Medical Center were evaluated. Two patients with congenital heart disease and nineteen patients who lacked sufficient data were excluded in this study. Ultimately, 41 patients were prospectively studied pre- and post-operatively (just prior to removal of the pectus bar) using the following indices.

Chest radiography, computed tomography (CT) and pulmonary perfusion scintigraphy were performed before surgery and at medium-term follow-up (2.8±0.3 years). Chest radiography was used to calculate the vertebral index (VI) and the left displacement index (LDI), which is the ratio between the left border of the mediastinum and the left border of the thorax to the transverse thoracic dimension on posterioranterior chest radiography. Visual interpretations of the pulmonary perfusion scintigraphy were performed and left-to-right count ratio for lung scintigraphy (Ls/Rs), and the left-to-right thorax volume ratio from CT (Lv/Rv) were also measured.

**Results:** The sternal depression expressed as VI and mediastinum displacement defined as LDI improved respectively after Nuss procedure (p < 0.0001). Preoperative left pulmonary perfusion and lung volume were significantly impaired compared with the right lung. After the Nuss procedure, Ls/Rs and Lv/Rv were significantly increased (Ls/Rs: 0.80±0.14 vs. 0.90±0.09, P < 0.001; Lv/Rv: 0.70±0.09 vs. 0.80±0.08, P < 0.001). To evaluate the usefulness of the chest radiography, we examined the relationships of two radiographic indices, VI and LDI, with Ls/Rs and Lv/Rv. LDI correlated with Ls/Rs (R = 0.470, P < 0.001) and Lv/Rv (R = 0.755, P < 0.001); there was no correlation for VI with Ls/Rs.

**Conclusions:** Our findings indicated that the imbalance of pulmonary perfusion and lung volume improves in PE patients after completion of the Nuss procedure. There is a clear relationship between the degree of left displacement of the mediastinum and decreases in left lung perfusion and volume.

**VII.11 Validation of tidal breathing analysis in the diagnosis of asthma among Filipino children aged 1 month – 6 years**

S.B. Corpuz, N.A. De Leon, M.D. Requiron-Sy, M.S. Bautista.

**Philippine Heart Center, Philippines**

The purpose of the study was to assess the accuracy of Tidal Breathing Analysis in diagnosing asthma in Filipino Children aged 1 month to 6 years as compared with the Philippine Consensus for Asthma as a reference standard.

This is a cross-sectional validation study. Lung function was measured and analyzed using the tidal flow-volume loops (masterscreen Paed Jaeger Pediatric) in 119 sedated young children (55 males, 64 females; mean age 2.6 years) who are suspected of having asthma, before and 15 minutes after inhalation of nebulized salbutamol. The result of the Tidal Volume per kilogram (VT/kg) and the ratios of the time and volume until peak expiratory flow to the total expiratory time and volume, respectively (TPTEF/TE and VPEF/VE) were recorded. Provocation test was also done and reversibility after salbutamol inhalation was recorded.

Results showed that the sensitivity of TBA was 36.2% and the specificity was 80.3%. The positive predictive value was 63.6% and the negative predictive value was 57.0%.

We conclude that Tidal Breathing Analysis is a good validating device to diagnose children with asthma who can not perform the pulmonary function test. However, the test is not a reliable screening method to children still suspected to have asthma. With these findings, all clinicians dealing with pediatric patients suspected with asthma should be vigilant in diagnosing and treating children with asthma.
The usefulness of airway evaluation and sleep study to assess decannulation readiness in children

N. Gurbani, N. Patel, U. Promyothin, N. Simakajornboon. Cincinnati Children’s Hospital Medical Center Pulmonary Medicine, Cincinnati, USA

Introduction: Various diagnostic tools are used to approach decannulation process in children. Direct airway evaluation by microlaryngoscopy is routinely performed prior to decannulation. Dynamic factors affecting the upper airway are most evident during sleep when the pharyngeal muscle tone is decreased; therefore polysomnography has been utilized as one of the important tools in evaluation for decannulation readiness. However, there is limited data on the predictability of these tools. Thus the aim of this study is to evaluate the usefulness of these tools.

Methods: A retrospective review of medical records, microlaryngoscopy and bronchoscopy (MLB) reports and polysomnograms was performed on all children preparing for tracheostomy decannulation at Cincinnati Children’s Hospital Medical Center. At our institution, the pulmonary and ENT physicians use several diagnostic modalities to assess for readiness for decannulation including clinical observation with progressive tracheostomy size reduction, capping trials, microlaryngoscopy, bronchoscopy, and polysomnograms (PSG). All subjects in our study underwent overnight polysomnography with a tracheostomy capping trial and microlaryngoscopy. Subjects with inadequate polysomnogram time (time less than 4 hours) were excluded from this study. The MLB was classified as favorable and unfavorable based on reports. The PSG was classified as normal and abnormal (the presence of central apnea, obstructive apnea or hypoventilation).

Results: A total of 60 subjects met the criteria for inclusion into analysis. The average age was 7.9 years. All tests were divided into ones belonging to subjects who were successfully decannulated (S) (without intervention for 2 years) and ones belonging to subjects who did not get decannulated or failed decannulation (F). 25.4% (15/59) of subjects with favorable MLB results, and 77.3% (17/22) of subjects with normal PSG results were successfully decannulated. 86.4% (19/22) of subjects with both favorable MLB and normal PSG results were successfully decannulated. From PSG, subjects who were successfully decannulated have significantly lower proportion of mild OSA (31% [S] vs 47% [F], P < 0.05), moderate OSA (13% [S] vs 37% [F], P < 0.001), and alveolar hypoventilation (20% [S] vs 40% [F], P < 0.05).

Conclusion: Assessment of airway and respiratory function during sleep with polysomnography is crucial in evaluation for decannulation readiness especially in children with complex airway problems. Our results indicate that polysomnography can be used in conjunction with other diagnostic modalities to assess for the likelihood of successful decannulation in children.

Support: Cincinnati Children’s Hospital Research Fund
we have learnt managing asthma cases as “not all that wheezes is asthma”. These 4 case studies illustrate the importance of vigilance in cause.

On CT scan of the thorax. He is currently being worked up for the radiograph showed evidence of bronchiectasis. This was confirmed recent follow-up, he was noted to have early clubbing and chest to manage’ asthma, on long term inhaled corticosteroids. During years ago. Bronchoscopy was advised but was declined, and patient in whole recently, and that it had been accidentally swallowed 4 this year, he offered a history that he had coughed up a pencil cap suboptimal, presumably secondary to non compliance. At follow-up with corticosteroids (since 10 years old but lung function tests were

We have learnt managing asthma cases as “not all that wheezes is asthma”. These 4 case studies illustrate the importance of vigilance in cause.

On CT scan of the thorax. He is currently being worked up for the radiograph showed evidence of bronchiectasis. This was confirmed recent follow-up, he was noted to have early clubbing and chest to manage’ asthma, on long term inhaled corticosteroids. During years ago. Bronchoscopy was advised but was declined, and patient in whole recently, and that it had been accidentally swallowed 4 this year, he offered a history that he had coughed up a pencil cap suboptimal, presumably secondary to non compliance. At follow-up with corticosteroids (since 10 years old but lung function tests were

A review of 4 interesting cases presenting as “asthma” – what we have learnt

PCP. Wong, A.E.N. Goh, O.H. Teoh. KK Women and children hospital, Singapore, Singapore

The prevalence of asthma has been increasing in recent years, and one may be tempted to diagnose every child with recurrent wheezing episodes as having asthma. We report 4 cases in the last 5 years which presented to our Respiratory Unit as “asthma”, but subsequently found to have alternative diagnoses.

Case 1 is an 18 year old boy with a history of asthma since young, on intermittent bronchodilator therapy. He was however noted to have recurrent haemoptysis and left lung atelectasis which never completely resolved on serial chest radiographs. CT scan showed a left hilar mass with subsegmental collapse; and bronchoscopy confirmed an endobronchial carcinoid tumour in the left lower lobe. He underwent resection of the tumour and lobectomy; and post surgery has remained well.

Case 2 is a 6 yr old girl who had a history of recurrent severe asthmatic attacks since infancy. She was started on inhaled corticosteroids in her native country but was otherwise well in between episodes. She presented to us with severe stridor and respiratory distress 2 months after relocating here with her family, and required intensive care. CT scan of the thorax showed an anomalous left pulmonary artery with long segment tracheal stenosis. Her family decided for surgery in her native country.

Case 3 is a 13 year old obese boy with moderately persistent asthma. He was treated with combination inhalers (long acting beta agonist with corticosteroids) since 10 years old but lung function tests were suboptimal, presumably secondary to non compliance. At follow-up this year, he offered a history that he had coughed up a pencil cap in whole recently, and that it had been accidentally swallowed 4 years ago. Bronchoscopy was advised but was declined, and patient is still on regular follow-up. Serial lung function tests show large and small airway disease with bronchial response.

Case 4 is an 14 year old boy, 1 of a set of twins with ‘difficult to manage’ asthma, on long term inhaled corticosteroids. During recent follow-up, he was noted to have early clubbing and chest radiograph showed evidence of bronchiectasis. This was confirmed on CT scan of the thorax. He is currently being worked up for the cause.

These 4 case studies illustrate the importance of vigilance in managing asthma cases as “not all that wheezes is asthma”.

A2

A review of 4 interesting cases presenting as “asthma” – what we have learnt

PCP. Wong, A.E.N. Goh, O.H. Teoh. KK Women and children hospital, Singapore, Singapore

The prevalence of asthma has been increasing in recent years, and one may be tempted to diagnose every child with recurrent wheezing episodes as having asthma. We report 4 cases in the last 5 years which presented to our Respiratory Unit as “asthma”, but subsequently found to have alternative diagnoses.

Case 1 is an 18 year old boy with a history of asthma since young, on intermittent bronchodilator therapy. He was however noted to have recurrent haemoptysis and left lung atelectasis which never completely resolved on serial chest radiographs. CT scan showed a left hilar mass with subsegmental collapse; and bronchoscopy confirmed an endobronchial carcinoid tumour in the left lower lobe. He underwent resection of the tumour and lobectomy; and post surgery has remained well.

Case 2 is a 6 yr old girl who had a history of recurrent severe asthmatic attacks since infancy. She was started on inhaled corticosteroids in her native country but was otherwise well in between episodes. She presented to us with severe stridor and respiratory distress 2 months after relocating here with her family, and required intensive care. CT scan of the thorax showed an anomalous left pulmonary artery with long segment tracheal stenosis. Her family decided for surgery in her native country.

Case 3 is a 13 year old obese boy with moderately persistent asthma. He was treated with combination inhalers (long acting beta agonist with corticosteroids) since 10 years old but lung function tests were suboptimal, presumably secondary to non compliance. At follow-up this year, he offered a history that he had coughed up a pencil cap in whole recently, and that it had been accidentally swallowed 4 years ago. Bronchoscopy was advised but was declined, and patient is still on regular follow-up. Serial lung function tests show large and small airway disease with bronchial response.

Case 4 is an 14 year old boy, 1 of a set of twins with ‘difficult to manage’ asthma, on long term inhaled corticosteroids. During recent follow-up, he was noted to have early clubbing and chest radiograph showed evidence of bronchiectasis. This was confirmed on CT scan of the thorax. He is currently being worked up for the cause.

These 4 case studies illustrate the importance of vigilance in managing asthma cases as “not all that wheezes is asthma”.

A3

Allergen and pet exposure and asthma morbidity in Puerto Rican children

E. Forno1, M. Cloutier1, S. Datta1, R. Kelly1, K. Paul1, J. Senter1, D. Calvert2, S. Thornton-Thompson1, D.B. Wakefield2, J. Brehm2, E. Acosta2, G. Canino3, J.C. Celedon3. 1University of Miami Pediatrics, Miami, USA; 2University of Connecticut Health Center Pediatrics, Farmington, CT, USA; 3Channing Laboratory, Boston, USA; 4Connecticut Children’s Medical Center, Hartford, CT, USA; 5University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; 6University of Puerto Rico Behavioral Sciences Research Institute, San Juan, PR, USA

Introduction: Little is known about the relation between pet and allergen exposure and asthma morbidity in Puerto Rican children.

Methods: We examined indoor levels of six allergens (dust mite, cockroach, mouse, rat, dog dander, and cat dander) in relation to asthma/asthma morbidity in a case-control study of 433 Puerto Rican children (ages 6-14 yrs) in Hartford, CT (USA). Protocol included questionnaires, spirometry with bronchodilator, methacholine challenge, serum total IgE and peripheral blood eosinophil count, and collection of house dust samples for allergen levels (D. pteronyssinus, B. germanica, Mus m 1, Rat n 1, dog dander, and cat dander) using two-site monoclonal ELISA. Logistic or linear regression was used for the multivariate analyses adjusting for age, sex, parental history of asthma, household income, and levels of other allergens when appropriate.

Results: Mean age was 10.4 yrs (SD = 2.9) and 49% of participants were boys. Compared to controls (n = 169), cases (n = 264) were more likely to have parental history of asthma, higher total IgE and eosinophil count, and lower FEV1 (P = 0.016), increased airway responsiveness to methacholine [AHR] (P = 0.005), and increased total IgE (P = 0.05) and eosinophil count (P = 0.009). Mouse allergen levels were inversely associated with having an FEV1 < 80% predicted (P = 0.045). There were trends towards an 8-fold increased risk of past intubation due to asthma with increasing levels of rat allergen (P = 0.058) and towards an 8-fold increased risk of hospitalizations or ER visits for asthma in children with the highest levels (> 90th percentile) of B. germanica (P = 0.054).

Indoor levels of cat dander were associated with lower total serum IgE (P = 0.008). Exposure to the highest levels (> 90th pct) of dog dander was associated with a decreased risk of having an FEV1 < 80% predicted (P = 0.049). Reported exposure to dogs or cats during pregnancy/infancy was associated with decreased AHR (P-values ranged 0.001–0.02 for dogs and 0.02–0.04 for cats). There were trends towards decreased bronchodilator responsiveness in children exposed to dogs during pregnancy (P = 0.076) and towards decreased total IgE in children exposed to cats during pregnancy (P = 0.095).

Conclusions: Increased levels of dust mite were associated with increased asthma morbidity in Puerto Rican children living in
Asthma education

A4 Asthma control test (ACT) versus intermittent oscillation system (IOS) assessment for control of asthmatic children

M. Shaheen, M. El Ganzoury, E. Mohamed. Ain Shams University Pediatric Department, Pulmonology Unit, Cairo, Egypt

Background: In spite of the great development of international guidelines for the diagnosis and the treatment of asthma, there is continuing evidence of poor control of childhood asthma.

Aim of this work: to evaluate the subjective asthma control test (ACT) against the objective impulse oscillation system (IOS) measures of the airways resistance in asthmatic children.

Subjects and Methods: This study included 35 asthmatic children diagnosed with bronchial asthma according to GINA guidelines 2009. All the study children were subjected to the following: full medical history, thorough clinical examination and basic spirometric FEV1 measurements (to fulfill GINA doctor's subjective assessment for asthma control). Then, the children's subjective assessment by ACT (using an Arabic version of ACT) was done. Finally; Impulse Oscillation test (IOS) was done for all children to compare their objective results with previous subjective results of asthma control.

Results: Score 19 was the cut off value differentiating children's asthma control (compared to the gold standard IOS cut off values). Thirty two patients were considered controlled by the CACT/ACT (score >19) versus 28 children using IOS assessment. Only 3 patients were considered uncontrolled by ACT tests (score ≤19) versus 7 children using IOS. Moderate agreement between CACT/ACT asthma control and IOS results; kappa test = 0.54 (P<0.0001) was reported. While agreement between IOS results and GINA tool for asthma control was much less significant; kappa test = 0.36 (P>0.05). Nevertheless; there was highly significant negative correlations between total scores of CACT/ACT and values of IOS (R5) and (R20); r =−0.47, r =−0.51 and P =0.004, P =0.002 respectively. The correlation coefficient for the internal consistency of the CACT/ACT was 0.89 as an evidence for ACT reliability. Also accuracy of CACT/ACT was assured by calculating area under the ROC curve (AUC) and it was 0.900.

Conclusion: This study confirms that asthma control test (ACT) is a valid and cost effective instrument for assessment of control in asthmatic children.

A5 Asthma education

L.S. Nordhagen. Rikshospitalet, Oslo, Norway

Background: Asthma is the most common chronic disease in childhood and the most frequent cause of hospitalization in Norwegian children's departments. The prevalence of asthma is increasing and the recent Norwegian study found asthma among 20% of the 10 years old children in Oslo [1]. Children with severe asthma are at risk of developing chronic obstructive pulmonary disease in adulthood [2]. The treatment of asthma is both pharmacological and non pharmacological. Asthma education is an important part of the non-drug treatment. Several studies have shown that education of children and their parents give increased knowledge about asthma, improve asthma control and reduce acute admissions.

Objective: Document that asthma education improves knowledge about the disease and that increased knowledge about the disease improves asthma control.

Methods: Knowledge test, Asthma Control Test (ACT), performed before asthma education, immediately after completion of asthma education and 2–3 months after completed asthma education to investigate the level of knowledge about asthma in children aged 8–12 years and parents of children with asthma.

Results: Both children and parents increased their level of knowledge about asthma after education, newly referred patients get also a better asthma control after education.

Conclusion: It needs more studies on the effect of asthma education. This project shows that asthma education improves knowledge about asthma. It is therefore important to provide more training and education of children with asthma and their parents.

References
A7 Comparison of mannitol, methacholine and exercise challenge test to evaluate bronchial hyperresponsiveness in asthmatic children
N.P. Consilvio, A. Palazzo, A. Scaparrotta, A. Cingolani, D. Rapino, S. Di Pillo, F. Chiarello, M. Verini. Allergological Service, Paediatric Clinic, University of Chieti, Chieti, Italy; Paediatric Department, University of Chieti, Chieti, Italy

Bronchial hyperresponsiveness (BHR) is one of the features of asthma. It is defined as episode of excessive airway narrowing in response to a provoking stimulus. There are two categories of stimuli for Bronchial Challenge Tests: Direct (histamine, methacholine) and Indirect (exercise, hyperpnea, hypertonic saline, AMP and mannitol). The direct agents are sensitive for identifying BHR but not specific for identifying asthma. The indirect agents are more specific for identifying asthma, though less sensitive for identifying BHR.

This study was designed to compare the response to inhaled mannitol to methacholine and to exercise in asthmatic children. Twenty children were recruited from the Paediatric Allergy and Respiratory Clinic of Department of Pediatrics, University of Chieti. All children have a history of asthma, atopy and house dust mites sensitization. All children first performed the methacholine challenge (Mch Test). Also total and specific IgE were determined. During the second visit children performed the exercise challenge and the mannitol challenge on subsequent visit.

All children had a positive response to Mch test with PC20 ranging from 0.25 to 2.9 mg/ml (mean±SD: 1.4±2.86 mg/ml); 1 child (5%) had a severe BHR (PC20 <0.25 mg/ml), 5 children (25%) had a moderate BHR (PC20 0.25–1 mg/ml) and 14 children (70%) had a mild BHR (PC20 1–4 mg/ml). There was a statistically significant relationship between PC20 and House Dust Mites Specific IgE (p = 0.02). All children had a positive response to mannitol challenge with PD15 ranging from 5 to 315 mg (mean±SD: 121±84.5 mg). Of the 20 children 4 (20%) had a severe BHR (PD15 <35 mg); 11 (55%) had a moderate BHR (PD15 35–155 mg) and 5 (25%) had a mild BHR (PD >155 mg). 12 children (60%) had a positive response to exercise challenge and 8 children (40%) had a negative response. Of the 12 children tested positive, 1 (8%) had a severe BHR (fall in FEV1 >50%), 5 (41%) had a moderate BHR (fall in FEV1 20–50%) and 6 (50%) had a mild BHR (fall in FEV1 10–20%). There was a significant difference in the % reduction in FEV1 after Mch test (mean±SD: −29±6.3%) compared to mannitol challenge (−18±4.4%, p = 0.000002) and to the exercise challenge (−16±15.7%, p = 0.01). Inhaled mannitol identifies correctly BHR in methacholine-responsive asthmatic children and appears to be an alternative for an exercise challenge to assess BHR. Furthermore it prevents a vigorous fall in FEV1 which is an important safety feature.

A8 Evaluation of the adrenal function in children age 0–48 months treated with high dose of inhaled corticosteroids for severe asthma
O. Afolabi-Brown, M. Marcus, I. Kazachkova, M. Kazachkov. Maimonides Medical Center Pediatrics, Brooklyn, USA

Background: Inhaled corticosteroids (ICS) are widely used for treatment of pediatric asthma. Asthma in children age 0 to 4 years is not common and is difficult to diagnose. Treatment modalities are not well-studied and safety profile of inhaled corticosteroids is not established in this age group.

The objective of the study is to evaluate adrenal function and growth in young children diagnosed with severe asthma and receiving high doses of inhaled corticosteroids.

Methods: We performed a retrospective chart review of five children with a mean age of 20.4±15.7 months (range, 10–48 months) who received high dose inhaled corticosteroids for treatment of severe asthma and underwent evaluation of their adrenal function. The diagnosis of asthma in these children was established by pediatric pulmonologist and based on clinical presentation of recurrent wheezing, which was not related to viral respiratory infections and responded to bronchodilator. (n=5), history of atopy confirmed by skin testing (n=5) and bronchoalveolar lavage sample containing eosinophils (n=2). In order to achieve optimal control of asthma high dose HFA-beclomethasone dipropionate (HFA-BDP) (160 to 320 micrograms per day) was used either alone (n=3) or in combination with budesonide/formoterol fumarate dehydrate (BFFD) (320 micrograms per day) (n=2). Medication was delivered using a large volume valved holding chamber with appropriate size mask. All children had evaluation of their adrenal function, which included clinical assessment by Pediatric Endocrinologist and standard adrenocorticotropic hormone (ACTH) stimulation test. A stimulated cortisol level above 18 micrograms/dl drawn 60 min after IV administration of 250 mcg of Cortrosyn was used to denote normal response. Height, weight and weight /height ratio percentiles were monitored during this period.

Results: Mean duration of high dose inhaled corticosteroids regimen was 16.6±9.7 months. There were no clinical signs of adrenal insufficiency during the course of treatment. All children had normal response to ACTH stimulation test judged by normal stimulated cortisol levels (24.48±2.21 micrograms/dl). Treatment with high dose ICS did not cause significant difference neither in height percentiles (21 [21,40] vs. 24 [22,87]) nor in weight to height ratio percentiles (63.2±38.04 and 67.8±34.1, p = 0.330).

Conclusion: Use of high dose HFA-BDP and BFFD did not cause suppression of adrenal function and growth velocity or excessive weight gain in our group of very young children with severe asthma.

A9 Gastroesophageal pH monitoring, exercise and atopic inflammation in children with recurrent respiratory symptoms
M. Barreto, C. Pacchiariotti, F. La Penna, A. Prete, A. Crescenzi, D. Chialant, S. Martella, M.P. Villa. Pediatric Unit, Sant’Andrea Hospital, University La Sapienza NESMOS Department, Rome, Italy

Background: Coexistence of gastroesophageal reflux (GER) and asthma presumably occurs as both conditions are common. The relationship between GER and exercise in children with respiratory symptoms is scarcely understood.

Aims: To compare the gastroesophageal acidity (GE pH) with lung function and markers of airway inflammation and acidity in children with recurrent respiratory symptoms.

Methods: In 12 asthmatic and 9 non-asthmatic (aged 5.9–15.8 yr, M/F 14/7) we assessed exhaled nitric oxide (FeNO), breath condensate acidity (EBC pH) and spirometry, then started a 24-h GE pH monitoring (GE pH24). In a second session, measurements were repeated before and after a 6-minute treadmill-exercise testing followed one hour later by gastroesophageal catheter removal. Prick test and blood samples for IgE and leukocytes were also measured, the sum of allergen-skin wheals was termed “prick index”.

Results: Median (IQR) GE pH24 values were found unrelated to post-exercise FEV1 decrease. GE pH24 correlated with prick index (r=0.58), percent blood eosinophils (r=0.58) and EBC pH (r=−0.64) only in asthmatic children (p<0.05); they also yielded higher GE pH24 than non-asthmatic children (7.25, IQR 0.18 vs 7.0, IQR 0.50– p<0.05). GE pH recorded 6 minutes before exercise decreased during exercise testing from 7.85 (IQR 0.73) to 7.30 (IQR 1.05) in asthmatic (p <0.059) while it increased from 7.20 (IQR 0.90) to 7.90 (IQR 0.85) in non-asthmatic children (p<0.043). Exercise-induced fall in GE pH correlated with FeNO (r=−0.58) while one-hour post-exercise GE pH increased only in asthmatic children (7.80, IQR 0.68; p<0.05).

Conclusion: Exercise-induced changes of GE pH in asthmatic children suggest vagal-induced transient relaxation of the lower esophageal sphincter but not exercise-induced change of GE pH in non-asthmatics. Further investigations are needed to establish if this mechanism is specific for asthmatic children and might represent a new target for the treatment of asthmatic patients with GER.
esophageal sphincter followed by compensatory mechanisms to reduce esophageal acidity. Atopic inflammation appears to stimulate these changes.

**A10**

**Methacholine challenge test in school-aged children with history of bronchopulmonary dysplasia**

T. Chaisupmongkollarp, H. Kamalaporn, A. Preutthipan. Ramathibodi Hospital Pediatrics, Bangkok, Thailand

**Introduction:** Bronchial hyperresponsiveness (BHR) and asthma has been reported as significant sequelae in children suffered from bronchopulmonary dysplasia (BPD). The purpose of this longitudinal study was to demonstrate prevalence, characteristics of BHR in BPD children and to identify factors contribute to BHR when they reach school age.

**Methods:** Between the year of 2001–2003, 21 premature children with BPD has been registered into the BPD program at our institute. The infant lung function tests and methacholine challenge test (MCT) have been performed at age of 18–24 months. In the year 2010, we recollected these children at age of 7–10 years. 7 of them could not be reached by telephone or mail. 1 refused to participate in this study. Informed consents were obtained from 13 children. Current clinical data of asthma symptoms, exercise-induced asthma, emergency department visits, hospitalization due to respiratory illnesses, asthma medication use, allergy, and smoking exposure were obtained from caregivers. Spirometry and MCT tests were then performed. Concentration of methacholine that makes 20% decrement of force expiratory volume in 1 second (FEV1) was defined as PC20. The degree of BHR was classified as severe, moderate, and mild according to PC20 of <1, 1–4, and >4 mg/ml respectively. The PC20 of >16 mg/ml was identified as no BHR.

**Results:** 13 children aged 7–10 years (8.9±1.2) were recruited. 9 of them were male. 10 of 13 children (76.9%) had clinical diagnosis of asthma. 2 of these had been diagnosed to have asthma and outgrew at the age of 6 and 8 respectively. 8 children (61.5%) still had asthmatic symptoms in the past 12 months but only 1 child was diagnosed by physician and received asthma treatment. 12 children were able to perform spirometry. 2 children (16.7%) had obstructive lung function demonstrated by spirometry whereas 11 children (91.4%) had positive MCT. The median of PC20 was 3.6 (0.02–8.5) mg/ml. 7 children were classified into moderate to severe BHR group and 4 children were in mild BHR group. All children in moderate to severe BHR group had clinical symptoms of asthma compare to 1 of 4 children in mild BHR group. 8 children with symptomatic asthma significantly had PC20 less than asymptomatic children (p=0.028). 6 of 7 children with moderate to severe BHR and 1 of 5 children with mild or no BHR had secondhand smoking (p=0.03). Birth weights, gestational age, duration of mechanical ventilation, duration of oxygen requirement and BHR in infancy were not significant correlated with PC20 at school age.

**Conclusion:** School-aged children with history of BPD have a high prevalence of BHR as demonstrated by MCT. Spirometry is not sensitive to screen BHR and may lead to delayed diagnosis and treatment of BHR in BPD children. Careful history taking of asthma symptoms and MCT should be integrated into optimal long-term follow up of BPD children.

**A11**

**Methods to improve effectiveness and retention of asthma education for children: a pilot project with 1 year follow-up**

C. Fernandez1, K. Kuriakose2, M. Cataletto1. ‘Winthrop University Hospital, Mineola, USA; 2Stony Brook University Medical Center, Stony Brook, USA

**Introduction:** Asthma accounts for over 750,000 emergency department (ED) visits per year for U.S. children alone. Both direct and indirect costs have made reduction in hospitalization and ED visits for asthma a priority focus of the Healthy People 2020. Motivation is essential to learning. We hypothesize that the need for emergency care for asthma is in itself an important motivator for children and their families to learn about asthma and become partners in their own care. This project addresses a combination of educational techniques to maximize interest, learning and retention of key asthma messages (KAM).

**Methods:** This study was approved by the IRB. Children between ages 5 and 18 years presenting to the pediatric ED because of asthma symptoms were invited to participate. After completing a baseline survey, facilitated discussions of KAM were interwoven with an interactive computer based educational tool (Quest for the Code™). Reinforced KAM were available on line and children were encouraged to use the interventional tool as often as they liked. Follow-up telephone contacts were made at 6, 9 and 12 months. Numbers of acute care visits and systemic steroid courses within the prior 3 months were compared to similar data during the year following the intervention.

**Results:** Twenty-seven parent–child pairs completed the initial program. The primary findings included:

1. Factors motivating participation included the need to be in the ED, parental involvement in the process, and effective use of technology.
2. Barriers identified were fatigue of child, unavailability of parent and ED visit during uncovered educator hours.
3. Baseline knowledge and disease control was poor as evidenced by an average of 2.5 ED visits and 1.5 admissions per child in the prior 3 months. Sixty-six percent of subjects had at least one systemic steroid course. At 6, 9, and 12 month follow-up there were no ED visits, systemic steroid courses and no hospitalizations.
4. Families reported development of confidence associated with better understanding of key asthma concepts, as well as improved family–provider communication.

**Conclusions:** While there are clear barriers to asthma education in the emergency department, poor control necessitating emergency room treatment is an effective motivator to participate in the educational process. The acute care setting did not detract from effective learning and children at 12 month follow-up were doing well.

**A12**

Not all who wheeze have asthma – tracheal diverticulum with stenosis of trachea in a 9-year-old boy

F. Kopriva1, V. Kolek2, K. Michalkova3, J. Potesil1. 1Palacky University Medical Faculty Pediatrics, Olomouc, Czech Republic; 2Palacky University Medical Faculty Pulmonology, Olomouc, Czech Republic; 3Palacky University Medical Faculty Radiology, Olomouc, Czech Republic

**Purpose of the study:** A tracheal diverticulum (TD) is usually an accidental rare finding TD was first described by Rokitaknsky in 1838. The prevalence is about 0.3% in children over 10 years of age according to fiberoptic bronchoscope studies and it is rarely reported in clinical practise. Two types of trachea diverticula exist, congenital and acquired, varying in site.

**Methods and Materials:** A 9-year-old boy was admitted to hospital with wheezing and progressive dyspnoe during the last 6 months to restrict basic locomotion with negative personal history. Multislice computed tomography of the chest showed surprising incidental finding of a tracheal diverticulum (arrow) (6 mm × 2 mm) and three-dimensional reconstruction CT-virtual bronchoscopy showed stenosis of trachea approximately 1.5 cm below vocal cord (the 2nd cartilage of trachea) and orifice of tracheal diverticulum. Pulmonary function tests revealed reduction of spirometric values, with no post-bronchodilator change. Subsequent flexible bronchoscopy showed circular stenosis of trachea and orifice of tracheal diverticulum.
Subsequently, the vaporization by Nd:YAG laser – Sharp plan 3000, was performed via flexible bronchoscopy. The dilatation by balloon (Boston Scientific) was performed to widen the diameter of trachea up to 8 mm.

Results: After one week pulmonary function test revealed normal parameters of lung function without pathological symptoms.

Conclusion: The interventional bronchoscopy is well funded in pediatric pulmonology.

A13 Quality of life in asthmatic children: a comparative study of patients’ and parents’ perceptions
M. Shaheen, S. El Said, E. Zaki. Ain Shams University Pediatric Department, Pulmonology Unit, Cairo, Egypt

Background: Pediatric asthma is one of the most important public health problems. Pediatric pulmonologists are not only responsible for clinical relief of children’s symptoms but also for providing a better health related quality of life for them and their families.

Aim of the work: The present study was designed to investigate the Health-related quality of life (HRQOL) for pediatric asthmatic patients and their caregivers’ perception compared to controls.

Methods: This study comprised 80 children and their parents. They were classified into two groups. Group I (known asthmatic children) which comprised 40 children; their ages ranged from 8 to 12 years and group II (controls) which comprised 40 matched healthy children.

All children in this study were subjected to full history taking, thorough clinical examination, pulmonary function tests and assessment of Pediatric Quality of Life using PedsQL™ Inventory both Child Self Report and Parent Proxy Report. The PedsQL™ Scales are comprised of parallel child self-report and parent proxy-report formats. The PedsQL™ covers five health domains: physical functioning, emotional functioning, social functioning, school functioning, and general well-being. Items are reverse-scored and linearly transformed to a 0–100 scale that higher scores indicate better HRQOL.

Results: In the current study, HRQOL (physical, emotion, social, school and psychosocial health) showed significant lower scores both in asthmatic children and their caregivers compared to controls (p<0.01). Patients with moderate to severe persistent asthma self-reported significantly the lowest overall HRQOL (HRQOL scores were negatively correlated to asthma severity scores and positively correlated to pulmonary function parameters). However; both asthmatic children and their caregivers suffered significant lower total HRQOL, the caregivers had significant lower total HRQOL, the caregivers had significant lower values compared to their asthmatic children (p<0.001) and % predicted forced expired volume in 1 second (FEV1, ) = 0.3, P = 0.04). Serum 25-hydroxyvitamin D levels and asthma symptoms (ACT) (r=0.49, P<0.001) and % predicted forced expired volume in 1 second (FEV1, ) = 0.3, P = 0.04). Serum 25-hydroxyvitamin D levels and asthma symptoms (ACT) (r=0.49, P<0.001) and % predicted forced expired volume in 1 second (FEV1, ) = 0.3, P = 0.04). Serum 25-hydroxyvitamin D levels and asthma symptoms (ACT) (r=0.49, P<0.001) and % predicted forced expired volume in 1 second (FEV1, ) = 0.3, P = 0.04). Serum 25-hydroxyvitamin D levels and asthma symptoms (ACT) (r=0.49, P<0.001) and % predicted forced expired volume in 1 second (FEV1, ) = 0.3, P = 0.04). Serum 25-hydroxyvitamin D levels and asthma symptoms (ACT) (r=0.49, P<0.001) and % predicted forced expired volume in 1 second (FEV1, ) = 0.3, P = 0.04).

In children with STRA, a positive correlation was found between serum 25-hydroxyvitamin D levels and BAL levels of the anti-inflammatory cytokine interleukin (IL-10) (r=0.51, P=0.03) and CD25+ FoxP3 regulatory cells (r=0.6, P=0.02). No significant relationship between serum 25-hydroxyvitamin D levels and BAL neutrophils and eosinophils.

Conclusion: In children with STRA reduced vitamin D levels are associated with worse symptoms and greater ICS usage, lower lung function, and more severe airway inflammation. Proof of concept that vitamin D deficiency causes steroid resistance requires intervention studies, but at the very least, on clinical grounds, vitamin D deficiency should be sought and treated in children with STRA.

A14 Serum vitamin D levels and severe therapy resistant asthma in children
A. Gupta1, A. Bush1, D. Richards2, C. Hawtrylocicz2, S. Saglani1. 1Royal Brompton Hospital & NHLI, Imperial College, Paediatric Respiratory Medicine, London, UK; 2King’s College MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

Background: Little is known about vitamin D levels and their impact on disease control in children with severe, therapy resistant asthma (STRA).

Hypothesis: Children with STRA have lower serum vitamin D levels than non-asthmatic controls and lower vitamin D levels are associated with more severe asthma [symptoms, inhaled corticosteroid (ICS) treatment, and spirometry; and worse airway inflammation measured in bronchoalveolar lavage (BAL)].

Methods: We measured serum 25-hydroxyvitamin D in 30 asthmatics and 16 non-asthmatic children; asthma severity was categorized using the asthma control test (ACT); ICS dose; spirometry; exhaled nitric oxide at 50 ml/s (FeNO50); BAL cytokines and CD25+ FoxP3 regulatory cells.

Results: In asthmatics, the prevalence of vitamin D insufficiency (<75 nmol/L) was 90%, with 78% being vitamin D deficient (<50 nmol/L). All age-matched non-asthmatic controls were vitamin D insufficient with 50% being vitamin D deficient. Children with asthma had lower median 25-hydroxyvitamin D serum levels (36 nmol/L, range 3–83) as compared to age-matched non-asthmatic controls (48 nmol/L, range 25–72) (P<0.03).

There was a positive correlation between serum 25-hydroxyvitamin D levels and asthma symptoms (ACT) (r=0.49, P<0.001) and % predicted forced expirered volume in 1 second (FEV1, ) = 0.3, P = 0.04). Serum 25-hydroxyvitamin D levels were significantly inversely associated with FeNO50 (r = −0.6, P = 0.001) and ICS usage (r = −0.4, P = 0.02).

In children with STRA, a positive correlation was found between serum 25-hydroxyvitamin D levels and BAL levels of the anti-inflammatory cytokine interleukin (IL-10) (r=0.51, P=0.03) and CD25+ FoxP3 regulatory cells (r=0.6, P=0.02). No significant relationship between serum 25-hydroxyvitamin D levels and BAL neutrophils and eosinophils.

Conclusion: In children with STRA reduced vitamin D levels are associated with worse symptoms and greater ICS usage, lower lung function, and more severe airway inflammation. Proof of concept that vitamin D deficiency causes steroid resistance requires intervention studies, but at the very least, on clinical grounds, vitamin D deficiency should be sought and treated in children with STRA.

A15 Sleep study of respiratory parameters in asthmatic children
M. Shaheen, A. El Husainty, M. El Khawaga. Ain Shams University Pediatric Department, Pulmonology Unit, Cairo, Egypt

Background: Many asthmatic children get awake with symptoms of their disease almost every night. A growing body of evidence indicates that the causal pathway of cytokine changes resulting from asthma may influence the neurochemistry of sleep regulation. Equally possible is that sleep disturbance resulting from asthma promotes further changes in neuropeptides, which in turn influence the course of asthma. Asthma, airway inflammation, and sleep may thus be linked in a complex set of relationships in need for evaluation.

Objectives: This observational cross sectional study was designed to monitor respiratory parameters during sleep in asthmatic children.

Methods: Fifty Egyptian children were recruited for assessment, 30 known asthmatic children and 20 matched healthy controls. All the children were subjected for: detailed medical history including night symptoms, thorough clinical examination including anthropometric measures, pulmonary function testing and recording of respiratory parameters during sleep using non-invasive Apnea Link screening system (RESMED system).

Results: History of recurrent night cough is found in 44% of asthmatic children, recurrent night wheezes in 77%, night snoring in 47%, night nasal obstruction in 53% and recurrent night dyspnoea in 17% of the studied asthmatic children. Repeated daytime naps were reported in 43% of children, sleep fragmentation in 40% and nocturnal awakening in 37% of children. Pathological Apnea–Hypopnea Index (AHI≥1) was documented among 96% of asthmatic children compared to 3.33% of controls; and AHI showed a significant negative correlation to FEV1, values (r = −0.379, p = 0.01). Similarly, Oxygen Desaturation Index (ODI) ranged from 0 to 26 with mean...
B. Bronchopulmonary and pleural infections (including tuberculosis)

B1 Acute bronchiolitis in former premature under 35 weeks of gestation
S. Hamouda, S. Maghraoui, F. Tinsa, I. Brini, L. Karboul, Kh. Boussetta, S. Bousnina. Children’s Hospital Medicine B, Tunis, Tunisia

Introduction: Bronchiolitis is a common disorder affecting younger and infant patients. The prevention of RSV bronchiolitis by monoclonal antibodies has improved its prognosis in the former premature less than 35 weeks of gestation in developed countries. In our country, this treatment is expensive and unavailable. The aim of our study is to assess the severity of bronchiolitis and its costs in this population.

Materials and Methods: From January 2008 to December 2009, 22 cases of bronchiolitis (first episode) in former preterm infants (≤35 weeks of gestation) and aged under 6 months were collected in the Department of Medicine B in Children’s Hospital of Tunis (4.1% of all hospitalization for bronchiolitis). For each infant, we have registered the clinical and radiological features and the outcome of the disease. The cost of each hospitalization was also calculated.

Results: The mean age of our 22 patients was 80 days (24d to 6 months). They were divided into 16 boys and 6 girls (sex ratio = 2.6). They had a mean term of 32 weeks of gestation (27–35) at birth. Three of them had bronchopulmonary dysplasia. Half of the patients received breastfeeding. On admission, bronchiolitis was mild in 6 cases, moderate in 8 cases and severe in 8 other cases with frequent apnea in 6 cases. The average of hospital stay was 7 days (1–27 d). Eight patients (36%) required transfer to intensive care unit and mechanical ventilation. About one third (7/22) of infants had a secondary bacterial infection. Two infants died after 9 and 10 days. Subsequently, 18 infants had a second episode of bronchiolitis and 2 developed asthma. The average of total cost of hospitalization was equal to 388 TD (30–1455 TD) [−6200 (615–754)].

Conclusion: Bronchiolitis in former preterm less than 35 weeks of gestation is often severe requiring sometimes cumbersome and expensive treatment. The death rate seems high, but our sample is reduced. The contribution of anti-RSV monoclonal antibody could improve the prognosis of the disease. However its cost is much higher than that of hospitalization.

B2 Acute-acquired pneumonia in children in hospital setting in Algeria
R. Boukari1, C. Kaddache1, S. Touri1, R. Mezeghrani1, N. Benali Khoudja1, M.L. Atifi1. 1CHU Blida, Pediatrics, Blida, Algeria; 2CHU Blida, Epidemiology, Blida, Algeria

Introduction: Community-acquired pneumonia remains a common and serious illness. It is the main causes of death in young children, especially in developing countries.

Objectives: Determine epidemiological, clinical characteristics and outcome of acute acquired pneumonia in our hospital.

Patients and Methods: We conducted a retrospective study from October 2008 to October 2010. All children (one month to 15 years old) admitted to the hospital with a diagnosis of community-acquired pneumonia were included. Diagnosis criteria were: fever >38°C and/or acute respiratory symptoms and radiological opacity. Exclusion criteria were: age <1 month, nosocomial pneumonia, chronic respiratory disease.

Results: There were 221 children (120 male, 101 female) with a mean age at admission of 11.9 (SD 20.5) months. 89 % were less than 2 years old. The most common clinical signs and symptoms were fever (79%), cough (72%), tachypnea (80%) and auscultation abnormalities (crackles, crepitations). The mean duration of symptoms before admission was 7 days. Severe symptoms were present, such as respiratory distress (38%), cyanosis (40%), lethargy (7%), unable to feed (12%), grunting (13%). 13% had partial immunization or lack of immunization. No one received pneumococcal vaccine (still not included in the national immunization program). 16% were overweight.

The most common radiological finding was unilobar consolidation (57%), bilateral pneumonia was present in 31% of children and pleural effusion in 15%. Microbiological investigations are lacking in this study: Blood culture (14), thoracoentesis (21), sputum aspiration (4) were rarely performed and poorly contributive (positive 18%).
40% of the patients received a monotherapy with amoxicillin as a first choice. 60% had an association of amoxicillin + aminoside (1/3) or cefotaxime + aminoside (2/3). There were 7 deaths. Age at death was less than 6 months. Mortality was associated with malnutrition and comorbidity.

**Conclusion:** Pneumonia is still a major public health problem. We need urgently to add conjugate pneumococcal vaccines to our national immunization program and to promote exclusive breastfeeding for at least 4 months.

### B3 Bacterial pneumonia in Senegalese children

**P.M. Faye, M. Ba, I.D. Ba, B. Camara, A.L. Fall, O. Ndiaye, M.F. Cissé, H.D. Sow.**

**Alpert Royer Children Hospital, Pediatrics, Dakar, Senegal**

Bacterial pneumonia is a major cause of child deaths in developing countries (18% of deaths in children under 5 years old). The study aim is to identify epidemiological factors, morbidity and mortality of bacterial pneumonia at Albert Royer Children Hospital of Dakar (ARCH).

A retrospective study including all children aged 0 to 5 years admitted at ARCH for pneumonia from January 2004 to December 2010 was made. Pneumonia diagnosis is based on the presence of cough, fever and tachypnea and confirmation by chest x-ray abnormalities. Bacteriological analyses including blood culture, CSF, pleural fluid and urine culture was performed.

334 children were admitted for pneumonia representing 2.15% of total admission. Mean age is 25.3 months and 60% of them are boys (M/F = 1.5:1).

Some patients had malnutrition (45%), sickle cell disease (10%). Only 2% of them were HIV positive. 99 (24.5%) bacteriological tests were positive.

**Streptococcus pneumoniae** (50 cases: 54% of positive bacteriological study); **Staphylococcus aureus** (20 cases: 21%) and **Haemophilus influenzae** b (9 cases: 10%). **Streptococcus pneumoniae** is the first bacterium responsible for children's pneumonia. We found serotypes 23F, 6B, 1, 5, 14, 15, 5, 6C, 7 and 17. There is a good pneumococcal sensitivity to penicillin. Mortality rate is 2.39%.

We conclude the need to introduce pneumococcal conjugate vaccine in Senegal's Expanded Programme of Immunization (EPI) to reduce pneumococcal disease in children.

### B4 Clinical utility of the quantiferon TB-Gold (in-tube method) test in the diagnosis of tuberculosis in children

**M. Mohsen El-Attar1, H. Masoud2.**

**Faculty of Medicine, Cairo University, pediatric pulmonology, Cairo, Egypt; 2Faculty of Medicine, Cairo University, Chest, Cairo, Egypt**

Interferon-gamma release assays (IGRAs) have been recently developed for the diagnosis of tuberculosis (TB) infection. The aim of the present study was to evaluate the performance of an enzyme-linked immunosorbent assay (ELISA)-based IGRA for detecting TB in children.

**Method:** A prospective study in 30 children clinically diagnosed as active TB infection in comparison with 15 clinically healthy children was carried out. All children were tested with tuberculin skin test (TST) and a commercial ELISA-based IGRA [QuantiFERON-TB Gold In-Tube (Cellestis)].

**Results:** TST were positive in 24 out of 30 (80%) and IGRA in 18 out of 30 (60%) children. The overall agreement between the 2 tests was good (80%, kappa = 0.70). IGRA was positive in all TB culture positive (100%) children with active disease detected by IGRA. In comparison with clinical diagnosis, QuantiFERON-TB Gold In-Tube was more specific 68.9/52.6 and slightly less sensitive 83.3/86.95 than TST, with higher NPV 76.9/62.5 and lower PPV 76.9/81.6.

**Conclusions:** Tuberculosis-specific QFT-IT testing is a promising tool that should be excessively evaluated as a potential diagnostic test for childhood tuberculosis. It is highly specific, is easy to perform, and requires only one visit. Discrepancies between IGRA and TST can be a result of higher specificity of IGRA that is not influenced by previous BCG vaccination.

### B5 Distribution of risk factors for pneumonia in hospitalized children

**P.N. Maiia, R.B. Aurilio, C.C. SantAnna, A.A.A.I. Parente, M.E.B.P. March, S. Ferreira.**

**Instituto de Puericultura e Pediatria, Maragao Gesteria, IPPMC, Rio de Janeiro, Brazil**

**Introduction:** Pneumonia represents a significant portion in the cause of child deaths in developing countries. It is estimated that there are about 5 million deaths in children under 5 years, 70% of those due to pneumonia. According to the literature, several risk factors for community acquired pneumonia (CAP) are related, especially malnutrition, low age, comorbidities, low birth weight, stay in daycare, prior episodes of wheezing and pneumonia, absence of maternal breastfeeding, incomplete vaccination, socio-economic and socio-environmental, and respiratory viral infections.

**Goals:** To describe risk factors for CAP.

**Method:** Transversal study in hospitalized children.

**Results:** Sixty-six children were evaluated, of whom 37 (56.1%) were male. There were 11 (16.7%) to 0–6 months, 10 (15.2%) to 7–12 months, 9 (13.6%) to 13–24 months, 26 (39%) to 25–61 months, and 10 (15%) to 62–120 months. The median age was 34 months. In respect to the caregiver, 54 (81.8%) corresponded to the biological mother and 2 (3%) to the biological father. Regarding maternal age, 3 (4.5%) were to 16–18, 8 (12.1%) to 19–21, and 54 (81.8%) over 22 years old. Of these, 44 (66.7%) unemployed, 4 (6.1%) waxier and other occupations with 1.5% each. Education level of mothers: 22 (33.3%) and 20 (30.3%) incomplete elementary school and incomplete middle high school, respectively. Sixty-one (92.4%) patients lived in urban areas, of which 49 (80.3%) in communities or slums, 59 (89.4%) used public sewer and 61 (92.4%) treated water. There was smoking at home in 25 (37.9%). There were 35 (53%) patients with comorbidities, which the most prevalent were hemoglobinopathies and neurological diseases (19, 4% each). Forty-seven (71.25%) cohabiting with 3 to 5 persons, and 17 (25.7%) with 6 or more. Fifty (75.8%) slept with 3 or more people in the same room. Forty four (66.7%) had birth weight greater than 2500g. On those with 6 to 24 months, 4 (21%) were fed exclusively to the maternal breast until 4 months, and 3 (15.8%), until 6 months. 12 (18.2%) were malnourished. Thirty four (51.5%) reported wheezing within 12 months, and 19 (28.8%) with previous hospitalization for CAP in the last 2 years.

**Conclusions:** The majority lived in urban areas, within slums, reflecting the low income population, in addition to cohabit with more than 3 residents and share a dormitory with more than 3 people. Passive smoking and early weaning were found relevant.

**Reflection:** Encouraging the implementation of governmental programs for the control of respiratory diseases through the reduction of risk factors.

### B6 Dynamics of Diaskintest (recombinant protein CFPI10-ESAT6) reactions in children at repeated tests

**I. Slogotskaya1, V. Litvinov1, P. Seltsovyk1, Ya. Kochetkov1, D. Kudlay2.**

1Scientific and Clinical Antituberculosis Center of Moscow Government Health Department, 2ISC “Pharmstandard”, Russia

**Research objective:** To trace the dynamics of skin tests in the same children observed in antituberculosis dispensaries.

1200 children had been surveyed using Mantoux (2 TU PPD-L) and Diaskintest (DST). Among 192 of them DST had been performed twice and its dynamics was then estimated. All the children had the first Mantoux positive reaction and only 56 had DST positive reaction (22 with respiratory tuberculosis and 33 children with latent tuberculosis infection).
Results of repeated reactions: DST reaction has changed as follows: it remained negative in 137 out of 142 (BCG-vaccinated and those, who had no sputum positive contacts, etc.) and became positive in 5. DST reaction in 31 out of 56 has decreased, including becoming negative in 11.

Conclusions: 1. There was no DST reaction decrease in those who had constant contact. Preventive treatment (uncontrolled in most cases) in such cases doesn’t lead to decrease in intensity of the reaction. The persons, who have not received preventive treatment, had a conversion of reaction from negative to positive.
2. As positive DST reaction in children with contact can appear later, than tuberculin reaction, it is necessary to repeat DST 3 months later if initially the reaction was negative. The reports, that BCG vaccination protects child organism from reproduction of mycobacterium for some time, but becomes insufficient in case of massive infection or proceeding contact, were confirmed.
3. The fact that after the first DST negative reaction in the majority of children (137 out of 142) repeated DST reactions remained negative, proves the absence of both sensitization to DST specimen and “booster-effect”.
4. There was no DST reaction reduction in children with chronic forms of intrathoracic lymph nodes tuberculosis and in children with constant contact with sputum positive parents. Controlled therapy in stationary conditions in children separated from contacts in general leads to DST reaction reduction.
5. Mantoux reaction didn’t become negative in any of the cases after the treatment.

B7 Idiopathic pulmonary hemosiderosis is susceptible to pulmonary zygomycosis

Case report: A 5-year-old girl was referred and admitted to our hospital with prolonged anemia. Based on detailed evaluation, she was diagnosed as having idiopathic pulmonary hemosiderosis. Her alveolar hemorrhage was controlled with oral prednisolone and azathioprine and regular intravenous dexamethasone palmitate. In early winter when she was 8 years old, she was admitted with dyspnea and hemoptysis for the seventh time. Her dyspnea was resolved with extra systemic glucocorticoids. However, after a while she had a fever of 38°C. Broad spectrum cephalosporin was not successful, and a chest X-p and a chest CT scan revealed multiple nodes and cavities in both of her lungs. Although serum β-D-glucan and candida and aspergillus antigens were negative, we suspected that she had a fungal infection and treated her with liposomal amphotericin B. Eight days later, Rhizopus species were isolated from her sputum culture and she was diagnosed as having pulmonary zygomycosis. Azathioprine was stopped, glucocorticoids were tapered down, and liposomal amphotericin B was continued. The nodes were significantly reduced in 2 months. One year after the development of pulmonary zygomycosis, idiopathic pulmonary hemosiderosis was relapsed twice but she is now well controlled with oral prednisolone and mizoribine without relapse of zygomycosis.

Discussion: Pulmonary zygomycosis is a rapidly progressive infection and its mortality rate is as high as 87 percent. In general, patients with elevated levels of available serum iron that is not bound to carrier proteins such as transferrin are reported to be susceptible to infection by Rhizopus species and other Zygomycetes. Patients with idiopathic pulmonary hemosiderosis have recurrent episodes of alveolar hemorrhage and it can result in the presence of free iron in pulmonary tissue. Furthermore, long-term treatment with immunosuppressive agents decreases the potency of alveolar macrophages to process free iron and that of immune systems to kill fungi. Pulmonary zygomycosis should be considered in the care of idiopathic pulmonary hemosiderosis patients and treated at its early stage.

B8 Incidence of complicated pneumonia in Belgian children and clinical evolution under conservative management
M. Proesmans1, P. Van De Wijdeven1, B. Gijssen1, F. Vermeulen1, D. Van Raemdonck2, C. De Boeck1. 1UZ Gasthuisberg Ped Pulmonology, Leuven, Belgium; 2University Hospital Gasthuisberg Thoracic Surgery, Leuven, Belgium

Introduction: The incidence and outcome of complicated pneumonia (CP) in our institution from 1993 until 2005 was reported in a previous retrospective study (Van Ackere et al 2009). Since 2006 treatment decisions are taken according to a standardized algorithm (Proesmans M et al 2009): antibiotics, chest drain (Seldinger technique) with intrapleural Urokinase® if empyema; surgical treatment if medical treatment fails.

Aim: Prospective follow-up of children with CP treated according to this standardized treatment plan.

Methods: Children admitted with CP in the University Hospital of Leuven, Belgium are registered. CP was defined as at least one of the following: (1) loculated effusion on US or CT, (2) analysis of pleural fluid compatible with empyema, (3) need for drain or surgery.

Necrotizing pneumonia was defined as signs of liquefaction and cavitation on chest X-ray and/or CT.

Results: 93 patients were registered over a period of 5 years. The number of patients treated per year varied between 13 and 36 compared to 4 to 12/year in the years 2002 to 2005. The median patient age was 3.53 years (IQR 2.36–5.01), 56 male/37 female. Underlying medical problems were present in 8 patients (5 asthma/allergy, 1 VSD/previous lobectomy, 2 mental retardation) and additional sites of infection at time of admission in 2. 57 patients were referred after a median admission of 8 days (IQR 3–7.75).

A causative agent was detected by hemoculture in 20/84 sampled patients, all S. pneumoniae; 4/59 pleural cultures were positive (2 S. pyogenes, 1 S. aureus, 1 CNS). Data are awaited for pneumococcal PCR analysis on pleural fluid.

21 out of 93 patients were treated with antibiotics only. For 41 patients a chest drain was placed, of which 27 were treated with Urokinase®. VATS was performed in 7 (1 primary, 4 failure of drain, 2 failure of drain +UK) and thoracotomy in 6 (4 primary and 2 after drain +UK). Nineteen patients developed a necrotizing pneumonia (4 with lung abscess, 3 with bronchopleural fistula and 8 with pneumatocele), of which only 3 patients underwent surgery, 1 with segmentectomy. The median hospital stay in our center was 11 days (IQR 7–17) with a total hospital duration of 18 (IQR 13–22).

Conclusion: Since 2003–2005 the incidence of CP in our center increased further, with a peak in 2009. Following a treatment algorithm with medical treatment as first step, failure rate and need for surgical intervention was low. Even in case of necrotizing pneumonia, lung resection only had to be performed in 1 patient. Median hospital stay has decreased compared to our previous report.

B9 Mediastinum mass in HIV-negative children – can it be extrapulmonary tuberculosis?
A.A.A.I. Parente1, T.M. Martinere1, L.C. Schettino2, P.B. Costa2, R. Meirelles2, R. Mannarino2, A. Peixoto2. 1IPPMG Pediatrics, Rio de Janeiro, Brazil; 2Federal University of the State of Rio de Janeiro, UNIRIO Pneumologia, Rio de Janeiro, Brazil

The incidence of tuberculosis is increasing and skeletal tuberculosis accounts for 10–20% of all extra-pulmonary cases. The most common manifestations of skeletal tuberculosis in children are
spondylitis. Tuberculous spondylitis involves the intervertebral disc only late in the disease.

The objective of this report is to present the imaging findings of skeletal tuberculosis in children. In our report, we describe an adolescent with a osteoarticular tuberculosis.

GPS, 11 years, referred weakness in the lower limbs, abdominal pain followed by thoracic and lumbar region and dyspnea. Reported lack of appetite, weight loss and high fever in the last few days. After physical effort, the pain recurred with a higher intensity and the child was taken to the emergency room, where she was referred to an orthopedist. The orthopedist observed weakness of the lower limbs and difficulty walking. Chest x-ray resulted in suspicion of mediastinal tumor due to its enlargement. Based on the neurological and orthopedic examinations-frankel A and on a simple thoracic teleradiograph which evidences mediastinum enlargement, then the pediatric pulmonologist’s diagnostic hypotheses were done.

The neurologist assessment: patient is bedridden, not walking, cooperative, both upper limbs are strong, presenting tonus and deep reflexes. Lower limbs, bilateral paraparesis more severe on the left side, painful tactile hypesthesia in the frontal region of the left thigh, and changes in bilateral distal deep sensitivity. Bilateral patellar and Achilles hyperreflexia, indifferent plantar skin reflexes bilaterally, without signs of meningeal irritation or radiculopathy. The Orthopedic hospital was then contacted because the procedure needed to be done by a pediatric column specialist.

The orthopedist assessment: The radiological abnormalities were osteolytic lesion, narrowing intervertebral disc space/joint space, cold abscess and vertebral collapse. The following tests were ordered: blood test, posteroanterior and left thoracic radiographs, tuberculin skin test, computed tomography of the thoracic column magnetic resonance.

Emergency surgery was indicated to decompress the spinal cord. Surgery with medical treatment was T5 and T6 laminectomy and T3 to T8 posterior arthrodexis. The results of treatment was spinal cord decompression surgery by posterior route. At the moment of the surgery procedure indicated: patient was with paraplegia – FRANKEL A; day 2 after the surgery – Frankel C; day 10 after it – Frankel D.

Resected specimen was submitted to histopathological examination. The diagnosis was confirmed by the histopathology, AFB and positive culture.

The pediatric pulmonologist’s diagnostic hypotheses were done.

The criteria for the possible diagnosis of dengue fever were fever for more than 72 hours, body pain, abdominal pain, conjunctival hyperemia with or without skin rash and signs of dehydration. The criteria for admission were low blood pressure, hematocrit ≥38 and platelets ≤100,000.

Half of the patients (12/24) were females and the other half, males. Their mean age was 8 years and 7 months. The youngest was 1 year and 8 months old and the oldest was 15 years old. All patients (100%) presented persistent fever. Serology was positive for 23/24 cases, however the results became positive only 7 days after admission. Unilateral or bilateral pleural effusion was detected by ultrasound in 15/24 (62.5%) of the patients. Of these, only 8/15 presented dry cough and 1 presented hemoptysis. Pleural effusion together with ascites was detected by ultrasound in 10/24 (41.6%) patients. Hemoconcentration occurred in all patients with pleural effusion. Hematocrits varied from 40% to 50%.

In some countries of the Americas, Brazil included, dengue fever diagnosis must always be considered for patients presenting with severe viral infections, thrombocytopenia with hematocrit above 38, with or without dehydration. Pleural effusion must always be investigated in all patients with hematocrit ≤40 with or without platelets <100,000, even if the chest ultrasound is normal at first.

Ultrasonography is an ideal non-invasive investigation to detect plasma leakage and area specific hematocrit values are useful as evidence of plasma leakage. Ultrasound is the most sensitive method to detect pleural effusion and should be done in series None of the cases required pleural drainage, not even one who had more than 2/3 of his hemithorax affected.

B11

Prolonged shedding of respiratory syncytial virus in a child with heart transplant and resolution after conversion from everolimus to MMF: a case report

N. Nawa1, S. Kogaki1, T. Uchikawa1, Y. Okada1, J. Narita1, S. Maekawa1, H. Ishida1, H. Ichimori1, S. Mihara1, S. Katsuragi1, N. Fukusima1, Y. Sawa2, K. Ozono1, 1Osaka University Graduate School of Medicine Department of Pediatrics, Suita, Osaka, Japan; 2Osaka University Graduate School of Medicine Department of Cardiovascular Surgery, Suita, Osaka, Japan

Background: Respiratory syncytial virus (RSV) is known to be one of the important causes of morbidity and mortality in transplant recipients. However, the clinical features of RSV infection in children with heart transplant using newer generation immunosuppressive drugs are less well characterized. We report a pediatric case with heart transplant who suffered from prolonged pulmonary infection of RSV and recovered after conversion from everolimus to mycophenolate mofetil (MMF).

Patient: A 6-year-old female underwent orthotopic heart transplantation at the age of 3 for dilated cardiomyopathy. She had been on immunosuppressive treatment with tacrolimus and everolimus. She was admitted to our hospital because of recurrent fever and chronic productive cough for 3 weeks. Auscultation revealed diffuse inspiratory crackles over both lungs. Laboratory testing revealed increases in a lactate dehydrogenase level of 419U/L and a C-reactive protein of 17.7mg/L. Chest X-ray and pulmonary CT scan showed bilateral pulmonary infiltrates, mostly in the inferior lobes. Culture results and tests for influenza virus, cytomegalovirus, Epstein-Barr virus, Pneumocystis jiroveci, and Mycobacterium tuberculosis complex were all negative. A rapid RSV antigen panel was found to be positive, and persistent RSV infection was confirmed by viral culture test. Her symptoms and positive rapid RSV antigen panel continued for 2 months until everolimus was stopped with a switch to MMF. This resulted
in gradual improvement of her respiratory status, and RSV rapid antigen panel became negative within 1 month. A repeat CT scan performed 5 months after discharge showed resolution of the previous radiographic features.

Summary: Prolonged RSV shedding in a child with heart transplant was successfully treated with conversion of immunosuppressive drugs. In addition to inhibiting T cell proliferation, everolimus has recently been implicated in association with the production of type interferons by plasmacytoid dendritic cells that are crucial for anti-viral immunity. Therefore, we may require more attention to prolonged viral infection when we use everolimus.

B12 Pulmonary amoebiasis in a 3-year-old Senegalese girl

PM. Faye, M. Ba, I.D. Ba, B. Camara, A. Thiongane, Y.D. Dieng, A.L. Fall, M.F. Cissé, H.D. Sow. Albert Royer Children Hospital, Pediatrics, Dakar, Senegal

Amoebiasis is the third most frequent parasitic infection throughout the world after malaria and schistosomiasis. Developing countries are most affected, particularly Sub-Saharan Africa. Pulmonary amoebiasis is the second common extra-intestinal pattern. It is frequently associated with liver abscess and occurs in 2–3% of patients with invasive amoebiasis. We report the case of a 3-year-old girl who developed pleuropulmonary amoebiasis.

Symptoms began 8 months previously with fever, cough and respiratory distress. Her examination showed right basal condensation with crackles. Chest X ray showed right basal pneumonia. Ceftriaxone and Spiramycine were administered for 2 weeks. Clinical improvement was obtained and the girl was discharged. On regular follow-up visits, the patient presented progressive weight loss and malnutrition, cough and persistent radiographic abnormalities. Despite several oral antibiotic courses, she remains symptomatic. An extensive search of other infections was negative including HIV test. After few months of evolution, she was readmitted for pneumonia, pulmonary abscess and empyema associated with liver abscess. Thoracentesis found brown pleural fluid with no trophozoite at microscopy. The diagnosis of invasive amoebiasis was confirmed by serology. Metronidazole and Chloroquine were started. Chest tube drainage produced 6 liters of brown fluid. The patient died six weeks later for acute respiratory distress and sudden and abundant expectoration of pus.

This clinical report emphasizes the difficulties to establish pulmonary amoebiasis diagnosis, even in high endemic area like Senegal. This diagnosis should be considered in persistent right basal pneumonia associated with pleural effusion in developing countries context.

B13 Pulmonary manifestations of pandemic 2009 influenza A (H1N1) virus infection in Thai children

T. Bunnpag, S. Lochindarat. Queen Sirikit National Institute of Child Health Pediatrics, Bangkok, Thailand

A novel influenza A (H1N1) virus of swine origin caused human infection and acute respiratory illness in Mexico during the spring of 2009. After that, the virus spread globally, resulting in the influenza pandemic.

Objective: To observe the clinical, pulmonary manifestations of the 2009 pandemic influenza A (H1N1), and the epidemic waves for the period of one year.

Method: A prospective observational study of children less than eighteen years old, confirmed having the 2009 pandemic influenza (H1N1) infection by real-time reverse-transcription-polymerase-chain-reaction (RT-PCR), admitted at Queen Sirikit National Institute of Child Health, Bangkok, Thailand during one year, from 1 June 2009 to 31 May 2010.

Result: A total of 83 pandemic influenza infected children were admitted during a one year period. There were two waves of epidemic outbreak, the first wave from June to August 2009 and the second wave from January to February 2010. There were 47 cases of males (56.6%), with the highest attack rates among children 1–5 years of age (48.2%). The youngest case was a 29 days old girl. The correct provisional diagnosis of pandemic influenza infection are 40%, the other initial diagnosis are pneumonia, bronchiolitis, tonsillitis, encephalitis, and dengue infection. Most patients coming for care have typical influenza-like symptoms with fever (98.8%), cough (92.6%), and rhinorrhea (74.1%). Systemic symptoms are frequent. Gastrointestinal symptoms (including vomiting (46.9%) and diarrhea (24.7%)) occur more commonly than seasonal influenza. Pneumonia is the most common complication (67.9%), other complications include bronchiolitis, hemoptysis, acute respiratory distress syndrome (ARDS), and encephalitis. In one case, a seven year old girl suffered from ARDS, sepsis, multi-organ dysfunction syndrome, and ventilator associated pneumonia, but survived with some neurological sequelae. Radiographic findings include diffuse interstitial, alveolar infiltrates, and some in lobar distributions. Apart from oseltamivir, the other antibiotics, including ceftriaxone, cefotaxime, ampicillin and azithromycin, were added for pneumonia.

Conclusion: The burden and character of pandemic influenza infection in developing country are still incompletely understood. Early therapy with oseltamivir in severely ill patients, without waiting for laboratory confirmation for diagnosis, will save patient from severe complications.

B14 Respiratory failure and diffuse pulmonary micronodule: acute pulmonary histoplasmosis – case report

P.B.M. Costa1, R. Barone1, S.A. Sias2, M. de C. Firmida1, A.F.M. Pimentel1, A.P. Mesquita1. 1Hospital Federal de Bonsucesso Pediatric Pulmonology, Rio de Janeiro, Brazil, 2Universidade Federal Fluminense Pediatric Pulmonology, Rio de Janeiro, Brazil

Introduction: Classic histoplasmosis is a micotic infection caused by dimorphic fungus *Histoplasma capsulatum var. capsulatum*. The agent is found in excrements of birds and bats, hollow caves, trees, old constructions and attics. The infections occur when mycelia become aerosolized by physical perturbation and are inhaled. Within the lung, hyphal fragments and conidia differentiate into yeasts that survive and proliferate within alveolar macrophages. The clinical forms can be asymptomatic infection (most common form), acute pulmonary infection, disseminated histoplasmosis and pulmonary chronic histoplasmosis. The laboratorial diagnosis is based on the direct examination, culture, sorological tests and intradermal reaction. The occurrence in childhood and in immunocompetent patients is rare.

Objectives: To describe clinical epidemiologic features of two cases of acute pulmonary histoplasmosis in childhood.

Case 1: Girl, 6 years, resident of rural area of Rio de Janeiro with respiratory symptoms (cough, dyspea, fever and limitation to efforts) lasting three weeks and treated with oral antibiotic without improvement. Survey: thin, pale, breathlessness to efforts) lasting three weeks and treated with oral antibiotic without improvement. Survey: thin, pale, breathlessness limitation to efforts) lasting three weeks and treated with oral antibiotic without improvement. Survey: thin, pale, breathlessness limitation to efforts) lasting three weeks and treated with oral antibiotic without improvement. Survey: thin, pale, breathlessness. Thoracentesis found brown pleura fluid with no trophozoite at microscopy. The diagnosis of invasive amoebiasis was confirmed by serology. Metronidazole and Chloroquine were started. Chest tube drainage produced 6 liters of brown fluid. The patient died six weeks later for acute respiratory distress and sudden and abundant expectoration of pus.

This clinical report emphasizes the difficulties to establish pulmonary amoebiasis diagnosis, even in high endemic area like Senegal. This diagnosis should be considered in persistent right basal pneumonia associated with pleural effusion in developing countries context.

Case 2: Boy, 12 years, with fever, cough, dyspea and chest pain did not improve with use of oral antibiotic. On examination, mild respiratory distress, RR: 32 bpm, without hypoxemia. Both patients were hospitalized. Blood count, PPD Intradermal, three sputum samples for *Mycobacterium tuberculosis*, HIV, immunoglobulins (normals), bronchoscopy with bronchoalveolar lavage, computed tomography (diffuse micronodules and bilateral mediastinal lymph node enlargement). Immunodiffusion to *Hystoplasma capsulatum* and e washed broncoalvear confirmed diagnosis of acute pulmonary histoplasmosis in siblings. The girl...
with the clinical severity required oxygen for 7 days, intravenous amphotericin B for 21 days and oral itraconazole. Her brother received outpatient treatment with Itraconazole. Both had a good outcome.

Discussion: These cases illustrate classical forms of acute pulmonary histoplasmosis, but a serious, which is not common. Epidemiological studies of the region and helped the suspected diagnosis. The differential diagnosis with pulmonary tuberculosis is important, particularly in Brazil, where high prevalence. The absence of immunodeficiency suggests massive exposure to the fungus as the cause of gravity.

Conclusion: Acute pulmonary histoplasmosis is a rare condition in childhood. In most cases the initial diagnosis is tuberculosis. Epidemiology is fundamental to the suspicion and treatment with drugs only recommended in severe cases.

C. Noninfectious respiratory disorders

C1
16-month old twin with noisy breathing and a pulmonary artery sling

E.M. Kuisle, K. Hanson, D. Doshi. William Beaumont Hospital, Royal Oak, USA

Case Report: EM is a 16-month-old former 36-week twin male who presented with cough and noisy breathing. His past medical history was significant for laryngomalacia diagnosed at 3 months of age. His past surgical history included a hernia repair with general anesthesia which was well tolerated. EM was growing steadily although appeared smaller than his twin brother. His loud breathing became apparent with feeds and ambulation. EM developed an acute onset of agitation and difficulty in breathing at 16 months of age with an absence of URI findings. His symptoms failed to improve despite bronchodilators and oral corticosteroids. Respiratory distress was noted and he was admitted to the hospital. Examination demonstrated hypoaxia which improved with supplemental oxygen. His examination was pertinent for a fixed inspiratory and expiratory stridor with decreased breath sounds in the right upper chest. Initial chest x-ray showed diffuse hyperinflation of the right upper lobe. An esophagogram showed anterior compression of the esophagus. Flexible fiberoptic bronchoscopy demonstrated distal tracheal stenosis with complete cartilage rings. A right-sided, tracheal bronchus was also identified. A chest CT with 3D reconstruction revealed a pulmonary artery sling with compression of the trachea above the carina (Fig. 1).

Fig. 1.

discussion: The combination of a pulmonary artery sling, tracheal stenosis, and a tracheal bronchus is exceptionally rare. Very few published case reports describe this combination of anomalies; those cases reported severe and often life-threatening respiratory symptoms within the first few weeks of life. Our patient was unique not only due to the triad of anomalies but also due to the late presentation of symptoms. Presenting symptoms of respiratory distress may be exacerbated by episodes of inflammation of cartilaginous structures of the external ear, nose, peripheral joints, larynx, and tracheobronchial tree. Airway involvement (laryngeal and tracheal stenosis) occur late in the disease process. Here, however, we present a case of a 17-year-old girl with RP, initial manifestations of cough and dyspnea that were treated as bronchial asthma for several months. Subglottic stenosis was found at the age of 14 years. The condition was successfully treated by tracheotomy and tracheal resection. Re-evaluation of the patient, 6 months later, demonstrated tracheal and bronchial stenosis. Computed tomography showed a decrease in diameter of the trachea and the right mainstem bronchus. Bronchoscopy revealed a concentric diminution of the tracheal lumen about 70%, fibrinous material, localized at the orifice of the right main bronchus, inducing a near 100% obstruction of its lumen. The histological analysis of biopsy specimens excluded malignancy, therefore, after exclusion of other immunologic diseases, the diagnosis of RP was made. The patient partially responded to steroid and moraxetane treatment.

C2
Airway stenosis as initial manifestation of relapsing polychondritis. Case report

F. Gacs1, L. Kadár2, N. Simon2. 1Heim Pál Children Hospital, Budapest, Hungary; 2Pest County Pulmonological Institute Children Department, Törökbálint, Hungary

Relapsing polychondritis (RP) is a rare multisystem disease of unknown origin characterized by recurrent and potentially severe episodes of inflammation of cartilaginous structures of the external ear, nose, peripheral joints, larynx, and tracheobronchial tree.

Patients may also present with apnea, or may have acute respiratory collapse after an acute “dying spell”. Physicians examining children presenting with fixed stridor should maintain a high index of suspicion for these types of congenital lesions.

C3
Are neck circumference and central adiposity predictors of OSA in children?

S. Katz1, J.P. Vaccani2, C. Bradbury3, N. Barrowman4, F. Momoli4, R. LaBerge3, K. Murto1. (1) Children’s Hospital of Eastern Ontario Department of Respirology, University of Ottawa, Ottawa, Ontario, Canada; (2) Children’s Hospital of Eastern Ontario Department of Otolaryngology, University of Ottawa, Ottawa, Ontario, Canada; (3) Children’s Hospital of Eastern Ontario Department of Anesthesiology, University of Ottawa, Ottawa, Ontario, Canada; (4) Children’s Hospital of Eastern Ontario Clinical Research Unit, University of Ottawa, Ottawa, Ontario, Canada; (5) Children’s Hospital of Eastern Ontario Department of General Pediatrics, University of Ottawa, Ottawa, Ontario, Canada

Purpose: Central adiposity and enlarged neck circumference are associated with obstructive sleep apnea (OSA) in adults, although they have not been well studied in children. It is important to identify OSA early, given its significant morbidity. Diagnosis of OSA is challenging, particularly as polysomnography, the gold standard diagnostic test, has limited availability. Simple clinical measurements that predict the presence of OSA in children are therefore needed. Our hypothesis was that anthropometric measures including neck and waist circumference would predict OSA in children.

Methods: We conducted a prospective observational cohort study of children scheduled to undergo polysomnography. Demographic variables including height, weight, neck circumference and waist circumference were recorded. A diagnosis of OSA was defined as an apnea-hypopnea index (AHI) greater than one event/hour and a physician interpretation that OSA was present. Children with central sleep apnea or being treated with positive airway pressure were
were reported. 24 patients with pulmonary AVMs were treated with pulmonary angiography, and 17 were symptomatic. One child required cerebral artery embolization. Cerebral AVMs were detected in 10%, mostly small and asymptomatic. Ranney’s score was performed in 44% of patients, 50% had a diagnostic work up. The median age was 10.6 (range 2.6–17.4) years, median BMI 20.4 kg/m^2 (IQR 16–27.3) and 54% were male. Of the participants, 44% had OSA. Mild (AHI 1–5 events/hour), moderate (AHI 5–10 events/hour) and severe (AHI >10 events/hour) OSA was found in 52%, 28% and 20% of the participants respectively. The recursive partitioning algorithm identified that of the children in this dataset with waist/height ratio >0.5 and height >20th percentile, 83% had OSA. Of those with waist/height ratio <0.5, if they had neck/height ratio >0.2 and neck/waist ratio >0.5, 50% had a diagnosis of OSA. In contrast, if they had waist/height ratio <0.5, neck/height ratio >0.2 and neck/waist ratio <0.5, 8% had OSA.

Conclusion/Reflections: Our initial data support the hypothesis that children with central adiposity or relatively larger neck circumference have increased risk of OSA. While these results require validation in a larger sample, they are consistent with a body habitus in adults that is associated with OSA and may lead to future screening strategies in children.

C4
Clinical and genetic characteristics of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu) – the national Israeli center experience

M. Mei-Zahav1, H. Blau1, N. Goldschmidt1, E. Yaniv1, H. Mussaffi1, D. Prais1, E. Brockheimer1, Schneider CMCI Respiratory Institute, Petach Tikva, Israel; 2Hadassah Medical Center Hematology Department, Jerusalem, Israel

Introduction: Osler-Weber-Rendu or Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant disease, more common than previously thought. Pulmonary and cerebral arteriovenous malformations (AVMs) are frequent in HHT and can present in childhood. The AVMs can be asymptomatic until presenting with life-threatening complications. The clinical and genetic characteristics of HHT and the prevalence of visceral AVMs in Israeli patients were not previously described.

Objectives: To characterize the genetic and clinical manifestations of patients with HHT.

Methods: All patients referred to the Israeli HHT national center were included. Diagnosis of definite and suspected HHT was made using the consensus diagnostic criteria (epistaxis, telangiectases, visceral AVMs, family history) or genetic analysis when informative. Bubble echocardiography followed by chest CT when indicated was performed to detect pulmonary AVMs. Cerebral AVMs were detected by head MRI.

Results: 189 patients (2–75y, median-37y) were included. 94 patients met the diagnostic criteria of definite HHT. Seventeen were diagnosed with suspected HHT. Familial genetic analysis confirmed the diagnosis of HHT, (Endoglin mutation) in 16 patients and HHT2 (ALK-1 mutation) in 31. No mutation was found in 31% of patients with definite HHT, similar to published series. Pulmonary AVMs were detected in 40% of patients with definite HHT, nine of them younger than 18y. The AVMs were asymptomatic in 54% of patients. Fifteen patients demonstrated significant pulmonary complications (cyanosis, hemotherax, brain abscesses, strokes). Pulmonary AVMs were more common in HHT, than HHT2 (p < 0.05). Two patients had severe pulmonary hypertension. Cerebral AVMs were detected in 10%, mostly small and asymptomatic. One child required cerebral artery embolization. 24 patients with pulmonary AVMs were treated with pulmonary artery embolization with improvement. No significant side effects were reported.

Conclusions: Pulmonary and cerebral AVMs are common in patients with HHT and are frequently asymptomatic. Children and adults with HHT or with a family history of HHT should be screened for visceral AVMs, since morbidity is significant and treatment is usually successful.

C5
Endobronchial primitive tumors in children: a twenty years retrospective study

P. Ang1, L. Hardy2, I. Gibertini3, A. Chantepe3, P. Diot3, E. Carpenteri2, E. Bonnemaison1, CHU Jean Verdier, 93000 Bondy, France; 2CHU Clocheville, 37000 Tours, France; 3CHU Bretonneau, 37000 Tours, France

Primary endobronchial tumors are rare in children and they cover a broad spectrum of lesions. The aim of the study was to determine the characteristic features, treatment and outcome of these tumors. A retrospective analysis of all patients treated for endobronchial tumor in 9 French Hospitals between 1990 and 2010 was performed and results were compared to those mentioned in medical literature.

8 girls and 4 boys were diagnosed over a 20-year period, 5 low grade mucoepidermoid carcinomas, 2 inflammatory myofibroblastic tumors, 2 hemangioma, 1 anaplastic large cell lymphoma, 1 carcinoid tumor and 1 juvenile xanthogranuloma. The mean age of the patients was 7.5±3.5 years, with an age bracket from 2 months to 14 years. The diagnosis took on average 6.5±5.6 months. The most common revealing cause was persistent atelectasis or recurrent pneumonia (8 cases). The other revealing modes were a persistent bronchospasm (3 cases) and haemoptysis (1 case). The clinical presentation, biology, serum tumor markers and chest X-ray abnormalities were not specific to a histological diagnosis. The chest CT scan revealed the presence of an endobronchial tumor in 11 cases. Only half of the cases could be diagnosed by a biopsy through fibre optic bronchoscopy. Complete surgical resection (1 bilobectomy, 3 lobectomy, 1 segmentectomy, 2 sleeve resections) was performed in 7 patients. A bronchoscopic removal was performed in 5 cases and was successful in 3 cases. Lymphoma was successfully treated by chemotherapy after endoscopic resection. The patients were followed during a median of 3.5 years [2 months–14 years]. 3 recurrences occurred. A recurrence of a hemangioma was observed one month after its endoscopic resection, treated by propanolol. One mucoepidermoid carcinoma relapsed 3 years after initial surgical treatment and the juvenile xanthogranulome relapsed 2 years after an endoscopic resection. No death occurred.

Endobronchial tumors are rare in childhood and involve multiple anatomopathologies. The most frequent presenting symptom is persistent atelectasis or recurrent pneumonia. A chest CT scan and per-endoscopic endobronchial biopsies are needed for the diagnosis. Surgical or endoscopic treatment must be discussed with a multidisciplinary team. In spite of multiple etiologies, the prognosis of these tumors is good when the diagnosis is early and if resection is complete. Long-term recurrences having been described, a long-term follow-up of these children is recommended.

C6
Intermediate respiratory care units (IRCU) in pediatric tertiary care hospitals

M. Braz, T. Nunes, A. Saianda, R. Ferreira, L. Pereira, T. Bandeira, Hospital Santa Maria, Lisbon, Portugal

Introduction: IRCU provide specific care to adult respiratory chronic patients with an intermediate level of disease severity between conventional wards and Intensive Care Units (ICU). IRCU, endowed with appropriate human and technical resources, reduced the burden on ICU, being cost-effectiveness. IRCU are not described in pediatrics, but technological developments and increased survival,
determined the referral of a growing number of pediatric patients dependent on respiratory technology.

**Objectives:** Description and characterization of chronic respiratory patients with technological dependence admitted in a Pediatric Respiratory Unit (PRU) from a tertiary care hospital in order to evaluate the organization and levels of service needed in respiratory units which treat or monitor these patients.

**Methods:** Retrospective descriptive study of patient’s clinical records admitted to the PRU between October 2009 and September 2010 dependent on respiratory technology: invasive ventilation with tracheostomy (VIt), chronic noninvasive ventilation (NIV) and long-term oxygen therapy (LTOT).

**Results:** From the 438 admissions (A), 176 (40%) occurred in 93 chronic patients (P); cystic fibrosis (CF) 49(28%) A in 19(20%)P, neuromuscular diseases 31(18%)A in 17(18%)P, cerebral palsy 14(8%)A in 10(11%)P and other neuropathic diseases 32(18%)A in 14(15%)P, genetic syndromes 20(11%)A in 11(12%)P, polyformative syndromes 6(3%)A in 5(5.5%)P, craniofacial syndromes 3(2%)A in 2(2%)P, bronchopulmonary dysplasia (BPD) 15(9%)A in 9(10%)P and others 6(3%)A in 6(6.5%)P. Sixty-five percent of admissions in chronic respiratory patients required some type of respiratory technological dependence: 71 (40%) ventilation [bilevel NIV 50 (70%), CPAP 12 (17%) and VIt 9 (13%)] and 63 (36%) LTOT. Respiratory technology care was distributed as shown in the table.

**Discussion and Conclusion:** This study supports the burden of care needed in a respiratory pediatric unit of a tertiary care hospital. NIV (70%) was the most frequently used type of ventilation in consonance with the criteria defined for IRCU. Distinctly from adults, we included children on LTOT, being one third of the admissions. These are patients mainly with BPD, CF or neurological or syndromatic diseases, who are particularly demanding and unstable in pediatric ages. These results strongly support the creation of IRCU adapted to the particular socio-psycho-behavioral needs of these pediatric patients.

**Distribution of respiratory technological care by chronic underlying disease, related to the total respiratory care dependence**

<table>
<thead>
<tr>
<th>Chronic underlying disease</th>
<th>Patient/admissions</th>
<th>Total chronic patients</th>
<th>LTOT</th>
<th>VIt</th>
<th>CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>0 (0%)/0 (0%)</td>
<td>2 (258)/4 (55)</td>
<td>0 (0%)/0 (0%)</td>
<td>4 (48)/2 (12)%</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>3 (31)/2 (25)</td>
<td>12 (135)/2 (13)</td>
<td>0 (0%)/0 (0%)</td>
<td>1 (13) (1)%</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>0 (0)/0 (0)</td>
<td>2 (25)/2 (25)</td>
<td>1 (13)/2 (25)</td>
<td>1 (13) (1)%</td>
<td></td>
</tr>
<tr>
<td>Neurogenic</td>
<td>0 (0)/0 (0)</td>
<td>0 (0)/0 (0)</td>
<td>1 (13)/1 (35)</td>
<td>5 (57) (109)</td>
<td></td>
</tr>
<tr>
<td>Genetic syndromes</td>
<td>1 (13)/3 (25)</td>
<td>3 (31)/1 (35)</td>
<td>2 (25)/1 (25)</td>
<td>0 (0) (0)%</td>
<td></td>
</tr>
<tr>
<td>Polyformative</td>
<td>0 (0)/0 (0)</td>
<td>0 (0)/0 (0)</td>
<td>1 (13)/1 (35)</td>
<td>0 (0) (0)%</td>
<td></td>
</tr>
<tr>
<td>Craniofacial</td>
<td>0 (0)/0 (0)</td>
<td>0 (0)/0 (0)</td>
<td>1 (13)/2 (15)</td>
<td>0 (0) (0)%</td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>0 (0)/0 (0)</td>
<td>0 (0)/0 (0)</td>
<td>0 (0) (0)%</td>
<td>7 (73) (175)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1 (13)/1 (35)</td>
<td>0 (0)/0 (0)</td>
<td>1 (13)/1 (35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers are referred as absolute and relative frequencies for each item: N (%).

**C7 Long-term oxygen therapy (LTOT): review of requirements in children**

L. Oliveira, J. Coelho, R. Ferreira, T. Nunes, L. Pereira, A. Saianda, T. Bandeira. University H. Santa Maria Respiratory Unit, Pediatric Service, Child and Family Department, Lisbon, Portugal

LTOT (long-term oxygen therapy) is recommended for children and adolescents with chronic respiratory insufficiency mainly hypoxemic lung disease because of its importance in providing and maintaining patients’ appropriate growth and development, and minimizing complications. In adults its importance is well recognized but there are many differences concerning to requirements for children.

This study aims to describe and characterize the population of children and adolescents under LTOT followed at the Pediatric Respiratory Unit of HSM for the last ten years and to compare with a previous similar review performed between 1991 and 2001, putting this information into perspective with local resource availability.

**Methods:** This is a retrospective descriptive study of 62 patients (40 males; 64.5%) followed-up from 2000–2010, who underwent home oxygen therapy. Non-compliant patients, intermittent LTOT or for less than 3 months were excluded from analysis.

**Results:** The main diagnosis of chronic underlying disease was bronchopulmonary dysplasia (BPD) and other lung interstitial disease (40; 64.5%). Other diagnoses were bronchiolitis obliterans (OB) 11; 11.7%, neuropathic disease (3; 4.8%), interstitial lung disease (3; 4.8%), polynformative syndrome (3; 4.8%), cystic fibrosis (CF) 2; 3.2%. The median duration of LTOT was 13.5 (3.0–202.0) months, and the average age of onset was 14.1 months. The main source was liquid oxygen with flows under 2L/min in 76.1% of patients (n=35). At the end of the study LTOT was successfully discontinued in 61.4% patients (n=57) and 5 died (spinal atrophy – 1; Rett syndrome with asthma and epilepsy – 1; polynformative syndrome – 1; BPD with diaphragmatic hernia and pulmonary hypertension (PHT) – 1; OB with rheumatic carditis and secondary PHT – 1.

**Conclusions:** We have shown that in a tertiary care hospital for highly complex diseases, LTOT was used in different chronic diseases most often in infants and preschool-aged patients. Obstructive lung diseases were the most prevalent diseases. Compared to the previous study we remark the inclusion of other underlying diseases as is now referred in the literature and the nurse specialist visit. Furthermore the prognosis and duration of LTOT depends on underlying disease.

<table>
<thead>
<tr>
<th>Underlying diagnosis</th>
<th>Number of patients N (%)</th>
<th>Age of onset of LTOT (months)</th>
<th>Duration of LTOT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD and other lung neonatal disease</td>
<td>40 (62.9%)</td>
<td>0.0 (0–22)</td>
<td>10.5 (3–51)</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>11 (17.7%)</td>
<td>13 (0–157)</td>
<td>23 (3–199)</td>
</tr>
<tr>
<td>Neuropathic disease</td>
<td>3 (4.8%)</td>
<td>0.0 (0–22)</td>
<td>36 (9–58)</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>3 (4.8%)</td>
<td>3.0 (7)</td>
<td>9 (3–18)</td>
</tr>
<tr>
<td>Polynformative syndrome</td>
<td>3 (4.8%)</td>
<td>0.0 (0–7)</td>
<td>14 (11–41)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>2 (3.2%)</td>
<td>157 (199–195)</td>
<td>18.5 (18–19)</td>
</tr>
</tbody>
</table>

*Median (min–max).*

**C8 Lymphoproliferative disorders in patients with primary immunodeficiencies**

G. Cinel1, E. Yalcin1, D. Dogru1, U. Ozcelik1, N. Kiper1, L. Tezcan2, O. Sana2, V. Ali3, D. Orhan4, I. Akcoren4, G. Kale4, B. Oguz2, M. Haliloglu1. Hacettepe University, Ihsan Dogramaci Children’s Hospital, Pediatric Pulmonology, Ankara, Turkey; Hacettepe University, Ihsan Dogramaci Children’s Hospital, Immunology, Ankara, Turkey; Hacettepe University, Ihsan Dogramaci Children’s Hospital, Pediatric Oncology, Ankara, Turkey; Hacettepe University, Ihsan Dogramaci Children’s Hospital, Pediatric Pathology, Ankara, Turkey; Hacettepe University, Ihsan Dogramaci Children’s Hospital, Radiology, Ankara, Turkey

**Introduction:** The incidence of lymphoproliferative disorders and lymphomas are increased in patients with primary immunodeficiencies. Here we report 3 patients with primary immunodeficiencies, who had non-Hodgkin lymphoma (NHL) and lymphomatoid granulomatosis (LG) diagnosis with the biopsies performed from the nodules in the lungs.

**Cases:** 11 years old male patient, having skin eruptions till 8 months of age, had fever, cough, weight loss and sweating; so thoracic computed tomography (CT) was performed and referred to our hospital with NHL suspicion. Hyper IgE syndrome was diagnosed with his clinical findings and immunological survey. Ultrasound guided interventional lung biopsy was performed from the giant masses in his lung seen on thorax CT, the pathologic diagnosis was diffuse large B cell lymphoma and we started chemotherapy.

7 years old male patient who had recurrent pulmonary infections and diarrhea referred to our hospital. He had splenomegaly and lymphadenopathies on his physical examination and the diagnosis...
was common variable immunodeficiency with immunological evaluation. He had mediastinal and hilar lymphadenopathies and multiple nodular lesions in the lungs seen on his thorax CT. Open lung biopsy was performed and the diagnosis was lymphomatoid granulomatosis (LG). He is now on steroid therapy. 4 years old male patient who has been followed up in our hospital because of having severe combined immunodeficiency (SCID), admitted with fever, vomiting and drowsiness for 2 weeks. He was given antiviral and antibacterial therapy with the diagnosis of meningocencephalitis. We recognised a cervical lymphadenopathy on his physical examination; biopsy was performed and the diagnosis was diffuse large B cell lymphoma. We started chemotherapy and on his follow up we noticed multiple nodules in the lungs on his thorax CT. We performed lung biopsy from these nodules for the differential diagnosis of fungal infection or the pulmonary involvement of lymphoma. It was compatible with diffuse large B cell lymphoma again. He had central nervous system involvement also, and he didn’t respond to therapy and unfortunately he had been exitus.

**Conclusion:** The incidence of lymphoproliferative disorders in primary immunodeficiencies varies between 0.7–15%. The nodular lesions seen in the lungs may be one of the findings of these disorders. For the differential diagnosis of the infections those can be seen in patients with immunodeficiencies, lymphoproliferative disorders must be kept in mind. Biopsy and tissue investigation is important in such patients for the exact diagnosis and planning the right therapy.

**C9 Primary ciliary dyskinesia: medical practice in Rennes**

E. Deneuville1, J. Beucher1, A. Chambellan1, C. Beloncle1, E. Kathgesu1, J. Segalen1. 1CHU Mère Enfant, Rennes, France; 2CHU Laennec Laboratoire de physiologie des explorations fonctionnelles, Nantes, France; 3CHU Pontchaillou, Rennes, France

**Introduction:** Primary ciliary dyskinesia (PCD) is an inherited disease responsible for a disrupted ciliary function. Its clinical presentation associates in early childhood pulmonary and otorhinolaryngologic symptoms. To prevent bronchiectasis early diagnosis is essential.

The aim of the study was to retrospectively review the medical records of children suspect of primary ciliary dyskinesia.

**Results:** A total of 89 children have had a bronchial endoscopy to perform a biopsy analyzed by transmission electron microscopy (TEM) in the children hospital of Rennes between 2000 and 2009. PCD was diagnosed in 17 children, excluded in 51 and uncertain in 21 children. Mean age at diagnosis was 6.5 years. In the PCD group, a history of neonatal respiratory distress was found in 40% of cases, 82% have had bronchopneumopathy, 37% sinusitis, 82% recurrent otitis and 23% situs inversus. These subjects had defects in ciliary structure, 59% in the dynein arms, 35% in the central complex and 6% had both. Nasal nitric oxide productions are in agreement with the results of TEM in 16 cases: 5 PCD, 11 without PCD. In 2 cases, the results were discordant.

**Conclusion:** The key clinical features of recurrent otitis, sinusitis, and situs inversus are highlighted, especially when occurring in combination with bronchopulmonary symptoms. Measures of nasal nitric oxide are useful for the diagnosis of PCD, in case of high levels of NO, PCD is unlikely. But results can be uncertain and TEM is still indispensible to make sure the diagnosis and to guide the genetics.

**C10 Pulmonary agenesis in Japan – three cases of pulmonary agenesis**

M. Isobe, K.T. Torigoe, O. Numata, J. Onozuka, T. Abe, Y. Soeno, J. Hoshina, S. Emura, S. Sasaki, M. Kaneko. Japanese Red Cross Nagaoka Hospital, Nagaoka, Japan

**Background:** Unilateral pulmonary agenesis is a rare disease, but one which is often associated associated with other congenital malformations.

**Objectives:** This study's aim is to report our experiences concerning three cases of pulmonary agenesis and to investigate the disease in Japan with a review of the Japanese literature: “Japana Centra Revuo Medicina” ( ).

**Methods:**

i. Case reports of three children with pulmonary agenesis.

ii. Review of the Japanese literature on pulmonary agenesis.

**Results:**

i. Case reports:

1. Case 1 was a male infant of 6 months of age. He was diagnosed as having right pulmonary agenesis at birth and was admitted to our hospital. Tracheal stenosis with right-side deviation of mediastinum and aortic compression were revealed by thoracic computed tomography with contrast enhancement. His bronchoscopy revealed that his trachea had pulsatile anterior compression and its diameter was small. Admission and discharge have been repeated 11 times in total due to croup symptoms since then.

2. Case 2 was a female infant with a gestational age of 38 weeks and 5 days, with a birth weight of 2,690g. She had cyanosis after birth, then, she underwent tracheal intubation. She was diagnosed with a right diaphragm hernia and right pulmonary agenesis on the chest x-ray. Her operation disclosed that her liver was attached to the right lung and hepatic vein passed into the right atrium directly. Since then, admission and discharge have been repeated 14 times in total due to pneumonia and ileus.

3. Case 3 was a male infant with a gestational age of 40 weeks and 2 days, with a birth weight of 2,400g. After birth, he had dyspnea and endotracheal intubation was attempted, but tracheal stenosis prevented this. Then, he was transferred to our hospital with a mask and bag ventilation. Through X-ray and bronchoscopy, we diagnosed him with left pulmonary agenesis, tracheal stenosis and bilateral absent radii. The patient was unresponsive to treatment and died. Postmortem examination revealed transposition of great arteries, esophageal atresia, and left kidney aplasia.

ii. Forty-two cases (male/female = 20/11, gender not described; 11) of pulmonary agenesis have been reported in Japan (from 1992 to 2010). Twenty-five cases survived (right/left agenesis = 18/7). The number of deaths has reached 17 cases (right/left agenesis = 14/3). In serious cases, respiratory failure appeared at an early stage (within one month). In cases of death, most patients had complications of heart disease and digestive anomalies.

**Conclusions:** Early onset of respiratory symptom with pulmonary agenesis seems to indicate the serious condition of the patient. The prognosis is poor especially in those with congenital heart disease and congenital anomalies of the digestive system. It is important to ascertain whether patients have respiratory symptoms and/or other anomalies in patient management.
C11 Pulmonary artery abnormalities with predominant respiratory expression

K.N. Benhalla1, L. Smati1, A. Boufersaoui1, D. Douiri1, F. Benhassine1, R. Boukar2, M. Baghrich1. 1EPH Bologhine Pediatrics, Algiers, Algeria; 2CHU Blida Pediatrics, Blida, Algeria

Background: Congenital malformations of pulmonary arteries other than pulmonary stenosis are rare conditions. Patients may be asymptomatic and the diagnosis may not be made until adulthood. However, there are usually pulmonary manifestations early in life.

Objective: The purpose of this study is to present 4 cases of pulmonary artery malformations and describe their symptomatology, their radiological findings and their outcome.

Results: We have compiled
- 2 right pulmonary artery hypoplasia
- 1 absence of right pulmonary artery
- 1 pulmonary artery sling.

Three patients were infants under one year of age. The signs are not specific: respiratory distress (3), cyanosis (1), chronic cough (1), recurrent pneumonia (1), stridor (1), failure to thrive (2). All patients have other malformations: lobar agenesis (1), anomalous venous return (2), ductus arteriosus (1) and anomalies of the urinary tract (1). The investigations included chest radiography (4), echocardiography (4) and bronchoscopy (4) but the definitive diagnosis was made by the contrast-enhanced CT scan in the 4 cases; No MRI was performed.

Three patients are alive and one is lost to follow up (died?). Pneumonectomy is required for one patient but surgery was delayed until the end of growth (owing to the risk of orthopedic complications as scoliosis). The patient with retrotracheal pulmonary artery is in fact, asymptomatic except for a single respiratory infection throughout 8 months of follow-up and the surgery was also delayed.

Conclusion: Pulmonary artery anomalies are rare. The first step of the investigations is the chest radiography, the echocardiogram may confirm the malformation but the concluding diagnosis requires CT scan and/or MRI. Only patients with significant respiratory symptoms should be considered for surgery.

Keywords: Pulmonary artery abnormalities, respiratory symptoms, CT scan, MRI.

Abbreviations: CT scan: computed tomography scanner, MRI: magnetic resonance imaging

C12 Usefulness of portable monitoring for diagnosis of sleep-disordered breathing in children less than 7 years of age

T. Sugiyama1, K. Masuyama2, K. Sugita1. 1University of Yamanashi Department of Pediatrics, Yamanashi, Japan; 2University of Yamanashi Department of Otorhinolaryngology, Head & Neck Surgery, Yamanashi, Japan

Background: The current standard test for investigating children with suspected obstructive sleep apnea syndrome (OSAS) is in-laboratory polysomnography (PSG). However, it can be difficult for children to undergo PSG because this examination requires numerous sensor attachments to the body which is very uncomfortable, especially for those less than 7 years of age. Furthermore, in Japan the availability of full PSG study for young children is limited, often resulting in long waiting times.

Objectives: To investigate whether portable monitoring (PM), which consists of an expiratory air flow sensor, pulse oximeter, and heart rate (HR) monitor, can identify OSAS candidates for adenotonsillectomy among otherwise healthy children.

Material and Methods: After obtaining written informed consent from the parents, healthy volunteer children <7 years of age with neither adenotonsillar hypertrophy nor habitual snoring underwent PM as a control group. From February 2009 to July 2010, adenotonsillar hypertrophy patients diagnosed by laryngolobescope examination, <7 years of age, underwent sleep studies using the PM in our laboratory. Patients with an apnea-hypopnea index (AHI) greater than 5 who had adenotonsillar hypertrophy underwent adenotonsillectomy, and, after answering a postoperative questionnaire survey, the PM study was repeated. PM was performed using the SAS2100 (NIHON KODEN, Tokyo, Japan), a monitor with respiratory flow pressure sensors applied with nasal cannula and pulse oximeter recording of both oxygen saturation (SpO2) and HR. The AHI was defined as the total number of apnea and hypopnea episodes divided by the number of artifact-free recording hours.

Results: Ten subjects (30% male, mean age 4yr 10mo) were studied as the control group. Twenty-five patients <7 years of age suspected to have OSAS (64.0% male, mean age 4yr 11mo) were admitted to our hospital. All underwent LF and PM. Fifteen patients (58.9% male, mean age 4yr 10mo) had AHI >5, and adenotonsillectomy was performed. The AHI and lowest SpO2 results are shown in the table below. There were significant differences (P<0.005) between preoperative and postoperative data for AHI, SpO2 (lowest and mean) and HR (minimum, mean, maximum). On the other hand, there were no significant differences between control and postoperative AHI, SpO2 (lowest, mean) and HR (minimum, mean, maximum) data.

Conclusion: Portable monitoring with the SAS2100 is useful for determining appropriate candidates for adenotonsillectomy for management of OSAS. The SAS 2100 is applicable to young children because of its low invasiveness and minimal discomfort.

Table: Apnea–hypopnea index and lowest SpO2 results

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>2.19±0.43</td>
<td>12.96±8.47</td>
<td>3.71±2.68</td>
</tr>
<tr>
<td>Lowest SpO2</td>
<td>89.0±3.63</td>
<td>78.9±8.76</td>
<td>88.9±4.50</td>
</tr>
</tbody>
</table>

Values are mean±SD. AHI: apnea–hypopnea index.

D. Fetal and neonatal respiratory disorders

D1 A case of spontaneous pneumomediastinum in the newborn by an uncomplicated delivery

Y. Su, Y.-T. Lin. E-Da Hospital/I-Shou University, Kaohsiung, Taipei, Taiwan

Spontaneous pneumomediastinum is frequently associated with birth insult, including prematurity, difficult delivery, pneumonia, meconium aspiration syndrome, or mechanical ventilation. It is rare in a newborn by a smooth delivery.

We present a term baby with spontaneous pneumomediastinum born by an uncomplicated vaginal delivery, defined by chest radiography and high resolution computed tomography (HRCT).

This 1 d/o male neonate was born by NSD with GA: 37+4 wks, G2P2, BBW: 2910 gm, apgar score 8′–9′. The delivery course was uneventful. However, he suffered from nasal flaring with grunting and respiratory distress with subcostal retraction after birth. He was transferred to ICU under the impression of respiratory distress R/O neonatal sepsis R/O congenital pneumonia.

The chest radiography showed ground-glass density over RUL, LUL, and superior mediastinum and relatively radiolucency over upper lungs. Bronchoscopy was performed and revealed a blind-end tracheal bronchus, without other trachea-bronchial airway anomaly. The HRCT revealed several giant bullae or air- cysts formation with mild internal septation over bilateral anterior lung zone (crossing the midline), DDx severe focal lobar emphysema(CLE) with giant bullae formation, or congenital cystic adenomatoid
malformation (CCAM) type 1, or spontaneous pneumomediastinum (less likely). Blind-end outpouching over right posterolateral wall of distal trachea, in favor of blind-end tracheal bronchus (tracheal diverticulum), and prominent soft tissue lesion at superior mediastinum. Owing to deterioration of respiratory condition, we changed the ventilator to Nasal IMV. The surgical intervention was arranged 5 days later. But the respiratory condition improved and the follow-up chest radiograph revealed spontaneous resorption of the radiolucency density. So the initial chest raphiogram was compatible with spinnaker sail or angel-wing sign. So spontaneous pneumomediastinum was the final diagnosis and spontaneous resolution by nature.

To our knowledge, there are only few case reports about spontaneous pneumomediastinum in a term neonate born by a smooth vaginal delivery. But it is important because the initial presentations of respiratory distress and radiograph are similar to other lung disease in neonatal stage (CLE, CCAM, etc.). But the treatment strategies are so different, one is supportive treatment, and the other is surgical intervention. So spontaneous pneumomediastinum should be take into differential diagnosis in a term neonate born by an uncomplicated delivery.

**D2 Clinical outcome beyond infancy in children treated for congenital hernia diafragmatica in the era of fetal balloon intervention**

A. Debeer1, M. Proesmans1, K. Allegaert1, T. Lerut1, J. Deprest4.

1University Hospital Gasthuisberg Pediatric Pulmonology, Leuven, Belgium; 2University Hospital Gasthuisberg Neonatology, Leuven, Belgium; 3University Hospital Gasthuisberg Thoracic Surgery, Leuven, Belgium; 4University Hospital Gasthuisberg Obstetrics and Gynecology, Leuven, Belgium

**Background and Aim:** Since 2002, fetal endoluminal tracheal occlusion (FETO) has been introduced as treatment for congenital diaphragmatic hernia (CDH) for selected cases. We aim to describe neonatal outcome and clinical outcome beyond 1 year of age for children treated for CDH in a in a single center cohort from 2002–2009.

**Methods:** From may 2008 patients were invited for standardized follow-up including clinical review and structured respiratory questionnaire (Powell et al 2008). After the historical cohort aged >1 year had been reviewed, children were invited for follow-up evaluation at the age of 1 year. Observed of expected head to lung ratio together with lower position was used for severity coding (Deprest et al 2009).

**Results:** 79 CDH patients were admitted between 1-2002 and 9-2009 of which 69 were diagnosed antenatally and 44 underwent FETO. Survival was 20/44 (45%) in the feto versus 29/35 (82%) in the non feto group (p=0.001). 34 patients were evaluated for follow up (12/20 feto and 22/29 non-feto), 15 survivors could not be evaluated (8 feto, 7 non-feto).

Median (IQR) ‘Observed over expected lung to head ratio’ (O:E) was 23% (19–32) for feto versus 41% (35–48) for no feto (excluding postnatal diagnosis) (p=0.001). In regression analysis PMA only significantly influenced the days ventilated, not CDH severity score nor fetal intervention.

Median age at evaluation was 1.6 y (1.0–4.6) in the feto group and 2.9 (1.1–4.9) for non feto (ns). Median height z score was lower for the feto group (−1.5 vs −0.2; p=0.03) but weight z score (−1.4 vs −0.8), head circumference (P20 vs P35) and chest circumference were comparable. Resting respiratory rate (RR) (42 vs 34), heart rate (HR) (122 vs 109), and oxygen saturation (96% for both) were not different. The feto group scored higher on night time symptoms (p=0.006), symptoms with colds (p=0.003), total symptoms score (p=0.024) and total impact on child (p=0.04) and family (p=0.002). Feeding gastrostomy was or had been in place for 6/12 feto and 2/22 non feto children (p=0.01). The feto group needed more chronic medication (p<0.001).

The non feto group consisted of 6 postnatal diagnosis, 13 with severity score ‘mild-moderate’ and 3 ‘severe’. The feto group all had a severity score ‘severe’. Due to the small number in the the group severe expectant, comparison with the severe feto group is difficult although the latter only scored higher on a few questionnaire items like symptoms outside cold and with exercise.

**Conclusion:** Children selected for feto represent a higher risk group. Compared to the no feto group, respiratory morbidity after the age of 1 is higher but for most patient acceptable. One feto patient has severe respiratory insufficiency. Feeding difficulties are however frequent and severe accounting for most of the morbidity. Further prospective evaluation of the patients is ongoing.

**D3 Maternal vitamin D level may affect occurrence of primary tracheomalacia**

J.E. Kurlandsky. Upstate Medical University Department of Pediatrics, Syracuse, New York, USA

Vitamin D and its metabolites have been shown to exert primary and synergistic effects upon the embryological development of chondrocytes in general and tracheal and laryngeal cartilage in particular. Estimated maternal ultraviolet B exposure levels in pregnancy have been shown to influence subsequent skeletal development of the child. Therefore it was hypothesized that birth month (reflecting the vitamin D status of the mother) may affect the incidence of tracheomalacia. Syracuse and its proximate referral area lie at latitude 43° north. Studies of adult human serum vitamin D levels in northern latitudes show that the lowest levels are found from January through March. April has the lowest birthrate, while the months of July through October have the highest birthrates in a year. Birth months of infants diagnosed with primary laryngo or tracheomalacia were reviewed. Diagnoses were established by airway endoscopy or a classic history and physical exam along with lack of response to bronchodilators, and exclusion of other diagnoses.

Sixty-nine infants born between November 2007 and November 2010 were identified with laryngo or tracheomalacia. Fifteen of 69 infants (21.7%) were born in April (where the low birthrate would lead to expectation of a much smaller amount). Thirty five of 69 infants (50.1%) were born between April and July. Eighteen of 69 infants (26%) were born from July through October – months that have the highest birthrates and months in which serum vitamin D levels are at their peak in the northern hemisphere.

No maternal or newborn serum vitamin D levels were assayed. Nevertheless these findings suggest that perhaps maternal vitamin D levels at certain critical trimesters of pregnancy may affect cartilage development. Future studies suggested by this observation include measurement of maternal vitamin D serum levels and determination of which points in fetal development are most affected by these levels. Consideration should be given to vitamin D supplementation to pregnant women to prevent mild but clinically significant problems with cartilage development.

**D4 Pleural effusion in the neonatal period: what is hidden?**

C. Kaddache, A. Hamidi, F. Sadaoui, Y. Sadi, Z. Daoudi, R. Boukari. CHU Blida, Pediatrics, Blida, Algeria

**Introduction:** The causes of neonatal respiratory distress are dominated by infectious, cardiac and metabolic diseases; however, it may be due to congenital broncho-pulmonary malformation leading to diagnosis and management difficulties.

**Case report:** We report the case of a full term newborn male 3200 g, with no neonatal distress, no family history. He was doing well until 25 days of life when we was admitted for respiratory distress. On
admission: normotherm newborn, with peribuccal cyanosis, rapid breathing at 80 cycles/min, signs of retraction, SpO2 90% (air). Auscultation found a decreased breath sounds on the left lung. Cardiovascular examination was normal. Otherwise, the rest of the examination is unremarkable. A chest X ray showed a large pleural effusion. After thoracocentesis and evacuation of pleural fluid, the radiological finding was an heterogeneous opacity of the left lower lobe.

An infectious cause is ruled out (no fever, no inflammatory markers, negative pleural fluid culture), the macroscopic aspect of the pleural effusion was not consistent with the diagnosis of a chylothorax. A malformative cause was suspected on the transthoracic ultrasound and was confirmed by a chest CT scan demonstrating an aspect of pulmonary extralobar sequestration of the left lower lobe.

Discussion: The pulmonary sequestration (PS) is a rare pulmonary malformation covering only 08% of all congenital pulmonary malformations; it is defined as a nonfunctional area with no normal vascular and bronchial connections. Its blood supply is ensured by a systemic artery. There are two types of PS: intralobar PS (IPS) are vascular and bronchial connections. Its blood supply is ensured by a systemic artery. There are two types of PS: intralobar PS (IPS) and extralobar PS.

PS can be detected before birth by ultrasound examination as an hyper echogenic aspect of the basi thoracic area. PS is most frequent (75% of cases) and extralobar PS can lead to respiratory distress with cyanosis, heart failure, pleural effusion. The posterior basal lesions on chest X rays is highly suggestive. The chest CT scan can accurate topography of lesions and their nature and search for other malformations. Angiography is useful in highlighting the preoperative systemic vascularisation, its origin, topography, and the number of arteries. Surgical treatment is necessary because of the inevitable risk of recurrent infections and potential complications.

Conclusion: Pulmonary sequestration, a rare congenital malformation, can be revealed early in life. The surgery is radical treatment to be given early.

E. Cystic fibrosis

E2

Modulation of granulocyte functions by the influence of Aspergillus niger and Toll like receptor agonists in children suffering from cystic fibrosis

D.R. Bokonjic1, D. Ducevic2, P. Minic1, S. Vasilijevic2, D. Mihajlovic2, M. Colic3, 1Medical faculty University of ES, East Sarajevo, Bosnia and Herzegovina; 2Military Medical Academy Institute for Medical Research, Belgrade, Serbia; 3Institute for Mother and Children Care Pulmology, Belgrade, Serbia

Introduction: Cystic fibrosis (CF) is a severe disease caused by dysfunction of a multifunctional cyclic-AMP regulated ion channel protein, cystic fibrosis transmembrane regulator (CFTR). The exact role of granulocytes and Aspergillus species in children suffering from CF is still not completely understood. Granulocytes express different pattern recognition associated receptors necessary for recognition of different species of fungi. The main aim of this study was to investigate the modulatory effect of Aspergillus niger and TLR-2, TLR-4 and TLR-9 agonists on granulocyte functions in CF patients.

Methods: Blood samples were taken from children suffering from CF and corresponding controls (healthy children). Granulocytes were purified by density gradient separation and erythrocytes were subsequently removed by lising in isotonic ammonium chloride solution. The cells were incubated with conidia of Aspergillus niger, zymozan (a TLR-2 agonist), LPS (a TLR-4 agonist) CpG (a TLR-9 agonist) for 120 min or 24 hours. Myeloperoxidase (MPO) activity was determined after 120 min incubation by modified Graham-Knoll protocol. The capacity for phagocytosis of Aspergillus niger was assessed as total number of internalized conidia/100 granulocytes. Apoptosis was evaluated by morphological analysis of chromatin condensation using light microscopy. N-acetyl-cystein (NAC) and cytohalazin B were used to check the possible mechanism involved.

Results: Granulocytes from CF patients showed lower MPO and phagocytic activity as well as lower levels of apoptosis in culture compared to healthy controls. Aspergillus niger inhibited MPO activity and apoptosis both in granulocytes of patients and healthy controls and the process was additionally potentiated by NAC. Similar results were obtained by the treatment of granulocytes with LPS. Zymosan inhibited MPO activity, whereas CpG was not modulatory. Granulocytes from CF patients showed lower phagocytic activity of Aspergillus niger compared to healthy controls and this function was additionally inhibited by NAC and cytohalazin B.

Conclusion: Our results suggests that lower phagocytic activity and MPO activity, together with higher survival of granulocytes and lower response of the cells to TLR-2 and TLR-4, may be responsible to higher susceptibility of CF patients to Aspergillus infection.

E3

Out-patient parenteral antibiotic therapy in cystic fibrosis unit

J. Clackin, F. Flanagan, M. Morgan, S. Deignan, J. Maye, D.M. Slattery, Children’s University Hospital, Dublin, Ireland

Aim: The aim of this study was to assess the efficacy of the out-patient parenteral antibiotic therapy (OPAT) program in our cystic fibrosis (CF) unit, with a view to expanding this for other services.

Methods: This is a retrospective study of the OPAT program in a tertiary paediatric hospital over a two year period from January 2008 to December 2009. Data was collected from our own patient records and also from the pharmaceutical company records. All antibiotics are pre-compounded in sterile conditions prior to dispatching. Our specialist nurses train parents in antibiotic storage and administration over two days prior to their first course and retraining is done over two hours prior to each subsequent course of antibiotics.

All first doses of antibiotics are administered in hospital. For some, the course is initiated as an inpatient and then completed at home once the patient is stable and clinically responding. Antibiotic choice is dependant on spumt culture and sensitivities, known patient reactions, recent antibiotic therapy, pharmacokinetics and the need for drug level monitoring.

Results: Thirty-one patients with CF were treated on the OPAT program during the two year period. A total of 78 courses of antibiotics were given with an average duration of 11.7 days as an outpatient. This was a saving of 916 inpatient days. All patients had a medical review by the cystic fibrosis consultant prior to starting and finishing their OPAT therapy, to assess suitability for the scheme and then to ensure an adequate clinical response. Drug levels, renal function and liver function were monitored as per medication guidelines and all results were discussed at a weekly multi-disciplinary meeting. Parents were advised to contact the CF specialist nurses immediately if they had any concerns or queries regarding the therapy or clinical condition of the child or to contact the medical registrar on-call for the hospital directly, outside of regular working hours.

Bacteria treated included Pseudomonas (PSA) (n=9), Staph. aureus (n=8), Haemophilus influenzae (n=3), methicillin resistant Staph. aureus (n=2) and combined PSA and Staph. aureus (n=9). There were no treatment failures.

Two patients reported side effects. One developed redman syndrome with vancomycin which resolved on discontinuing the drug. One child developed a serum sickness reaction to piperacillin-tazobactam however parents delayed presenting to the hospital for three days despite the advice given. She had renal impairment
due to dehydration which subsequently resolved, but developed a unilateral hearing impairment due to a high tobramycin level, which does not affect speech range or require intervention.

Conclusion: Our study confirms that the OPAT program is cost saving, clinically effective and decreases potential hospital transmitted infections, as previously reported [1]. The Irish Health Service Executive has funded the development of a national OPAT program for expansion into other areas of adult and paediatric medicine based on its potential benefits.

References

E4 Septifast and blood culture for identification of bloodstream pathogens in patients with cystic fibrosis during febrile infective exacerbation

J. Grosse-Oennbrink1, J. Steinmann2, F. Stehling1, E. Tschiedel3, M. Olivier1, P.M. Rath2, U. Mellies1. 1University Hospital Pediatric Pneumology, Essen, Germany; 2University Hospital Institute of Medical Microbiology, Essen, Germany; 3University Hospital Department of Pediatrics, Essen, Germany

Blood culture (BC) is the gold standard for diagnosis of blood stream infections (BSIs). However, in patients with cystic fibrosis (CF) BSIs are rarely diagnosed. Whether by a multiplex real-time polymerase chain reaction assay like SeptiFast (SF) bloodstream pathogens are found more frequently than by BC has not been determined yet. Aim of this study was to compare the results of BC and SF in patients with CF during febrile infective exacerbation.

This retrospective study was conducted between December 2009 and October 2010 in patients with CF (age 12–38) who were hospitalized for febrile infective exacerbation. We obtained one blood sample for BC and SF (LightCycler® SeptiFast® Test (Roche Diagnostics, Mannheim, Germany)) prior to initiation of antibiotic treatment. Baseline characteristics, inflammatory biomarkers and impact on clinical management were determined by chart review.

49 episodes from 18 patients were eligible for analysis. The number of positivity was 8 (16.3%) for SF and 4 (8.2%) for BC. SF has detected 3 cases of candida albicans, 2 cases of pseudomonas aeruginosa and one case each of stenotrophomonas maltophilia, klebsiella pneumoniae and enterobacter cloacae. BC has identified two cases each of candida albicans and staphylococcus epidermidis. 39 (79.6%) tests were concordantly negative, 2 (4.0%) were concordantly positive, 6 (12.2%) were SF positive only and 2 (4.0%) were BC positive only. We did not find any significant correlation between positivity of SF and baseline characteristics or inflammatory biomarkers (white blood count, C-reactive protein, procalcitonin, immunoglobulin G, fibrinogen). Two results of SF accounted for an adjustment of treatment: a catheter associated sepsis by candida albicans led to early initiation of therapy with fluconazole. In another case due to the detection of stenotrophomonas maltophilia trimethoprim/sulfamethoxazole was added to the antibiotic treatment. The results of SF and BC were considered as contamination in 2 cases each.

In CF during febrile infective exacerbation SF detects more frequently bloodstream pathogens than BC. In cases of suspected catheter associated BSI the results of SF can lead to earlier initiation of adequate treatment. The clinical context must be considered for the interpretation of SF and BC results. Whether the use of SF is of general advantage in CF should be assessed in future clinical trials.

G. Respiratory manifestations of extra-pulmonary diseases (including AIDS)

G1 An unusual cause of breathlessness

R. Chodhari1, H. Ching2, E. Gunning2, A. Giardini1, M. Kostolny1. 1University College London Department of Paediatrics & Child Health, London, UK; 2Royal Free Hospital NHS trust, London, UK; 3Great Ormond Street Hospital, London, UK

We describe here an intriguing case with the most ordinary of presentations but the least expected of diagnoses.

Boy N is a 7 year old boy who presented to us having recently returned from Switzerland. A previously well child with an unremarkable medical history, he had developed pyrexia, headache, joint pain and abdominal discomfort. Examination revealed evidence of respiratory distress; tracheal tug, tachypnoea and oxygen saturations of 90%. Auscultation of the chest however was normal. Furthermore, the remaining examination revealed no additional useful information.

Blood analysis revealed a neutrophilia with a markedly raised C-reactive protein. Given the clinical findings, a chest X-ray was requested which was interpreted as bilateral basal pneumonia. Management was enforced promptly with intravenous antibiotics. Urine was sent for pneumococcal antigen and blood cultures taken.

On review 9 hours later, Boy N had deteriorated clinically with blood gases revealing type 1 respiratory failure. Auscultation now revealed bilateral crackles. There was no evidence of a palpable liver or raised JVP to suggest cardiac failure but it was apparent that he was becoming exhausted. The repeat chest x-ray evolved into a widespread haziness of both lung fields. Clarithromycin was added in an attempt to cover atypical organisms but his clinical state had warranted intubation and immediate transfer to Great Ormond Street Hospital for tertiary care.

In view of the clinical picture and the need for inotropic support, echocardiography was performed. A much unanticipated diagnosis of infective diagnosis was made; large vegetation on the mitral valve culminating in severe mitral regurgitation. What was perceived as an infective cause for respiratory distress was in fact flash pulmonary oedema secondary to valvular failure. Blood cultures returned with evidence of Staphylococcus aureus.

Intriguingly, the only bedside evidence of this diagnosis was that of vascular and thromboembolic changes in the retina.

After a much protracted course of complications including a pseudoaneurysm of the aorta and poor nutrition, Boy N is now clinically well with a mitral valve replacement and aortic coronary cusp repair in situ. So far, no mechanical or immunological predisposing factors are identified.

Learning Point: Bilateral Basal pneumonias are uncommon – a differential diagnosis should be considered. S. aureus remains a highly pathological organism with the potential to cause devastating disease in an otherwise well child unprovoked.

(We are thankful to the CICU and Cardiology team at Great Ormond Street Hospital for their support.)
Primary ciliary dyskinesia (PCD) is characterized by recurrent respiratory tract infections due to reduced mucociliary clearance caused by dysfunction of motile cilia. It is an autosomal recessive disorder, approximately with a situs inversus totalis ( Kartagener syndrome) in about 50% of cases.

There is a considerable genetic heterogeneity for PCD and several genetic defects have been identified in PCD (DNAH5, DNAH11, DNAI1, DNA12, TXNDC3, LRRC50, KIT, RSPH4A, RSPH9, OFD1, RPRGR, CCDC39, CCDC40). PCD does not only cause recurrent respiratory tract infections ( rhino-sinusitis, bronchitis and bronchiectasis) due to reduced airway clearance, but is also associated with other medical disorders. Male infertility is a widely recognized medical condition in PCD. Approximately half of the men with PCD are infertile caused by poor sperm mobility.

Interestingly, in the female reproductive system multiciliated motile cilia line the oviducts. Therefore ciliary dyskinesia of oviductal cilia has been speculated to be a cause of infertility in women with PCD. Likewise, an increased risk of ectopic pregnancy has been postulated for PCD female patients. However, the incidence of infertility and ectopic pregnancy has not yet been investigated systematically and therefore the role of dyskinesia of oviductal cilia is still a matter of debate.

To address this important question, we performed a systematic survey of our female patients with PCD to study the incidence of infertility and gestational abnormalities. Therefore we searched our PCD database for information on pregnancies and births of adult female PCD patients. Here we report female patients with genetically proven PCD variants, which gave birth to healthy offspring. This finding indicates that the beating of oviduct cilia is not essential for fertilization of the egg.

X-linked Alport syndrome may be associated with diffuse esophageal leiomyomatosis. We describe the pulmonary complications and outcome of three family members (mother, daughter and son). The three underwent esophagectomy at different age (22 years, three years and 15 months respectively). Their current forced expiratory volume in the first second (FEV1) range from 33% in the mother to 60% in the daughter and 97% in the son. It is suggested that earlier intervention may lead to improved pulmonary functional tests.

Neonatal data have been identified in medical records. Respiratory and digestive symptoms have been listed by standardized interrogation to parents and the child. Each child received a clinical examination and a chest x-ray. Thirty children have done a complete respiratory functional test. Finally, cardiopulmonary response to effort was evaluated in 25 children from a test on bicycle ergometer.

Results: The most common respiratory symptoms were: early and repeated respiratory infections with trend to improve with age, clinical signs of bronchial hyperresponsiveness, occasional hoarse cough, and effort dyspnea. Only 2 children had growth retardation with less than ~2 SD weight. Eight children received an antiasthmatic treatment. The lung parenchyma was normal on 27 chest x-ray (90%). Six respiratory functional tests (20%) were strictly normal. Bronchial obstruction, concerning essentially distal airways, was found in 8 cases (27%). Six children (20%) had isolated bronchial hyperresponsiveness. A restrictive syndrome was found in 5 cases (17%). CO diffusing capacity value was reduced in 7 cases (24%). Thirteen children had a limited ventilatory response (43%). This respiratory evaluation helped to adapt or begin an antiasthmatic treatment in 14 children.

Conclusion: Due to frequent, although moderate intensity, respiratory functional abnormalities and respiratory symptoms: a specialized, early and long-term respiratory follow-up of this population seems desirable. This monitoring will ideally include regular paediatric pulmonology specialized consultations, respiratory functional test and exercise-test.

Method: Thirty children, operated in children hospital of Rennes between 1990 and 2004, have been treated by a pneumologist.

Primary ciliary dyskinesia (PCD) is characterized by recurrent respiratory tract infections due to reduced mucociliary clearance caused by dysfunction of motile cilia. It is an autosomal recessive disorder, approximately with a situs inversus totalis ( Kartagener syndrome) in about 50% of cases.

There is a considerable genetic heterogeneity for PCD and several genetic defects have been identified in PCD (DNAH5, DNAH11, DNAI1, DNAI2, TXNDC3, LRRC50, KIT, RSPH4A, RSPH9, OFD1, RPRGR, CCDC39, CCDC40). PCD does not only cause recurrent respiratory tract infections ( rhino-sinusitis, bronchitis and bronchiectasis) due to reduced airway clearance, but is also associated with other medical disorders. Male infertility is a widely recognized medical condition in PCD. Approximately half of the men with PCD are infertile caused by poor sperm mobility.

Interestingly, in the female reproductive system multiciliated motile cilia line the oviducts. Therefore ciliary dyskinesia of oviductal cilia has been speculated to be a cause of infertility in women with PCD. Likewise, an increased risk of ectopic pregnancy has been postulated for PCD female patients. However, the incidence of infertility and ectopic pregnancy has not yet been investigated systematically and therefore the role of dyskinesia of oviductal cilia is still a matter of debate.

To address this important question, we performed a systematic survey of our female patients with PCD to study the incidence of infertility and gestational abnormalities. Therefore we searched our PCD database for information on pregnancies and births of adult female PCD patients. Here we report female patients with genetically proven PCD variants, which gave birth to healthy offspring. This finding indicates that the beating of oviduct cilia is not essential for fertilization of the egg.

X-linked Alport syndrome may be associated with diffuse esophageal leiomyomatosis. We describe the pulmonary complications and outcome of three family members (mother, daughter and son). The three underwent esophagectomy at different age (22 years, three years and 15 months respectively). Their current forced expiratory volume in the first second (FEV1) range from 33% in the mother to 60% in the daughter and 97% in the son. It is suggested that earlier intervention may lead to improved pulmonary functional tests.

Neonatal data have been identified in medical records. Respiratory and digestive symptoms have been listed by standardized interrogation to parents and the child. Each child received a clinical examination and a chest x-ray. Thirty children have done a complete respiratory functional test. Finally, cardiopulmonary response to effort was evaluated in 25 children from a test on bicycle ergometer.

Results: The most common respiratory symptoms were: early and repeated respiratory infections with trend to improve with age, clinical signs of bronchial hyperresponsiveness, occasional hoarse cough, and effort dyspnea. Only 2 children had growth retardation with less than ~2 SD weight. Eight children received an antiasthmatic treatment. The lung parenchyma was normal on 27 chest x-ray (90%). Six respiratory functional tests (20%) were strictly normal. Bronchial obstruction, concerning essentially distal airways, was found in 8 cases (27%). Six children (20%) had isolated bronchial hyperresponsiveness. A restrictive syndrome was found in 5 cases (17%). CO diffusing capacity value was reduced in 7 cases (24%). Thirteen children had a limited ventilatory response (43%). This respiratory evaluation helped to adapt or begin an antiasthmatic treatment in 14 children.

Conclusion: Due to frequent, although moderate intensity, respiratory functional abnormalities and respiratory symptoms: a specialized, early and long-term respiratory follow-up of this population seems desirable. This monitoring will ideally include regular paediatric pulmonology specialized consultations, respiratory functional test and exercise-test.

Method: Thirty children, operated in children hospital of Rennes between 1990 and 2004, have been treated by a pneumologist.
Technical cough assist improves ventilation inhomogeneity in NMD

F. Stehling, C. Dohna-Schwake, J. Grosse-Onnebrink, M. Olivier, U. Schara, U. Mellies, University Hospital Essen, Essen, Germany; University Hospital Essen Department of Pediatric Pulmonology, Essen, Germany

Problem: Progressive respiratory muscle weakness of patients with Duchenne's muscular dystrophy (DMD) results in progressive ventilation inhomogeneity determined by LCI elevation and might be related to insufficient clearance of airway secretions [1]. The reduction of peak cough flow (PCF) in neuromuscular disorders (NMD) is effectively treated by technical assisted cough. We hypothesised that ventilation inhomogeneity are reduced by repeated technical cough assist in NMD.

Methods: We determined the lung clearance index (LCI) employing multiple breath washout technique (EasyOne Pro, MBW Module (n.d Medical Technologies, Switzerland)) in 11 patients with various NMD (2× DMD, 4× spinal muscular atrophy, 2× congenital muscular dystrophy, 3× congenital myopathy). VC was determined employing ZAN 100 (ZAN Meßgerät, Obertulba, Germany) and PCF employing PocketpeakTM (Ferraris Medical Ltd., Enfield, UK). Intermittent positive pressure breathing (IPPB) assisted cough was applied as previously described [2]. LCI was determined before and after the IPPB manoeuvre.

Results: All patients had a significant reduction of vital capacity [l: 0.59±0.25 (0.31–1.10); % predicted 16.6±5.4 (8–26)] and PCF [l/min: 127±62 (70–270)]. LCI was elevated in all patients [8.56±1.16 (7.09–11.33)]. The IPPB manoeuvre resulted in a decrease of LCI [8.07±0.54 (6.88–8.75)], but failed to show significance (p = 0.16).

Conclusion: IPPB assisted cough may decrease ventilation inhomogeneity in advanced stages of NMD. The cohort that entered this study might be to small to show significance, as all studies monitoring therapy effects employing MBW technique in Cystic Fibrosis examined min. 17 patients. However, the greatest decrease of LCI was seen in patients with significant LCI elevation above 8.

References

[1] Stehling et al. The progressive decline of vital capacity in Duchenne’s muscular dystrophy is associated with increasing ventilation inhomogeneity. ERS 2010, F427.

in the last 12 months (20%) and 6.8% of children had wheezing per year that limited daily activity. It was found that 6.6% of the students had a physician-diagnosed asthma.

In contrast, during Phase III, 983 children completed the questionnaire. Ever wheezing was found in 304 students (31%), wheezing in the past 12 months was significantly lower in 128 boys (13%) (p: 0.0000) compared to Phase I results. 53 students showed symptoms at night during the last 12 months that were significantly lower in the comparison (5.3 vs 20.0) (p: 0.0000), 4.3% of them presented limitation of daily activities due to wheezing. The medical diagnosis of asthma was found in 4.6% in phase III.

Conclusions: This epidemiological study suggests that recurrent wheezing is highly prevalent in primary school children from Cordoba, Argentina. A significant reduction of the positive replies concerning wheezing in the last 12 months and night-time disorders during phase III was detected but not in other variables. Asthma in primary school students is an important public health problem in Cordoba, Argentina. This study was funded by LIBRA Foundation Argentina.

J3 Examination of respiratory syncytial virus (RSV) infection in the western part of Okayama prefecture in Japan

S. Watabe, Kurashiki Central Hospital, Pediatrics, Kurashiki, Japan

Introduction: We examined the conditions of the RSV infection in our hospital during July 2000 to April 2010.

Methods: The subjects of this study were children who detected positive for RSV antigen in nasal discharge by standard antigen kit at the pediatric outpatient clinic or emergency care center between July 2000 and April 2010. All children had wheeze or some symptoms of nasal discharge, cough and wheezing. Subjects were examined in terms of age, monthly incidence rate, underlying disease, and severity including status of admission to ICU.

Results: During this study period, 1995 children were detected with RSV infections. Infected children were found in all months, increased from November, and reached a peak in January. Forty-two of the children administered palivizumab were possible of myocarditis as a complication of RSV infection. Cardiomyositis and ARDS could develop into more severe condition. Palivizumab was very effective to prevent severe RSV infection in case of patients with underlying diseases.

K. Investigation and diagnostic tests

K1 Classification of asthma severity in children: the importance of symptoms and lung function measures


According to current guidelines, severity of asthma is based on the frequency of symptoms, use of medication and lung function measures. However, little is known about the relationship between lung function and symptoms in children with asthma. For obstructive disorders, the severity of lung function impairment is graduated based only on the forced expiratory volume in 1 second percentage (FEV₁%) predicted, but the FEV₁ and the forced vital capacity (FVC) ratio, in association with FEV₁% predicted, could be used for this purpose, considering the most severe result in case of discordance.

The objectives of this study were to describe the association between the classification by clinical symptoms and the pulmonary function tests (PFTs), and to evaluate if the FEV₁% associated to the ratio FEV₁/FVC could be a better parameter than the isolated FEV₁% predicted for the assessment of the obstruction severity. This cross-sectional study was conducted in the pediatric pulmonary clinic of a university hospital, from 2005 to 2010. Asthmatic patients without comorbidities were included. Cropto et al predictions equations were utilized. Patients were classified as: normal or obstructed (mild, moderate, and severe). We evaluated the same patient at least twice.

We enrolled 52 patients, from 6 to 17 years old, 33/52 (63%) were male. When severity was defined by symptom frequency according to the Global Initiative for Asthma (GINA), 43/52 (83%) patients were classified either as controlled 25/52 (48%) or as partially controlled 18/52 (35%). The uncontrolled patients were 9/52 (17%). On the other hand, FEV₁% showed that 30/52 (58%) had normal tests results and 22/52 (42%) were obstructed (19 mild, 1 moderate and 2 severe). Utilizing two parameters, FEV₁% and FEV₁/FVC%, 28/52 (54%) had normal PFTs and 24 (46%) were obstructed (21 mild, 1 moderate and 2 severe). Similar results were found in the second evaluation. No restricted dysfunction was found.

The present study demonstrated that, in the absence of PFTs, the degree of asthma control could be overestimated, as showed by other authors. In addition, the FEV₁% predicted associated to the ratio FEV₁/FVC did not prove to be a better parameter than the isolated FEV₁% predicted for the assessment of the obstruction severity. We concluded that spirometry is really recommended for the diagnosis and treatment follow-up of patients with asthma.

K2 Comparison of bronchoscopic and non-bronchoscopic methods of obtaining distal airway cultures in tracheostomized children

O. Alfabili-Brown1, M. Marcus2, J. Periami3, P. Speciale4, M. Pagala2, M. Kazachkov2, 1Maimonides Medical Center, Staten Island, USA; 2Maimonides Medical Center, Pediatrics, Brooklyn, USA

Introduction: Distal airway secretions can be sampled by bronchoscopic bronchoalveolar lavage (B-BAL), blind protected BAL (BP-BAL) and tracheal aspirates (TA). Previous studies have shown that BP-BAL has similar accuracy to B-BAL in diagnosis of ventilator associated pneumonia. Our hypothesis was that BP-BAL is as effective as B-BAL and more effective than TA in sampling of lower airway secretions in tracheostomized patients.
The objective of the study was to quantitatively compare the cultures of distal airway secretions from BP-BAL, B-BAL, and TA and to assess the efficacy of the three above methods in diagnosing bronchitis in tracheostomized children.

**Method:** Children with tracheostomies who were scheduled for their surveillance bronchoscopy were enrolled in the study. All patients were free of antibiotics for at least one month before the study. All patients underwent BP-BAL using a double lumen plugged catheter followed by B-BAL and TA. The samples were sent for quantitative bacterial cultures. Positive culture was defined as 100 or more colony forming units per milliliter (cfu/mL) obtained in BP-BAL, and 10,000 cfu/mL obtained by B-BAL or TA. Amount of secretions present in the tracheobronchial tree was assessed visually during bronchoscopy based on a validated grading system.

Diagnosis of bronchitis was made based on this grading score as well as on positive quantitative culture in the BAL fluid. The diagnostic agreement between quantitative cultures obtained by the three different methods and visual grading scores was determined by kappa analysis.

**Results:** A total of 20 patients were enrolled in the study. Diagnosis of bronchitis by visual grading score had substantial agreement (Kappa 0.7, concordance 85%) with BP-BAL quantitative cultures, but only moderate agreement (Kappa 0.5, concordance 75%) with B-BAL, and fair agreement (Kappa 0.3, concordance 63%) with TA. Within the three techniques, the diagnostic agreement was substantial between BP-BAL and B-BAL (Kappa 0.76, concordance 90%), but only moderate between BP-BAL and TA (Kappa 0.49, concordance 80%). A total of 29 different bacterial strains were isolated of which 15 were potentially pathogenic organisms and 14 were non-pathogenic. The median (25th and 75th percentile) pathogenic colonies were 40,500 (18,000, 78,550) cfu/mL in TA, 32,500 (8,100, 57,600) cfu/mL in B-BAL, and only 150 (0, 16,050) in BP-BAL. One-way Analysis of Variance showed that BP-BAL had significantly lower pathogenic colonies (P < 0.05) than either B-BAL or TA.

**Conclusion:** We conclude that BP-BAL is potentially more accurate in the diagnosis of bronchitis and allows for more accurate sampling of lower airway secretions in tracheostomized children.

---

**K3**

**Evaluation of an anatomically realistic infant face and upper airway model**


**Objective:** Demonstrate the applicability of a newly developed 7-month old nasal breathing infant face model for the evaluation of valved holding chambers (VHCs) with facemask intended for this patient population.

**Methods:** A model infant face having a realistic tactile response to that of skin and underlying soft tissues together with an anatomically correct nasopharynx (ADAM-III) was validated by comparing the mass of salbutamol [label claim dose (LCD) = 100 µg/actuation] retained in the airway and the mass delivered to the exit of the model (equivalent to the carina) with published data by Tal et al. (J. Pediatr. 1996; 128(4): 479–84) who reported 1.28±0.77 LCD (≡1.28±0.77 µg) upper airway deposition and 1.97±1.4% total lung deposition (≡1.97±1.4 µg) in infant patients treated with radiolabeled salbutamol delivered by pMDI and a similar sized VHC to the current product [anti-static AeroChamber Plus* Flow-Vu* Inspiratory Flow Indicator (IFI), Trudell Medical International (n=5 replicates)]. The effect of varying tidal volume (Vt; 30 to 90 mL) and respiration rate (RR: 15 to 35 breaths/min) with fixed (25%) duty cycle was evaluated by determining the mass of salbutamol/actuation deposited on the face (FACE), retained in the model airway (AIRWAY) and delivered mass on filter media located at the distal end of the model (DM).

**Results:** DM (mean±SD) was lowest with the smallest Vt (30 mL) and RR (0.3±0.1 µg). An increase in RR from 15 to 35 cycles/min at this Vt improved DM to 1.2±0.4 µg. The mass in the AIRWAY was negligible (≤0.2 µg) at either condition. The mass on the FACE varied from 1.1 to 1.7 µg, but there was no correlation with RR. At the highest Vt (90 mL), DM ranged from 9.4±2.3 µg (RR = 15 cycles/min) to 6.7±0.7 µg (RR = 35 cycles/min) with 10.0±0.5 µg and 3.6±0.4 µg respectively recovered from AIRWAY. The mass on the FACE also increased, varying from 3.6 to 4.8 µg, again with no correlation to RR. DM and AIRWAY were closest to the values of total lung deposition and upper airway deposition reported by Tal et al. with Vt at 30 mL, irrespective of RR.

**Conclusions:** The data reported for these model validation studies bracket the in vivo measurements reported by Tal’s group in the only study available for direct comparison. The present measurements support findings of increased medication delivery to the lungs as Vt increases, with changes in RR having only a minor effect. Deposition to the face and within the model airway also increases at higher values of Vt, likely due to increased inertial impaction of the larger particles exiting the VHC.
This retrospective study affirms the utility of flexible bronchoscopy with BAL in the evaluation of immunocompromised patients with respiratory infections. The procedure is generally safe.

K5
Spirometric reference values of Thai Bangkok children
A. Preuthiphan1, C. Boonlarpvacevchoke1, S. Suwanpromma2, U. Udomsupbayakul1, 1Ramathibodi Hospital, Pediatrics, Bangkok, Thailand; 2Lerdsin Hospital, Division of Pediatrics, Bangkok, Thailand; 3Ramathibodi Hospital, Mahidol University Section for Clinical Epidemiology & Biostaticks, Bangkok, Thailand

Background: Spirometry is essential for pulmonologist to diagnose and monitor treatment. Its reference values vary with ethnicity.

Objective: To establish an update predicted reference values, and derive summary equations of spirometric parameters specifically for 6–18 years Thai children in Bangkok.

Materials and Methods: A cross sectional study of spirometry measured with Jaeger spirometer (Jaeger, model: 97342 Hoechberg, Germany) was carried out in 1,104 healthy non-smoker Bangkok Thai children, aged 6–18 years (476 boys and 628 girls from 5 schools). Prior to pulmonary function testing the parents was asked to complete the questionnaire for detailed medical history. Various regression models treating two sexes separately were applied to spirometric parameters including FVC, FEV1, FEF25–75 and PEF.

Results: 395 children were excluded due to presence of respiratory illnesses within 4 weeks before testing (n = 156), inability to achieve ATS criteria for reproducibility and acceptability (n = 199), chronic illnesses (n = 39), Caucasians (n = 1). Results from the remaining 709 (292 boys and 417 girls) were analyzed. The correlation of FVC and FEV1 were highest with height followed by weight and age in both sexes. FEF25–75 and PEF were also significantly correlated with height, weight and age respectively. Boys had greater FVC and FEV1 than girls in all separate height. Regression equations to predict normal spirometry were derived for both sexes in Bangkok. Our measurements were similar to those reported for children in Singapore and lower than those reported for Caucasians.

Conclusion: Our predicted values of spirometry can be used for Thai Bangkok children aged 6–18 years. The results of the study will improve clinical diagnosis, treatment outcomes monitoring and future epidemiological research of respiratory diseases in Thai children.

K6
Spirometry vs. resistance in children with asthma suspicion: evaluating bronchodilation response
L.G. Gochicoa-Rangel, L. Torre-Bouscoulet, J.C. Vazquez-García, C. Vargas-Domínguez. Instituto Nacional de Enfermedades Respiratorias Fisiología Pulmonar, Mexico D.F., Mexico

Introduction: Spirometry is the gold standard to evaluate airflow obstruction; however, other techniques are available such as the interrupter technique (Rint) and the Impulse Oscillometry (IOS) which evaluate airway resistance.

The aims of this study were (1) to explore the correlation between forced expiratory flow in the first second (FEV1) with the resistances measured by Rint and IOS; (2) to analyze the agreement between Rint and IOS; (3) to evaluate the effect of the forced maneuver and bronchodilation over the resistance obtained by Rint and IOS and (4) to compare the proportion of bronchodilation positive tests among the methods.

Methods: We included children (< 6 years old) with clinical asthma suspicious. A written consent was obtained from the parents. The following sequence of maneuvers were performed: Rint–IOS–Spirometry–Rint–IOS. After 200 mcg of Albuterol the sequence was repeated.

Results: 32 children were enrolled; 62.5% males, 43.3±1.2 years of age (min 2.4 – max 6.6). Rint maneuver was performed during expiration and it was completed in 81% of patients, 78% completed the IOS; and 78% completed at least 1 acceptable spirometry maneuver pre and postbronchodilator. The Pearson’s correlation coefficient between FEV1 vs. Rint was −0.57 (p = 0.004), FEV1 vs. IOS (R5Hz) was −0.53 (p = 0.008). The agreement (intra-class correlation coefficient) between Rint and IOS was 0.73, 95% CI 0.56–0.90, p = 0.0001.

After forced spirometry, the mean change in Rint was −0.06 kPa/L/s (p = 0.08) whereas it was −2.5% in IOS (p = 0.13). Bronchodilation response was positive in 48% patients measured by Rint with a mean decreasing of 0.48kPa/L/s; while it was positive in 57% when IOS was used with a mean decreasing of 27.5%. Regarding spirometry, the bronchodilation test was positive only in 2 patients (8%).

Conclusions: A good correlation between FEV1 vs. Rint and IOS was observed as well as the agreement between Rint vs. IOS (R5Hz), even though the agreement limits were width. Forced maneuver did not significantly modify the measurements obtained by Rint and IOS. Rint and IOS (R5Hz) appear to be more sensitive methods than spirometry to evaluate bronchodilation response in children with asthma suspicious.

K7
Unilateral hyperlucent lung: the important role of pulmonary ventilation and perfusion in the diagnosis of children
L.-C. Chen, Y.-W. Chen, J.-H. Hsu, J.-R. Wu, Z.-K. Dai. Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Unilateral hyperlucent lung on chest X-ray is uncommon in children. It is often found incidentally and always refers to Swyer-James syndrome, with decrease of pulmonary vascularity and air trapping during expiration. However, it may occasionally mimic other serious lung disease such as pulmonary hypoplasia/aplasia, defect of pulmonary artery, and other primary pulmonary disorders.

In this study, we hypothesized that there would be characteristic patterns in pulmonary ventilation-perfusion (V/Q) scan in children with different etiologies accompanied with unilateral hyperlucency on chest film, which could play an important role in differential diagnosis of this disease group explicitly. Except unilateral hyperlucency noted on chest film, all patients had a detailed clinical examination and underwent echocardiography, chest computed tomography, selective pulmonary angiogram, flexible bronchoscopy and pulmonary V/Q scan.

Totally, 10 cases were enrolled, including 2 cases of unilateral pulmonary artery agenesis (UPAA), 3 cases of Swyer-James syndrome (SJS), 2 cases of agenesis of the right lung, 1 case of lobar emphysema, and 2 cases of Tetralogy of Fallot with left pulmonary artery stenosis. Besides, an overview of children with unilateral hyperlucent lung is provided, reviewing 9 studies (171 patients), including our clinical experience, and finally an algorithm for diagnosis and management of SPM is proposed, based on the characteristics of V/Q scan.

L. Therapeutic procedures

L1
A 4 years follow up in children with moderate/severe asthma after discontinuation of 1 year treatment with omalizumab
C.E. Baena-Cagnani1, A. Tejeiro1, H. Badellino1, M.E. Zernotti1, G.W. Canonica2, V.H. Croce1, R. Baena-Cagnani1. 1CIMER Research Center of Respiratory Medicine, Cordoba, Argentina; 2Genoa University, Allergy and Respiratory Medicine, Genoa, Italy

Background: Asthma guidelines include omalizumab in the step up management in those patients with moderate/severe non-controlled asthma despite the use of the highest dose recommended treatment. This communication describes the 4 year follow up of
children with moderate/severe allergic asthma treated for one year with add-on omalizumab after discontinuation.

Methods: 8 children (≥ 6 to <12 years) with moderate/severe uncontrolled asthma following strict inclusion/exclusion criteria. The patients completed a one year treatment with omalizumab according to the DBPC CIGE025 clinical study protocol. Four years follow up after discontinuation of the study medication was performed. It included clinical assessment, different asthma-related variants and lung function in outpatient hospital office.

Results: All patients that received Xolair during the study period achieved good asthma control and could suspend the previous medications. Surprisingly, the 8 patients that received Xolair for one year were completely free of asthma symptoms during the first 3 years of follow up. They did not use any additional asthma medication. After the third year of follow up, 3 patients began with persistent asthma symptoms and exacerbations. These patients have required rescue medication and then regular controller medication (budesonide 400 mcg).

Conclusion: Most of these patients still remain asymptomatic 4 years after discontinuation Xolair. They are still not using any controller medication only 3 patients had exacerbations and at present show persistent mild asthma controlled with medium ICS therapy. This follow up would generate the hypothesis that omalizumab could have a modifier effect of asthma beyond the improvement of symptoms control in children with moderate/severe uncontrolled asthma. Further studies are needed to test this hypothesis.

This study was funded by Novartis and Fundacion LIBRA Argentina

L2
Biphasic Cuirass Ventilation for pandemic A (H1N1) influenza virus infection in children
Y. Ueda1, K. Okada2. 1Japanese Society of Pediatric Pulmonology Pediatrics, Kumagaya, Japan; 2Japanese Society of Pediatric Pulmonology Pediatrics, Morioka, Japan

Introduction: There was reported 1st patient infected by A (H1N1) influenza virus from WHO in April, 2009. It expanded all parts of the world. In Japan, after a small scale regional epidemic in May, it expanded rapidly in August. The peak was in November, 2009. It was estimated that 1 person in 6 people consulted a doctor. 1 person in 1200 patients who consulted a doctor was hospitalized. 1 person in 11 patients who was hospitalized was into serious illness. And 1 person in 100,000 patients who consulted a doctor died. Japan Pediatric Society reported about the feature of patients in serious pneumonitis infected by A (H1N1) influenza virus. The median age was 6 years old, majority of the reasons for hospitalization was respiratory distress with severe hypoxia, and short strength from appearance of disease to respiratory distress. Moreover, some cases were reported that they presented the plastic bronchitis. We showed the effect of Biphasic Cuirass Ventilation (BCV) for the acute respiratory failure last year. We introduce our experience of using BCV for pandemic A (H1N1) influenza virus infection.

Objective: To show the effect of BCV for acute respiratory failure through the patient of pandemic A (H1N1) influenza infection.

Patients: There were 58 subjects who needed hospitalization by pandemic A (H1N1) influenza virus infection from May 1, 2009 to March 31, 2010 in our hospital. 36 cases were selected by their reason for hospitalization was respiratory distress.

Result: We use BCV (Continuous Negative mode: CN) as respiratory management were 4 cases, and BCV (Secretion Clearance mode: SC) as airway clearance were 8 cases. 28 cases didn’t need any mechanical ventilation. Both 4 BCV (CN) cases had pneumonitis, respiratory distress and severe hypoxia. 3 cases in BCV (CN), the atelectasis was accompanied, were possible to be plastic bronchitis. We use BCV (SC) with BCV (CN) cases to clear their airway 3 or 4 times a day, they recovered without intratracheal intubation.

There was a case, 7 years old man, needed Conventional Mechanical Ventilation (CMV) and BCV for his severe respiratory failure. As he was in ARDS, we selected Airway Pressure Release Ventilation (APRV) mode of CMV. In this case, tidal volume increased 26.6 ml to 84.2 ml after airway clearance using BCV (SC). He was extubated on 4th day and left hospital on the 9th day.

Conclusion: BCV was effective for pandemic A (H1N1) influenza. Especially, they were direct effects that BCV (CN) introduction from early respiratory distress was able to prevent being into serious illness, and airway clearance by BCV (SC) was possible to prevent being into plastic bronchitis or recover from it. More effective use was done by understanding the characteristic of the disease.

L3
Inhaled corticosteroids and adrenal insufficiency: prevalence and clinical presentation
M. Fayon1, P.O. Girodet2, C. Pollet2, A. Fourrier-Réglat2, A. Daveluy2, F. Haramburu2, A. Tabarin2, M. Molimard2. 1Hôpital Pellegrin-Enfants, CHU de Bordeaux Pneumologie pédiatrique, Bordeaux, France; 2Université Victor Segalen Bordeaux 2, Bordeaux, France

Objective: Adrenal insufficiency (AI) is a potentially life-threatening condition. It is known that high doses of inhaled corticosteroids (ICS) can induce systemic adverse effects. Currently, there are no data on the prevalence of AI associated with the use of ICS. This study aimed to investigate the prevalence and clinical presentation of AI (associated or not associated with exogenous Cushing’s syndrome) in patients who were prescribed ICS by French physicians during the period 2000–5.

Methods: All metropolitan French paediatricians, endocrinologists, pulmonologists and intensive care physicians (n = 11,783) were mailed questionnaires requesting information regarding cases of AI associated or not associated with exogenous Cushing’s syndrome between 2000 and 2005. Data collected included patient demographics, oral corticosteroid or ICS used during the year preceding the diagnosis of AI, underlying condition(s), concomitant treatment(s), presenting clinical signs and symptoms, results of laboratory investigations and outcome. The French pharmacovigilance database was screened for spontaneous reports to determine the frequency of AI associated with the use of ICS, using the capture-recapture method.

Results: Forty-six cases of AI were identified. Twenty-three cases presented with clinical symptoms of AI alone and 23 with exogenous Cushing’s syndrome. ICS prescribed were fluticasone propionate (n = 24), budesonide (n = 12) and beclometasone dipropionate (n = 5). In 82% (n = 32) of cases for which data were available, ICS were prescribed at high doses. A potential drug interaction was found in 12 cases. Thirty-three cases of AI were identified in the French pharmacovigilance database, one of which was common with the questionnaire survey. The capture-recapture method provided an estimation of 598 (95% CI 551, 648) cases of AI associated with the use of ICS for the 2000–5 period in France.

Conclusion: The results of this study confirm the occurrence of adrenal insufficiency in patients treated with ICS. Although the prevalence of ICS-induced AI reported in this study is low, the likelihood of under-diagnosis underlines the need to consider this risk in patients when prescribing these drugs.

L4
Tracheal stenosis in children, old problem, new techniques
T.J.H. Zimmermann1, R. Cesnjevar2, S. Dittrich3, M. Glückler1, T. Radkow4. 1University Erlangen-Nürnberg Pediatrics, Erlangen, Germany; 2FAU Erlangen-Nürnberg Department of Pediatric Cardiac Surgery, Erlangen, Germany; 3FAU Erlangen-Nürnberg Department of pediatric cardiology, Erlangen, Germany; 4Pediatric Radiology FAU Erlangen, Erlangen, Germany

Tracheal stenosis is an unusual and sometimes lethal condition. Its treatment is basically surgical and different techniques have
been proposed. Infants with congenital tracheal stenosis may also have unilateral lung agenesis or severe lung hypoplasia. Different techniques were developed for diagnosis and tracheal stenosis repair.

**Imaging:** HR-CT Thorax and volume rendering technique. With the flat detector CT it is possible to visualize the relationship between trachea and the great vessels with high spatial resolution during cardiac catheterization. 3D volumes can be created in a high quality to plan surgery. During surgery, children are on the heart-lung-machine (Stöckhert to plan surgery. Cardiac catheterization. 3D volumes can be created in a high quality during surgery with Olympus BF N20 or XP 60 flexible Bronchoscopes.

**Surgical technique:** The tracheal surface is usually exposed via median sternotomy. In case of sliding plasties cardiopulmonary bypass (CBP) is used (case 1&2). Surgery is performed on the empty heating heat at tepid temperatures (30–32°C). Two arterial cunnals are used (innominate artery and ascending aorta) in order to disconnect the innominate artery temporary from the ascending aorta. Thus complete exposure of the anterior tracheal surface is possible for long-segment stenosis. In the present of LSS a slide plasty with bronchoscoptic control (Olympus BF N20 or XP 60 flexible Bronchoscopes) is performed. Tracheal stenosis from external compression is released without CPB by aortopexy or resection of compressing ligaments (Case 3). If additional Tracheomalacia is present an external suspension to a Gore-Tex-prosthesis is used. The postoperative care is characterized be a longer time of mechanical ventilation (up to weeks) and a difficult weaning from the respirator. A modified heart-lung-machine (Stöckhert S-5, Highlight 800 Oxigenator MEDOS) may be used at the ICU, if necessary.

We report 3 children suffering from different types of tracheal stenosis:

1. 6 months old boy with unilateral agenesis of the left lung, tracheal stenosis with closed cartilage rings and malacia of the trachea. Oesophago-tracheal fistula close to the larynx: enlargement of the stenotic trachea and pericard patch, external stenting with an anterior gore-tex patch.

2. 3 months old girl with severe long tracheal stenosis, kinking of the truncus brachiocephalicus, A. suclavia dextra closely related to the trachealstenosis, aletectasis and AV-malformation in the right upper lobe: slide tracheoplasty, reposition of the right truncus brachiocephalicus and wedge-resection of the AV-malformation in the right upper lobe.

3. 1 month old boy with double outlet right ventricle, malposition of the great vessels, PS, ASD, PDA and tracheal stenosis due to extrinsic vascular compression: 3.5 mm gore-tex-shunt, ligation of the ductus botalli, Age 4 months: CT tracheal stenosis, tracheomalacia, extrinsic vascular compression (aorta): Aortopexia, external stenting, gore-tex-patch-suspension (Hagl-OP).

**Conclusion:** All children were suffering from tracheal stenosis and further malformations of the cardiac-, renal- or gastrointestinal system. A highly specialized team and individual management are essential for good results. No surgical technique corrects all of the anatomic variants of this disease. Long-segment tracheal stenosis is best treated using slide tracheoplasty and concomitant repair of cardiovascular lesions. Unfortunately this technique was not possible in case 1.

---

**M. Cellular and molecular biology**

**M1**

**Antioxidants inhibit neutrophil elastase-induced mucus cell metaplasia**

J. Voynow1, M. Meyer2, R.M. Fischer1, E. Potts3, W.M. Foster1, 1Duke University Medical Center, Pediatric Pulmonary and Sleep Medicine, Durham, NC, USA; 2Duke University Medical Center, Pediatric Critical Care, Durham, NC, USA; 3Duke University Medical Center, Division of Pulmonary, Allergy and Critical Care Medicine, Durham, NC, USA

**Rationale:** Mucous cell metaplasia (MCM) and neutrophil-predominant airway inflammation are common pathological features of chronic inflammatory airways diseases. Neutrophil elastase (NE), an inflammatory protease found at high concentrations in the airflow of CF and COPD subjects, upregulates MUC5AC, a major secreted respiratory tract mucin, and induces mucus cell metaplasia in a mouse model. NE-induced upregulation of MUC5AC is mediated by reactive oxygen species (ROS) in airway epithelial cells. We hypothesize that NE-generated ROS are required for NE-induced mucous cell metaplasia in mice.

**Methods:** We exposed C57Bl6 mice to N-acetylcysteine or control vehicle in drinking water, 1 week prior to and during 1 week of treatment with NE or control vehicle via intratracheal aspiration as we have previously reported (AJP-Lung 287: L1293, 2004). On days 8 and 11, lung tissues and bronchoalveolar lavage (BAL) samples were obtained and evaluated for the presence of inflammation and MCM. Inflammation was evaluated by BAL cell counts and cytokine quantitation by multiplex assay. MCM was evaluated by histological analysis of the airways with Alcian blue/periodic acid-Schiff staining.

**Results:** After NE treatment, mice demonstrated an increase in neutrophils on day 8, which persisted on day 11. In addition, there was an increase in eosinophils on day 11. Both of these effects were attenuated in N-acetylcysteine-treated mice. After NE treatment, both II-5 and MCP-1 levels were elevated on day 8 in control-treated mice vs. N-acetylcysteine-treated mice. MCM was induced in NE-treated animals; but MCM remodeling was greater in control-treated mice compared to N-acetylcysteine-treated mice.

**Conclusions:** NE aspiration results in an inflammatory response, and induction of MCM; inhibition of ROS with oral N-acetylcysteine, decreased NE-induced inflammation and MCM. We are currently evaluating the mechanism of how ROS mediate NE-induced MCM remodeling.

Support: Children’s Miracle Network (MM); NIH HL082504 (JAV); NIH ES016347 (WMF).

**M2**

**Attenuation of pulmonary hypertension secondary to left ventricular dysfunction in the rat by HMG-CoA reductase inhibitor**

K.-H. Chen, Z.-K. Dai, B.-N. Wu, I.-C. Chen, J.-R. Wu. Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

Pulmonary hypertension (PH) in left ventricular dysfunction is attributable not only to backward failure of the left ventricle, but also to increased pulmonary vascular resistance (PVR) in some patients. Accordingly, the HMG-CoA reductase inhibitors (Statins) can provide antiproliferative and anti-inflammatory cardiovascular effects. During the recent years, there have been evidences in which Statin is demonstrated to reduce various forms of pulmonary hypertension (PH), such as hypoxia-induced pulmonary hypertension (PH) and monocrotaline-treated PH, and human beings with PH. But, little is known about the role of statin in left ventricular dysfunction-induced PH, classified as the group II PH.
We utilized the ascending aortic-banded rat and assessed the effect of Simvastatin on the development of PH secondary to left ventricular dysfunction. Subsequently, in rats subjected to aortic banding for 6 weeks, there were increases in mean pulmonary arterial pressure, pulmonary arteriolar medial thickness, Rho-kinase II, Rho-kinase activity, endothelial nitric oxide synthase (eNOS) and endothelin-1 (ET-1) concomitant with decreased levels in NO and cGMP in the lung. Treatment with Simvastatin at a dose of 30 mg/kg/day from day 1 to day 42 (early treatment) or from day 29 to day 42 (late treatment) decreased the mean pulmonary arterial pressure, mean left atrial pressure, right ventricular hypertrophy, pulmonary arteriolar medial thickness and pulmonary expression of Rho-kinase II and Rho-kinase I, respectively, as well as augmented pulmonary expression of NO, respectively, when compared with the vehicle controls. In addition, Simvastatin significantly decreased the pulmonary ET-1 and increased the pulmonary cGMP in the early treatment group, not the late treatment group.

In conclusion, these results suggest that inhibition of HMG-CoA reductase may provide therapeutic potential for preventing and attenuating the development of PH in left ventricular dysfunction. Further translational study in human is needed to substantiate the findings.

M3
Inflammatory myofibroblastic tumor in the lung with feeding vessel: mimicking a congenital lung malformation

C.M. Layal, M. Bautista. Philippine Heart Center, Pediatric Pulmonology, Quezon City, Philippines

Numerous literatures have cited that Inflammatory Myofibroblastic Tumor can behave as a malignant tumor both clinically as well as radiologically. However, there is paucity of article reported that it can mimic as a congenital lung malformation. In this report we describe a unique occurrence of an inflammatory myofibroblastic tumor of the lung with feeding vessel. An asymptomatic 15 year old female patient had chest radiograph that incidentally showed a solitary parenchymal mass on the left lower lung lobe. Further investigations of her condition by Chest CT scan revealed a well defined homogeneously hypodense mass lesion with no internal calcification and with a large pulmonary vessel supplying the lesion. Initial impression then was pulmonary sequestration versus pulmonary arteriovenous malformation, considering the presence of a feeding vessel. Resection of the mass was done with gross findings of a tan ovoid globular tissue with a well circumscribed white to yellow surface with punctuate hemorrhages. Histopathological report was consistent with an inflammatory myofibroblastic tumor.

Surgical resection is the treatment of choice resulting to an excellent outcome, as was done to patient who was discharged improved. Long term follow up however is imperative to detect possible recurrences.

M4
Role of human coronavirus in Brazilian hospitalized children with respiratory lower infection

P.F.B.M. Costa1, C.H.A. Lima2, J.-N. Telles3, G. Vernet3, G.P. Baccalà3, M.A.M.T. Siqueira2. 1Hospital Federal de Bonsucesso, Pediatric Pulmonology, Rio de Janeiro, Brazil; 2Fundação Oswaldo Cruz, Respiratory Viruses laboratory, Rio de Janeiro, Brazil; 3Fondation Mérieux, IFR128 BioSciences Lyon-Gerland, Emerging Pathogens Laboratory, Lyon, France

Acute lower respiratory infections (ALRI) are a major cause of morbidity and mortality worldwide, particularly in children under 5 year of age. These respiratory infections are mainly caused by bacteria and viruses. With the expansion of molecular diagnostics assays, human bocavirus (HBoV), human metapneumovirus (hMPV), Rhinovirus, human coronaviruses, and others viruses were discovered and easily detected in respiratory specimens compared with conventional methods such as viruses culture. Bronchiolitis (BVA) and Pneumonia (PNM) are frequent and constitute an important cause of hospitalization in Brazil and others countries in Latin America. An understanding of the Brazil epidemiology is crucial for identifying target groups and appropriate timing of public health preventive measures such as therapies.

In this study, we aimed to investigate epidemiological of a Human coronavirus associated to a well defined clinical patients with lower respiratory infection.

Materials, Patients and Methods: Patients: This is a substudy of an ongoing prospective brazilian investigation of respiratory tract infections in children and adults in the city of Rio de Janeiro, Brazil. This study was approved by all participating institutional review boards.

Samples: The specimens were collected from infants within the first 48 hours after admission and up to five days of clinical manifestation before admission. All the patients included were submitted to a clinical examination, case history and nasopharyngeal aspirate (NPA).

Respiratory Virus Nucleic Acids detection: Nasopharyngeal aspirates were submitted to nucleic acid extraction using the NucliSENS EasyMAG platform (bioMérieux, France), in combination with the NucliSENS magnetic extraction reagents (bioMérieux, France) and NucliSENS lysis buffer (bioMérieux, France).

Results: A total of 217 children with well documented diagnosis of pneumonia (n=53/217, 24.4%), bronchiolitis (n=160/217, 73.3%) or ARDS (n=4/217, 1.8%) admitted in the emergency room (n=174, 80.2%) or ICU (n=43, 19.8%). Only one agent was detected in 49% and more than one was detected in 31%. The negative samples represented 13, 8% of all NPA submitted. The most common virus detected were RSV. The Human Coronavirus was detected in 15/217 samples (7%). Of these, five were presented alone and in 10/15 codetection with other agents. Five children had diagnosis of BVA and two of these required admission to the intensive care unit. The median age was 31 months, ranging from 1 month to 144 months. The BVA cases occurred in children under 1 year. The average days of symptoms before admission was 4 days, all cases had wheezing on physical examination and respiratory insufficiency occurred in 3 children (all with BVA). Respiratory symptoms, hypoxemia and need for mechanical ventilation was not different in group with and without co-detection by another virus and there were no differences.

Discussion: In this study, we applied multiplex RT-PCR of nasopharyngeal aspirate samples for prospective evaluation of respiratory viruses associated with hospitalized with ALRI. HCoV-NL63 was usually identified in younger children, primarily those less than 2 years of age, which could reflect greater susceptibility because of immunologic immaturity of young children. We analyzed the clinical characteristics of those with HCoV-NL63 infection with and without co-detection by another virus and there were no differences.

Conclusions: Despite these limitations, this study compared prevalence, epidemiology, and clinical manifestations of Human coronavirus in ALRI. There are few reports with this results.
N. Pediatric pulmonology in developing countries

N1 Abdominal tuberculosis in children: case series
W. Indawat, Faculty of Medicine, University of Indonesia, Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Background: Abdominal tuberculosis is considered as rare disease. Although it is the sixth most frequent site of extra pulmonary involvement of tuberculosis, it is very difficult to be diagnosed. It can have varied presentations, frequently mimicking other diseases. Unfortunately, chest X-ray showing evidence of concomitant pulmonary lesion only appears in less than 25 percent of cases.

Objective: We would like to report our experience with 12 cases of abdominal tuberculosis regarding their clinical course, tuberculin test and other important supporting findings.

Results: Subjects were twelve patients (8 boys and 4 girls) of mean age 8.8 years old. All of them were suffered from undernourishment while 6 of them were in severe malnutrition. Anorexia was found in 10 patients as well as weight lost. Fever was seen on almost all of them (11/12). All cases had abdominal pain but only half of them had intra abdominal mass. Six out of 12 had ascites while 7 patients had abdominal distention. Only 4 patients were suffered from diarrhea or constipation. Cervical or inguinal lymph nodes enlargements were observed in 6 patients. The source of infection was not well defined in half of patient as well as positive tuberculin skin test. Chest X-ray findings varied from infiltrate and hilar lymphadenopathy to milary.

Conclusions: The most common manifestation of extrapulmonary TB was spondilitis TB. The majority of subjects were 1 to 5 years-old, under-nourished and TST positive. BCG scar was found in 42.9% patients who suffered from severe extrapulmonary TB.

N2 BCG immunization in severe extrapulmonary TB in children
N. Kaswandani, B. Supriyatno, Faculty of Medicine, University of Indonesia, Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Background: Extrapulmonary TB is a manifestation of TB that may lead to mortality and permanent disability. Some previous studies reported the efficacy of BCG to prevent the severe manifestation of TB in children such as meningitis TB, bone TB and miliary TB. The incidence of ETB is unknown, however studies reported the efficacy of BCG to prevent the severe manifestation of TB in children such as meningitis TB, bone TB and miliary TB. The aim of this study was to know the prevalence of BCG scar and identify the clinical features and supporting examination findings in in extrapulmonary TB in children.

Methods: This was a retrospective study which evaluated all children with extrapulmonary tuberculosis. Subjects were all patients with extra pulmonary TB who were admitted to Ciptomangunkusumo Hospital Jakarta Indonesia during 2008 to 2009. All data were taken from medical records.

Results: There were 28 children (15 males and 13 females) diagnosed as extrapulmonary TB. The diagnosis of bone TB (spondilitis, coxitis and osteomylitis) was found in 14 (50%) children while CNS TB (menigitis and tuberculum) was found in 9 (32.1%) children. The age of patients is mostly 1–5 years old (42.9%); under 1 year-old patients and over 5 years old were 5 (17.9%) patients and 11 (39.3%) respectively. History of TB contact was identified in 13 (46.4%) subjects. Tuberculin skin test (TST) was performed to all subjects and the positive rate was 50%. The majority of subjects (64.3%) were under-nourished. Eighteen (64.3%) parents stated that their children were BCG immunized, but BCG scar was identified in 12 (42.9%) subjects. Chest X-ray findings varied from infiltrate and hilar lymphadenopathy to milary.

Aims: To review the role of FB in the investigation and management of ETB and IRIS in HIV children
C. J. Mendoza Fox, Clínica Ricardo Palma, Clínica Anglo-Americana, Hospital Hipolito Unanue, Lima, Peru

Introduction: Endobronchial tumors (ET) in children are extremely rare, with real incidence unknown. The majority of reports are small group of cases, with bronchial adenoma and bronchogenic carcinoma representing 70–90% of the tumors. Other frequent diagnosis are: papilloma, inflammatory polyps, leiomyoma and hemangioma. The exact incidence of endobronchial tuberculosis (ETB) is unknown. The role of bronchoscopy (FB) in the evaluation of immune reconstitution inflammatory syndrome (IRIS) has not been determined.

Aims: To review the role of FB in the investigation and management of ETB and IRIS in HIV children.

Case: A 12 year old boy, HIV C3, with HAART since February 09. In treatment since June 09 for multidrug resistant tuberculosis (MDR TB), with clinical and radiological improvement. In September 09 presents 5 days of fever, cough and a new consolidation in the left upper lobe (LUL). Work-up included a FB, finding two ETs with obstruction of >90% of the right main bronchus and one obstructing 100% of –2 segment LUL. Results of bronchoalveolar lavage revealed 3 colonies of mycobacterium TB and biopsy showed chronic granulomatous inflammation with Ziehl Neelsen ++/+++. Patient continued anti-MDR TB treatment and received prednisone 2 mg/kg/d with a reduction of >90% of lesions at the month control.

Discussion: The incidence of ETB is unknown, however studies that investigated the results of FB in children with suspected TB have shown bronchial involvement in 41–63% of cases. The lesions described are: compression of the airways (42–59%), granulation tissue (18–29%), caseating material (12–39%) and polyp formation (6%). Airway involvement may be multifocal (41%) and in both bronchial trees (12%). Lymphoma, Karpof sarcoma and Cryptococcosis neoformans cause lymph node enlargement in HIV that can be confused with that of TB. Besides it is easy in this group, to get confused between a failure of TB treatment, presentation of an undiagnosed disease or IRIS. The last one is an exclusion diagnosis, that has a 7% incidence in HIV with TB treatment and in >19% of HAART patients. Most cases resolve spontaneously, but also can be severe and lethal.

Conclusion: The role of FB in the evaluation of ETB and IRIS has not been determined yet; but we show that in this patient (after 7 months of HAART and 3 of anti-MDR TB) it was essential for the diagnosis, management and follow-up.
N4 Childhood household contact: is a single screening sufficient?
K.N. Benhalla1, L. Smati1, J.P. Grangaud1, R. Boukari1, M. Baghriche1.
1EPH Bologhine, Pediatrics, Algiers, Algeria; 2Algers Faculty of Medicine, Pediatrics, Algiers, Algeria; 3CHU Blida, Pediatrics, Blida, Algeria

Tuberculosis in children is often acquired by contact with a family or household member and contact investigations are recommended as a strategy by the IUATLD and the WHO.

Objective: Our objective was to assess the efficiency of a simple active case finding strategy in a developing country with high BCG vaccination coverage.

Methods: We performed a prospective study of 242 children under 15 years among household contacts of index cases with active tuberculosis, enrolled in the Setif Regional TB Center (Algeria). All contacts were systematically evaluated with medical history, physical examination, CXR and TST. Contacts with signs or symptoms of tuberculosis were considered tuberculosis suspects; these suspects were evaluated for bacteriological investigations (sputum samples for children older than twelve or gastric aspirates for the younger’s). After the baseline evaluation, the 242 children were followed up at 1, 6, 12, 18 and 24 months.

Results:
- Index cases: 54 patients with smear-positive pulmonary TB agreed to participate in this study.
- Contacts: We identified a total of 242 close contacts within the 54 index cases. 76 (31.4%) are children under 5 years; the median age was 7 years (range: 9 months to 14 years). BCG vaccination was noticeable in 205 (85%) children.
- TB among contacts: A total of 35 tuberculosis (14.5%) were found: 30 children had tuberculosis disease (12.5%) and 5 had tuberculosis infection (2%). In most cases (57%), the diagnosis was within 3 months of the initial assessment but for twelve patients (43%), the diagnosis was made between 6 and 24 months after their baseline evaluation. This finding has important implication for the follow-up of TB contacts in childhood.

Conclusions: Our results call for early examination of all exposed children, in order to prevent infection and progression to active disease, and for, at least, a routine second evaluation. An additional program of education in order to explain the symptoms which should lead the parents to consult would be very useful.

Keywords: TB, household contact, follows up.


N5 Increasing incidence of asthma, allergy and eczema in rural Honduran children
J.C. Stevens1, S. Ball1, H. Eigen1.
1Indiana University, Pediatrics, Indianapolis, USA; 1Indiana University, Bloomington, USA

We have previously demonstrated a very high prevalence of ever wheezing (89.6%) and wheezing in the last 12 months (72.9%) in children of the valley of Rio Grande O Choluteca in rural Honduras where the main crop, sugar cane, is burned 6–8 months of the year.

To determine if environmental factors play a role in this very high prevalence of asthma, we performed a pilot study to investigate the change in incidence of asthma, allergies and eczema in 29 children who moved into this valley. After obtaining informed consent a modified, locally validated, Spanish version of the International Study of Asthma and Allergies in Childhood questionnaire was administered serially, once a year for 4 years, to children age 6–16 who had moved into the valley of Rio Grande O Choluteca in the year prior to study initiation. Pulmonary function testing was also performed by the children. The tables summarize questionnaire findings from 2006 and 2010.
Lung function values in healthy children in the community: comparison between lung function and nutritional status

D.A. Wulandari1, C.B. Kartasasmita1, S. Sudarwati1, A.U. Suardi1, W. Saptaputra2. 1Department of Child Health, School of Medicine, Padjadjaran University, Bandung, Indonesia; 2Health Research Unit, School of Medicine, Padjadjaran University, Bandung, Indonesia

Introduction: Measurements of lung function greatly enhance diagnostic in many respiratory problems even in pediatric. The test provides an assessment on severity of airflow limitation and confirmation of asthma diagnosis. However Indonesia does not have a national data about lung function values in children.

Objective: To know the lung function values in healthy children in Bandung-Indonesia as a preliminary study in developing national values, and correlation between lung function and nutritional status.

Methods: A cross sectional study on healthy children 8 to 13 year-old in the Pediatric Department Hasan Sadikin General Hospital from January to November 2010. Weight, height, and BMI of the children were examined, and lung function test were performed with vitalograph computerized spirometry. This study is part of a nested case control study entitled "RSV and recurrent wheezing in Indonesia: 7–9 year follow-up study with lung function studies".

Results: Subject were 218 children age 8 to 13 year-old (mean: 10.04), 46.8% male and 51.4% female. The height were 107 to 161 cm (mean: 138.33), and the mean weight were 32.796. The body mass index (BMI) was 12 to 28.8 (mean: 16.896), 168 (77.1%) children with well nourished, 30 (13.8%) mild malnutrition, 12 (5.5%) moderate malnutrition, 6 (2.8%) overweight, and 2 (0.9%) obese. The FVC were 0.83 to 3.82 (mean: 1.936), FEV1 were 0.64 to 3.01 (mean: 1.7667), FEV1/FVC were 39.1 to 140.5%, FEV1/FVC were 53.44 to 99.87% between BMI and FEV1, FEF25–75, FEV1/FVC (p: 0.00 r: 0.469; p: 0.009 r: 0.176; p: 0.27 r: −0.150, respectively). There was weak correlation between BMI and FVC (p: 0.000 r: 0.494). There were significant differences between lung function measurement (FEV1and FVC) and nutritional status.

Conclusion: There is a weak correlation between BMI and FVC, and significant different between lung function measurement (FEV1and FVC) and nutritional status.

Keywords: lung function, BMI, nutritional status, children, community

Management of children with broncho-oesophageal fistula due to tuberculosis

P. Goussard1, R.P. Gie1, A. Vanker1, D. Rhode1, S. Andronikou2, D.A. Wulandari1.

Aim: To describe clinical, radiological and bronchoscopic features and management of children less than 12 years with BOF as a result of complicated MTB. To describe the course of TB BOF and determine if the BOF caused by tuberculosis close spontaneously or require surgical intervention.

Methods: Retrospective, clinical study of all children younger than 12 years treated for BOF caused by MTB at Tygerberg Children’s Hospital since 2000 is described.

Results: 17 children (59% female with a median age of 24 months (range 4–120 months) of whom one was HIV positive is described. The clinical presentations were lower left lobe pneumonia (53%), left sided empyema (12%) and large airway obstruction with associated aspiration (18%). There was a case each of BOF presenting with TB meningitis and marasmus and one following TB glandular enucleation. Of the cases 65% was culture positive and 12% ZN positive. With the aid of a flexible bronchoscopy the BOF was visualized in the left main bronchus in 94% (n=15) of cases. Of the 17 cases 71% survived. 7 required ventilation at or shortly after presentation and and 5 (71%) of the ventilated children did not survive. Mean albumin of survivors was 30ug versus 17ug of the non-survivors. Of the survivors 50% (n=6) was closed with surgery, 17% (n=2) closed after TB treatment alone, 17% (n=2) was closed with glue and 17% (n=2) closed with the aid of a stent in the oesophagus.

Conclusion: The majority of TB related BOF is left sided. Children needing ventilation for BOF had 71% mortality. Most fistulas do not close spontaneously of TB treatment and needs intervention.

Pulmonary hydatidosis in children

C.J. Mendoza Fox1, K. Quevedo1. Clinica Ricardo Palma, Clinica Anglo-Americana, Hospital Hipolito Unanue, Lima, Peru; 2Hospital Hipolito Unanue, Pediatrias, Lima, Peru

Introduction: Cystic echinococcosis (CE), caused by the larval stage of Echinococcus granulosus (EG), is recognized as a public health problem. CE is endemic to more than 100 countries in Latin America, Asia, and Africa. Studies in Peru have shown high prevalence of CE in humans, particularly in the central and southern highlands. During 1997–1999, Moro et al. found that prevalence in the central Andes was 5.7–9.3% according to ultrasonography, radiography, or both and up to 18.2% according to immunoblot testing. Like Gavidia and et al in 2008, found that the CE prevalence according to ultrasonography and radiography was 5.5%. But a lower number was found by Moro in 2005, the prevalence of human CE using portable ultrasound and the enzyme-linked immunoellectrotransfer blot assay were 4.9% and 2.6%, respectively. Tuberculosis has similar clinical manifestations and Peru is one of the countries with the highest prevalence (100 cases per 100,000), even more, in the area were our Hospital is located the prevalence is 263.9–275/100,000.

Aims: Find and establish the demographic and clinical characteristics, radiology, serology, complications and treatment of pathological confirmed pulmonary hydatidosis in children.

Methods: The clinical files of 27 patients hospitalized since October 2002 to December 2009 in the Paediatric Department of Hospital Hipolito Unanue (Lima, Perú) were reviewed. We excluded patients without pathological confirmation of pulmonary hydatidosis. Laboratory used indirect immunoellectrofluorescence to determine antibodies against sclex of EG in blood and biological fluids.

Results: There were 16 (59%) boys and 11 (41%) girls in the group. The age range from 4 to 14 years, mean of 9 years. The 37% of patients lived in Lima (capital of Perú), 18.5% from the surrounding towns of Lima, and the rest (41%) from the Andean region of the country. In all cases from low socioeconomic status. The most frequent clinical manifestations were cough (81%), fever (74%), dyspnea (41%), hemoptysis (41%) and thoracic pain (37%). Only 18 patients were serological tested, with positive results in 67% of them. The left lung was the most frequent localization with 14 (52%) cases, right 10 (37%) and in 3 (11%) both. The left lower lobe was the most frequent (52%) involved. Complicated cysts represented the 85.2% of cases. Hepatic cysts were found in 8 patients (30%)
and splenic cyst in one case (4%). All patients were treated with surgery. In 12 patients (44%) the cysts were viable, 4 (15%) non-viable and 11 (41%) cases it was not specified.

Conclusion: Pulmonary hydatidosis is an endemic disease in Perú. It has common clinical characteristics with tuberculosis. Radiology is helpful in many cases to difference between both, but in some cases a high suspicion index is needed.

N10
The lack of correlation between lung uptake of 18FDG PET/CT and inflammatory and disease activity markers in children with human immunodeficiency virus-related bronchiectasis
R. Masekela1, H. Gongxeka2, R.J. Green1, M. Sathekge3.

Background: 18Fluorine fluorodeoxyglucose (FDG) PET/CT has an increasing role in diagnosis of inflammatory conditions. FDG has a high avidity for neutrophil granulocytes, macrophages and lymphocytes making it an attractive tool in the diagnosis and management of inflammatory pulmonary disease.

Aim: The primary aim of this study to assess the role of FDG PET in assessing inflammatory changes in children with human immunodeficiency (HIV) virus-related bronchiectasis, by measuring the standard uptake value (SUVmax) in four zones of the lungs. The secondary end-points were to assess whether PET can help to distinguish active versus non-active lung lesions; as well as to assess whether FDG PET has any correlation to inflammatory and HIV disease activity markers.

Methods: HIV-related bronchiectasis patients over the age of 6 years underwent 18FDG PET/CT. Balla scores were performed on the CT scans. Serum was collected for CD4 count, HIV viral load, C-reactive protein (CRP) and interleukin (IL)-8 determinations. Serial induced sputum was collected monthly over a period of one year for microscopy, sensitivity and culture as well as one sample of sputum IL-8. Data on the presence or absence of an exacerbation at study entry was recorded. Statistical analysis using the Fisher exact test was used for categorical variables and the Mann-Whitney U test for non-parametric variables.

Results: A total of 41 subjects were enrolled of whom 25 (61%) were male, mean (range) age of 8 years (6–14). There was a lack of correlation between SUVmax uptake and presence of previous tuberculosis, presence of an exacerbation at time of PET and presence of an organism on culture (p=0.698; p=0.613 and p=0.728) respectively. There was a correlation between the presence of consolidation and SUV uptake (p=0.01). There was no statistically significant difference between subjects with positive FDG uptake compared to those with no uptake, with respect to number of months on antiretroviral therapy (p=0.367), CD4 percentage (p=0.988), HIV viral load (p=0.235), severity of bronchiectasis on Balla score (p=0.185), CRP (p=0.109), serum IL-8 (p=0.322) and sputum IL-8 levels (p=0.370).

Conclusion: There is a limited role of PET/CT in HIV-related bronchiectasis, with its value being limited to demonstrating disease activity in acute pneumonia with presence of lobar consolidation. FDG PET does not show uptake/accumulation in patients with non-active previously diagnosed TB. There are no differences in FDG uptake related to severity of the bronchiectasis.

P. Miscellaneous

P1
A case of intrapericardial extra lobar pulmonary sequestration
Jichi Medical University, Pediatric Surgery, Simotuke, Japan

Extra lobar pulmonary sequestration (ELS) is usually located between the lower lobe of the lung and the diaphragm. In about 10–15% of cases, ELS occurs below the diaphragm, but ELS at other sites is rare. We present a rare case of intrapericardial extra lobar pulmonary sequestration.

Fetal ultrasound findings at 23 weeks of gestation demonstrated an intrathoracic cystic lesion. Magnetic Resonance Imaging (MRI) showed a cystic lesion measuring 19 × 29 mm to the left of the heart. On ultrasound examination, there was no remarkable change in the lesion size until the baby was delivered vaginally at 38 weeks. Birth weight was 2916 g. He had no respiratory problems. The intrathoracic cystic lesion detected prenatally was shown to be an intrapericardial lesion composed of cystic and solid portions and measuring 40 × 17 × 17 mm on echocardiography and computed tomography (CT) obtained after birth. Differential diagnoses were intrapericardial extra lobar pulmonary sequestration, teratoma and bronchogenic cyst. Intrapericardial extralobar pulmonary sequestration was highly suspected because CT showed a vague aberrant artery arising from the ascending aorta. At 3 months of age, the infant underwent surgery by median sternotomy. The intrapericardial mass was found between the left pulmonary artery and left antrum after incising the pericardium and initially seemed to be the left auricle. Careful observation demonstrated that the mass in front of the left auricle had developed from the right to left side of heart, passing behind the pulmonary artery and ascending aorta. The mass connected laterally to the right pulmonary artery and medially to the vena cava superior. The intrapericardial mass was first extracted from the left to right side of the heart through the transverse pericardial sinus. Two aberrant arteries from the right pulmonary artery and one drainage vein flowing into the vena cava superior were identified and ligated, then the mass was resected. Histopathological diagnosis was intrapericardial extra lobar pulmonary sequestration because lung components such as mature pulmonary tissue, tracheal cartilage, and tracheal gland were identified in the solid lesion. Elastic artery and vein were also identified by Elastica Van Gieson stain. The presence of many cavities surrounded by ciliary mucosa filled with mucus secretion in the cystic lesion implied cystic dilatation of trachea secondary to bronchial atresia.

The postoperative course was uneventful. On the 8th postoperative day, he was discharged from our hospital. In conclusion, CT findings performed after birth in this case facilitated the early diagnosis, making it possible to perform elective surgery safely.

P2
Bronchopleural fistula complicating empyema associated with necrotising pneumonia in children
V. Rasiah1, S. Sonnappa2.
1Newham General Hospital, Paediatrics, London, UK; 2Great Ormond Street Hospital, Respiratory Medicine, London, UK

Introduction: Invasive pneumococcal disease has increased in frequency in recent years and consequently necrotising pneumonia complicated by empyema is on the rise [1]. Children with necrotising pneumonia are at increased risk of developing bronchopleural fistulas (BPF), resulting in high morbidity and prolonged hospital stay [2], but evidence to inform best management for empyema in these children is lacking. The primary objective of our study was to ascertain if the incidence of BPF
was increased in children with necrotising pneumonia and whether the incidence of BPF was influenced by choice of management for empyema.

**Methods:** We retrospectively reviewed medical notes of children with radiographic evidence of empyema, treated at Great Ormond Street Hospital for Children NHS Trust from January 2008 until February 2010. We compared the incidence of BPF between children with necrotizing pneumonia and non-necrotizing pneumonia; and explored the incidence according to management of empyema: chest drain with urokinase vs. video-assisted thoracoscopic surgery (VATS).

**Results:** Fifty-three children were identified; mean age 5.5 (±4.5) years; 27 male; 26 were treated with chest drain and urokinase and 27 with VATS. Eighteen (34%) children were identified as having necrotising pneumonia on chest X-rays. The incidence of BPF was significantly higher in children with necrotising pneumonia compared to those without (39% vs. 3%; p = 0.001). Children with necrotising pneumonia were significantly younger (mean age 3.3 y vs. 7.3 y; p = 0.01) and had significantly longer hospital stays (13.4 days vs. 8.3 days; p = 0.0003), than those with non-necrotising pneumonia. The incidence of BPF in children treated with chest drain and urokinase was not significantly different from those treated with VATS (43% vs. 36%; p = 0.7).

**Conclusions:** Children with necrotising pneumonia have a significantly higher risk of developing BPF. Both chest drain with urokinase and VATS are safe management options for the primary treatment of empyema in children, including those with necrotising pneumonia, but the authors recommend the former approach based on past evidence [3].

**References**


**P3**

**Comparison of short and long term complications of treatment with oral ibuprofen versus fluid restriction in preterm infants with patent ductus arteriosus**

S. Mehralizadeh, E.N. Zakieh, D. Gholamreza. Semnan University of Medical Sciences, Semnan, Iran

**Introduction:** Patent ductus arteriosus (PDA), is one of the most common congenital cardiac anomalies in premature infants. Nonsteroidal anti-inflammatory agents are the treatment of choice for ductal closure in premature newborns, but as in Iran, the only available drug is oral ibuprofen, therefore the study was conducted to determine short and long-term complications as well as the effectiveness of oral ibuprofen in the treatment of PDA in premature infants.

**Methods:** In this clinical trial, for all preterm infants below 38 weeks admitted at Amir Hospital, with a murmur but without any symptoms of heart failure transthoracic echocardiography was performed, and if having PDA, were enrolled. Infants were divided into two groups. 38 neonates with a gestational age of below 38 weeks were included. The first group (19 patients) was treated with three doses of oral ibuprofen, with first day dose of 10 mg/kg and 5 mg/kg on the second and third days. Control group (19 patients) were under restriction of fluids (serum level of 2/3, maintenance and limitations of breast milk).

In addition to the first day and the third day of treatment, a third and sixth month echocardiography were performed in both groups, and the rate of closure of PDA and the rate of pulmonary hypertension in both groups were compared. The presence of intraventricular hemorrhage and periventricular leukomalacia were detected by brain ultrasound at the age of one week and one month.

The presence of retinopathy was checked at the time of hospital discharge. Other findings such as duration of hospital stay, pulmonary hemorrhage, ventilator time dependence, duration dependence on oxygen and nosocomial infections were recorded. Then the obtained data in both groups were compared.

**Results:** No case of pulmonary hypertension, PVL or retinopathy was observed in oral ibuprofen group. Regarding to other criteria such as hospital stay, IVH, sepsis, ventilator time dependence, duration dependence on oxygen, time to reach the birth weight, pulmonary hemorrhage and mortality rate no significant difference between the two groups was observed. Patent ductus arteriosus remaining open was seen in control group more than the case group but was not significant.

**Conclusion:** Oral ibuprofen is a low risk drug for the treatment of PDA in premature infants, and compared with non-pharmacologic treatment, it does not increase the rate of pulmonary hypertension.

**P4**

**Diffuse lung disease in Danish infants: application of the ChILD classification system**

F. Buchwald1, B.L. Petersen2, R. Deterding3, C. Langston4, G. Deutsch5, K.G. Nielsen1. 1Copenhagen University Hospital, Ped Pulum 5003, Copenhagen, Denmark; 2Copenhagen University Hospital, Pathology, Copenhagen, Denmark; 3Children’s Hospital, Respiratory Department, Denver, USA; 4Baylor College of Medicine and Children’s Hospital, Pathology and Pulmonary Medicine, Texas, USA; 5Children’s Hospital, Laboratory Medicine, Seattle, USA

**Aim:** Categorize a Danish infant cohort with diffuse lung disease according to the clinical presentation, pathological subtype at lung biopsy, and outcome.

**Methods:** Danish children presenting with persistent respiratory symptoms before the age of 2 years and signs of diffuse lung disease who underwent diagnostic lung biopsy were identified over a 12 year period. Neonatal deaths from NICU were not included. The biopsies were categorized in collaboration with the ChILD Clinical and Research Network, USA. Clinical data was retrospectively retrieved from hospital files.

**Measurements and Main results:** Thirty-one infants (77% males) were identified. Seventeen infants (55%) were categorized as disorders predominating in infancy including 10 infants (32%) with alveolar growth abnormalities (GA) in which 4 also exhibited patchy Pulmonary Intertitial Glycogenosis (PIG); 6 infants (20%) with Neuroendocrine Hyperplasia of Infancy (NEHI) and 1 infant (3%) with changes of surfactant dysfunction mutations with Pulmonary Alveolar Proteinosis (PAP) histology. Fourteen biopsies (45%) showed early post infectious airway injury (PIAI). Pulmonary hypertension was more frequent in infants with GA (p = 0.04) who also tended to have more need for oxygen supplementation (p = 0.12).

Mean gestational age was higher in infants with NEHI (40.5 wks) and PIAI (39.3 wks) compared to those with GA (36.5 wks) (p = 0.006).

**Measurements and Main results:** Thirty-one infants (77% males) were identified. Seventeen infants (55%) were categorized as disorders predominating in infancy including 10 infants (32%) with alveolar growth abnormalities (GA) in which 4 also exhibited patchy Pulmonary Intertitial Glycogenosis (PIG); 6 infants (20%) with Neuroendocrine Hyperplasia of Infancy (NEHI) and 1 infant (3%) with changes of surfactant dysfunction mutations with Pulmonary Alveolar Proteinosis (PAP) histology. Fourteen biopsies (45%) showed early post infectious airway injury (PIAI). Pulmonary hypertension was more frequent in infants with GA (p = 0.04) who also tended to have more need for oxygen supplementation (p = 0.12).

Mean gestational age was higher in infants with NEHI (40.5 wks) and PIAI (39.3 wks) compared to those with GA (36.5 wks) (p = 0.006).

Tachypnoea (70%) with a mean (range) RF of 51/min (24–90), failure to thrive (43%) with mean (range) weight = −1.3 SD (−3.9 to 0.5) and height = −0.65 SD (−5 to 2.5) were frequent symptoms and signs at diagnosis.

Onset of persistent respiratory symptoms was at a median (range) age of 3 months (0–18). Final diagnosis with lung biopsy was delayed to 12 months (1–24) of age (p < 0.001).

Five infants were tested for surfactant dysfunction mutations (SP-C and ABCA-3). The infant with PAP was homozygous (two different mutations) for ABCA-3 mutation; one other infant (GA and PIG) was heterozygote. All others were without identified mutations.

At present, 7 infants are free of symptoms (equally distributed between subgroups), 11 infants receive no further specific treatment but have variable persistent respiratory symptoms.
Twelve infants remain under treatment including one awaiting lung transplant (GA). The infant with PAP died 5 months of age.

**Conclusions:** PIAI and GA predominated in infancy among neonatal survivors. Patchy PIG was noted in nearly half of the biopsies with GA. Symptoms and signs did not differ between the various subgroups apart from oxygen supplementation and pulmonary hypertension, which, in combination with low gestational age, were more frequently found in infants with GA.

This cohort differs in the frequent presence of PIAI and in reduced mortality, but exhibit a common symptomatology despite subgroups. A substantial group (61%) has significant morbidity despite treatment.

**P5**

**Reunion Island pulmonary alveolar proteinosis: A new, rare, familial, chronic lung disorder**

L. Enaud1, A. Coulomb2, L. Berteloot3, V. Boulay4, F. Lacaille5, V. Verkarre6, E. Fleurence7, S. Losi8, F. Darcel9, M. Renouil1, L. Boccon-Gibod2, J. de Blic2. 1Groupe Hospitalier Sud Réunion Service de Pédiatrie, Saint-Pierre, Réunion Island, France; 2Hôpital Armand Trousseau, Département de Pathologie, Paris, France; 3Hôpital Necker Enfants Malades, Service de Radiologie Pédiatrique, Paris, France; 4Groupe Hospitalier Sud Réunion Service de Pneumologie, Saint-Pierre, Réunion Island, France; 5Hôpital Necker Enfants Malades, Service d’Hépato-Gastroentérologie Pédiatrique, Paris, France; 6Hôpital Necker Enfants Malades, Département de Pathologie, Paris, France; 7Hôpital d’Enfants, Service de Pédiatrie, Saint-Denis, Réunion Island, France; 8Hôpital de Bellepierre Pédiatrie, Saint-Denis, Réunion Island, France; 9Groupe Hospitalier Sud Réunion, Centre de référence des maladies neuromusculaires rares, Saint-Pierre, Réunion Island, France; 10 Service de Pneumologie et Allergologie Pédiatriques, Hôpital Necker Enfants Malades, Paris, France

**Purpose:** Postnatal pulmonary alveolar proteinosis (PAP) and endogenous lipid pneumonia (ELP) with cholesterol granulomas are two rare diseases, strikingly frequent in Reunion Island, often familial.

**Patients and Methods:** 32 cases (PAP = 23, ELP = 9) followed between 1970 and 2010 were included. Family history, clinical, biological, radiological and pathological data were analysed retrospectively.

**Results:** There was a male predominance (SR = 1.7). Early onset occurred in 30/32 (median 3 mo, range 0.5–29 mo). Most common symptoms were anorexia, failure to thrive (90%), polypnea (72%), and hepatomegaly (38%). Oxygen therapy was required by 52%. Chest X-ray revealed bilateral diffuse alveolar syndrome in 97%. Posterior and basal alveolar consolidation was commonly observed on CT scan. Biochemical abnormalities included hyper IgG and IgM (86%), hypoalbuminemia (79%), agenesis normocytic anaemia, thrombocytosis and hyperleucocytosis.

PIAP cases (23/32), were confirmed at median age 5 mo (range 3–46 mo) by surgical biopsy or CT scan and typical findings at bronchoalveolar lavage. GPA, SPB and ABCA3 gene mutations, GMCSF antibody, immunodeficiency, metabolic or autoimmune disorders were ruled out. In 10 cases, liver biopsy revealed important steatosis, with fibrosis in 6. Hepatomegaly was observed at some point in 19 children. Liver tests were normal or mildly abnormal. Portal hypertension, without liver failure, developed in 5 patients.

ELP cases (9/32) were hospitalized later (median 124 mo; range 3–22 y) for dyspnea, chronic clubbing, respiratory syndrome, DLCO reduction, diffuse interstitial pattern on chest X-ray and diffuse crazy paving with frequent fibrosis pattern at CT scan. All had hyper IgG. Surgical biopsy confirmed ELP with cholesterol granulomas.

In 10 children diagnosed initially as PAP, subsequent transbronchial biopsy, or autopsy, revealed ELP lesions progressively associated with cholesterol granulomas and fibrosis. CT scan showed progressive disappearance of alveolar consolidation and apparition of crazy paving and fibrosis.

In 44% of cases, patients were family related. Transversal distribution and coexistence of PAP and ELP in 1 family suggest an autosomal recessive disease.

The prognosis is severe, death occurring early in 10 cases (4–19 mo), later in 9 cases (4.5–36 y), due to chronic respiratory failure, malnutrition and infection. Thirteen patients are still alive (median 111 mo, range 2–30 y).

**Conclusion:** We report the most important cohort of postnatal PAP and ELP with cholesterol granulomas over a 40 years period, in patients all originated of Reunion Island. Our results emphasize the precocity of first symptoms, frequent liver involvement, and severity of prognosis, with early death or progressive evolution towards lung fibrosis. Frequent familial cases, and pathological continuum, suggest that both conditions are the same inherited disease.

**P6**

**The antioxidant role of Prdx6 on acute lung injury**

Y. Wang. Chinese Medicine Society. Shanghai, China

**Objective:** To establish the antioxidant function role of Peroxiredoxin 6 (Prdx6) to acute lung injury in vivo or in vitro.

**Methods:** 100% O2 exposure or H2O2 treatment was used to induced acute lung injury models on intact mice or isolated lung type 2 cells; mice or cells survival rates and lung lavage analysis were applied for evaluating the common defending effect of Prdx6; Tunel assay observed cell apoptosis; Diphénylphosphine (DPPP) fluorescence was used to probe the degree of cell membrane lipid peroxidation.

**Results:** Prdx6 knockout (KO) mice showed most susceptibility to 100% O2 exposure with shorter survival time and more severe lung injury; on the contrary, Prdx6 overexpression (Tg) mice presented enhanced defending against oxidative lung injury; under varied doses of 50 to 500 μM H2O2 treatment for 1 to 24 h, Prdx6 KO mice presented dose- and time-related cell injury by increasing the percentage of apoptotic cells, and Tg Prdx6 mice showed least percentage of apoptotic cells; while, the degree of lung type 2 cell membrane lipid peroxidation was probed most serious remarkable in Prdx6 KO mice compared to WT mice and less least in Tg Prdx6 mice under oxidative stress.

**Conclusions:** Prdx6 plays critical antioxidant function role in defending acute lung injury, which associated with its function of anti-apoptosis and anti-lipid peroxidation of cell membrane (HL79063).

**P7**

**The role of rhinomanometry after nasal decongestant test in the assessment of adenoid hypertrophy in children**

L. Leonardi, A.M. Zicari, G. Ragusa, A. Rugiano, C. Celani, S. Caggiano, G. De Castro, L. Indinnimeo, G. Tancredi, M. Duse. Policlinico Umberto I, Roma, Italy

**Introduction:** Nasal respiratory obstruction is the most common problem in otolaryngology often due to adenoid hypertrophy (AH). The gold standard to diagnose AH is Nasal Fiberoptic Endoscopy (NFE) while rhinomanometry (RM) represents a valid support.

**Objective:** Our study want to analyze the diagnostic value of RM after ND test for evaluation of AH obstruction.

**Materials and Methods:** Were studied 71 children, aged 6–12 years, hospitalized in the Department of Pediatric Immunology of the Policlinico Umberto I of Rome for upper airways obstructive symptoms with AH.

Enrolment was used a standardised questionnaire in order to define the condition of “chronic oral breather”. At the first clinical evaluation, the subjects underwent a complete physical examination, anterior rhinoscopy and anterior active RM. To patients positive to RM, the exam was repeated after administering nasal decongestant (ND), naphazoline. Afterwards was accomplished a NFE.

**Results:** of 71 patients who underwent RM, 73.2% showed obstruction and 26.8% normal nasal airflow. Among the patients...
Discussion: When it comes to public health, Butantan female prison showed a high level of smokers, among the participants of the talk about passive smoking. Compared to the incidence of 20% of the general population, 63.15% of women who attended the talk were smokers. The information from the Board of the unit is that 50% of the prisoners use tobacco regularly. The addiction level measured by the Fagerström Scale within the prison group showed statistical differences compared to the women in general population.

Conclusion: There should be an intervention in prison units against tobacco smoking, for the consumption rate is very high, and the level of addiction among young people is much higher, compared to the general population. This is a serious problem of public health.

Table 2. Degree of dependence (Fagerström scale)

<table>
<thead>
<tr>
<th>Fagerström score</th>
<th>Smokers among female prisoners (n=24; 63.15%)</th>
<th>Smokers among female prisoners (n=35; 56.5%)</th>
<th>Fagerström level of general population, n=220</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 (weak)</td>
<td>1 (4.2%)</td>
<td>3 (8.5%)</td>
<td>27.1%</td>
</tr>
<tr>
<td>3-4 (low)</td>
<td>9 (37.5%)</td>
<td>7 (20.0%)</td>
<td>47.9%</td>
</tr>
<tr>
<td>5 (medium)</td>
<td>3 (12.5%)</td>
<td>4 (11.3%)</td>
<td>12%</td>
</tr>
<tr>
<td>6-7 (high)</td>
<td>6 (25%)</td>
<td>17 (48.5%)</td>
<td>9.9%</td>
</tr>
<tr>
<td>8-10 (very high)</td>
<td>5 (20.8%)</td>
<td>4 (11.5%)</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

*Statistically significant differences between prison and general populations.

Discussion: When it comes to public health, Butantan female prison showed a high level of smokers, among the participants of the talk about passive smoking. Compared to the incidence of 20% of the general population, 63.15% of women who attended the talk were smokers. The information from the Board of the unit is that 50% of the prisoners use tobacco regularly. The addiction level measured by the Fagerström Scale within the prison group showed statistical differences compared to the women in general population.

Conclusion: There should be an intervention in prison units against tobacco smoking, for the consumption rate is very high, and the level of addiction among young people is much higher, compared to the general population. This is a serious problem of public health.
Discussion: The level of urinary cotinine in passive smokers is minimal, but enough to make the diagnosis of a passive smoker. The general population does not show levels of urinary cotinine. It is always important to make the interconnection between creatinine/cotinine, since the cotinine is eliminated in urine.

Conclusion: It is possible to confirm the active and passive smoker through the measurement of urinary cotinine. In the air we breathe in São Paulo, the active non-smoking and the passive non-smoking population does not show levels of urinary cotinine.
Author index

Abe, T., S80 (C10)
Abid, H., S58 (VI.3)
Acosta, E., S67 (A3)
Afolabi-Brown, O., S69 (A8), S87 (K2)
Akcoren, Z., S79 (C8)
Ali, V., S79 (C8)
Alimova, Y.B., S61 (VII.1)
Allegaert, K., S82 (D2)
Ammouche, C., S60 (VI.4)
Andronikou, S., S95 (N8)
Ang, P., S78 (C5)
Antono, S.E., S99 (P9)
Arakawa, H., S65 (VII.10)
Atif, M.L., S72 (B2)
Aur´ilio, R.B., S73 (B5)
Avital, A., S58 (A6)
Bacal`a, G.P., S92 (M4)
Badellino, H., S89 (L1)
Badellino, H.A., S86 (J2)
Baena-Cagnani, C.E., S86 (J2), S89 (L1)
Baena-Cagnani, R., S86 (J2), S89 (L1)
Baghriche, M., S81 (C11), S94 (N4)
Balfour-Lynn, I.M., S44 (IV.4.2)
Ball, S., S94 (N5)
Ba, I.D., S73 (B3), S76 (B12)
Ba, M., S73 (B3), S76 (B12)
Baba, K., S96 (P1)
Baccal`a, G.P., S92 (M4)
Baccal`a, G.P., S92 (M4)
Bader, R., S87 (K1)
Barretto, M., S69 (A9)
Barrowman, N., S77 (C3), S85 (H1)
Bautista, M.S., S65 (VII.11)
Behbod, B., S64 (VII.8)
Beloncle, C., S80 (C9)
Benali Khoudja, N., S72 (B2)
Benhassa, F., S81 (C11)
Bentur, L., S85 (G3)
Berman, M., S68 (A6)
Berraies, A., S58 (VI.3)
Berteloot, L., S98 (P5)
Best, L., S85 (G3)
Beucher, J., S80 (C9), S85 (G4)
Beydon, N., S54 (V.2.3)
Blau, H., S78 (C4)
Blay, G., S99 (P8)
Boccon-Gibod, L., S98 (P5)
Bokonjic, D.R., S83 (E2)
Bonnemainson, E., S78 (C5)
Boonlarpaveecoke, C., S89 (K5)
Boufersaoui, A., S87 (K2)
Boukari, R., S72 (B2), S81 (C11), S82 (D4), S94 (N4)
Bounoua, V., S72 (B1)
Bousmina, S., S72 (B1)
Boussetta, Kh., S72 (B1)
Braudury, S., S77 (C3)
Breese, M., S78 (C6)
Breinh, J., S67 (A3)
Brini, L., S72 (B1)
Brockheimer, E., S78 (C4)
Buchwald, F., S97 (P4)
Bunnag, T., S76 (B13)
Bush, A., S2 (I.5), S13 (III.3.2), S45 (IV.5.1), S71 (A14)
Caggiano, S., S98 (P7)
Calvert, D., S67 (A3)
Campillo, B., S73 (B3), S76 (B12)
Canino, G., S67 (A3)
Canonica, G.W., S89 (K7), S91 (M2)
Cateletto, M., S70 (A11)
Celani, C., S98 (P7)
Cedroni, E., S67 (A3)
Cesnjavec, R., S90 (L4)
Chaisupmongkollarp, T., S70 (A10)
Chambellan, A., S80 (C9)
Chantepe, A., S78 (C5)
Chen, L-C., S89 (K7), S91 (M2)
Chen, K-H., S91 (M2)
Cheung, Y.F., S76 (B12)
Chodhari, R., S84 (G1)
Cinel, G., S62 (VII.3), S79 (C8)
Cingolani, A., S69 (A7), S72 (A16)
Cis´e, M.F., S73 (B3), S76 (B12)
Cloutier, M., S67 (A3)
Coghe, J., S79 (C7)
Cohen, S., S68 (A6)
Cohen-Cymberknoh, M., S63 (VII.5)
Colic, M., S83 (E2)
Colin, A., S1 (I.1), S54 (V.2.2), S88 (K4)
Consilvio, N.P., S69 (A7), S72 (A16)
Corpez, S.B., S65 (VII.11)
Costa, P.B., S74 (B9)
Costa, P.F.B.M., S75 (B10), S76 (B14), S92 (M4)
Coulomb, A., S98 (P5)
Cremoni, A., S69 (A9)
Croc, J.S., S86 (J2)
Croc, V.H., S86 (J2), S89 (L1)
Cruse, E., S99 (P9)
Custovic, A., S8 (I.3.1), S13 (II.2.2)
Czóvek, D., S62 (VII.2)

Dabatie, A., S85 (G4)
Dagan, R., S43 (IV.4.1)
Dagli Sezginer, E., S47 (IV.5.3)
Dai, Z-K., S89 (K7), S91 (M2)
Daoudi, Z., S82 (D4)
Darcel, F., S98 (P5)
Datta, S., S67 (A3)
Daveluy, A., S90 (L3)
de Blic, J., S98 (P5)
de Boeck, C., S74 (B8)
de Castro, G., S98 (P7)
de Leon, N.A., S65 (VII.11)
Debeer, A., S82 (D2)
Deignan, S., S83 (E3)
Della Volpe, A., S88 (K4)
Deneuveille, E., S80 (C9), S85 (G4)
Deprest, J., S82 (D2)
Deraznez, E., S68 (A6)
Deterding, R., S97 (P4)
Deutsch, G., S97 (P4)
Di Pillo, S., S69 (A7), S72 (A16)
Dieng, Y.D., S76 (B12)
Diot, P., S78 (C5)
Dittrich, S., S90 (L4)
Dogrul, D., S62 (VII.3), S79 (C8)
Dohna-Schwake, C., S86 (H2)
Donato, L., S60 (V1.4)
Doshi, D., S77 (C1)
Douriri, D., S81 (C11)
Drajal, D., S99 (P8)
Ducharme, F.M., S71 (II.5.2), S57 (VII.1)
Dumas De La Roque, E., S63 (VII.4)
Duse, M., S98 (P7)

Efrati, O., S63 (VII.6)
Eigen, H., S94 (N5)
El Ganzoury, M., S68 (A4)
El Husainy, A., S71 (A15)
El Khawaga, M., S71 (A15)
El Said, S., S71 (A13)
Elleau, C., S63 (VII.4)
Emura, S., S80 (C10)
Enaud, L., S98 (P5)