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Foreword

The International Congress of Pediatric Pulmonology (CIPP), the only global meeting entirely devoted to pediatric respiratory medicine, in its 18th edition, is being held this year in Tokyo (Chiba), Japan, June 27-30.

Over the period of more than two decades, CIPP has acquired a reputation among practicing pediatricians and clinical academics as the premiere forum for sharing new information in all areas of pediatric pulmonology. The congress is also known and appreciated for the excellent postgraduate courses and outstanding state of the art presentations, covering all topics in our field.

Through the continuing partnership with Pediatric Pulmonology, the abstracts of the contributions that will be presented in Tokyo will reach a wider audience. These presentations cover a broad range of pediatric respiratory disorders, such as interstitial lung diseases, sleep disordered breathing, respiratory infections (including tuberculosis), chronic suppurative lung diseases, poorly controlled asthma, neonatal lung diseases and their outcomes, with cutting edge information relevant to both clinical and academic communities.

As a collection, they reflect the global perspective of the Congress and the current developments in the field.

Giovanni A. Rossi, MD
President, CIPP XVIII

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Keynote Lecture

Macrolides – From Diffuse Pan-Bronchiolitis to CF and Beyond

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The term "macrolide" describes drugs with a macrocyclic lactone ring of twelve or more elements. The nonantimicrobial properties of macrolides were suspected as far back as the 1960s, however their dramatic clinical effectiveness in treating diffuse panbronchiolitis has served to extend their use to a number of chronic inflammatory diseases including cystic fibrosis, non-CF bronchiectasis, chronic obstructive pulmonary disease, and chronic rhinosinusitis. Macrolide antibiotics administered in subantimicrobial doses improve pulmonary function and decrease exacerbation frequency for persons with bronchiectasis or cystic fibrosis. Data also suggest a beneficial effect of macrolide antibiotics in the treatment of steroid-dependent (neutrophil dominant) asthma and chronic obstructive pulmonary disease.¹

The immunomodulatory effects of macrolides in patients with chronic inflammatory airway disease are independent of their antimicrobial properties and have been demonstrated in 14- and 15- (but not 16-) member macrolides that are devoid of antimicrobial activity. Immunomodulation, which differs from immunosuppression or anti-inflammation, is a nonlinear resetting of the immune response by modifying or regulating one or more functions of the immune system. We use the term immunomodulation to describe the downregulation of a hyperimmunity or hyperinflammation without impairing the normal immune or inflammatory response to defend against infection. Macrolides initially decrease, then increase, and have finally a sustained suppression of cytokine secretions from normal human bronchial epithelial cells through inhibition and activation of extracellular signal-regulated kinases (ERKs) and then reversibly retard cell proliferation probably through ERK. Macrolides are not anti-inflammatory but are true immunomodulators.²³

Consistent with this, macrolide antibiotics reduce mucin production as well as neutrophil migration by interfering with ERK signal transduction. Macrolides accumulate within cells, suggesting that they may associate with receptors or carriers responsible for the regulation of immune cell activities.⁵

Chronic macrolide use at low dosage as an immunomodulator drug will inevitably induce antimicrobial resistance. There are two principal forms of acquired macrolide resistance. Low level resistance or Mef, by far the most common, involves the activation of efflux pumps to drive the antibiotic out of the target cell. This can be overcome by higher doses of the drug and is reversible if antibiotic pressure is reversed. High level, or Erm, resistance involves an irreversible modification of the bacterial ribosome target. This is heritable and cannot be overcome by a higher concentration of drug.⁵ Other ERK inhibitors that can be administered as an aerosol are under development as novel therapy for neutrophil dominant airway disease.⁶

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Plenary Sessions

1 | The Impact of the Lung Microbiota on Mucosal Immunity

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With the advances of culture-independent techniques, we now know that microbes, which were present on this planet way before we were, have adapted to live in extreme conditions which were previously thought to be inhospitable. It is therefore no surprise that the lung is frequently exposed to microbes and can easily harbor a complex microbiota. After all, it is a moist mucosa, exposed to more than 10 thousand liters of air every day, and in direct communication with another mucosa that has one of the highest microbial burden in the body: the oral cavity. Therefore, it is time to eradicate the preconception of sterility of the lower airways which has been fostered by the rapid growth of data based on culture-independent methods. Recent recognition of this has led to improved understanding of the roles of these lower airway microbes to lung mucosal immunity. The lung has several features with ecological impact: a) lipid-rich biofilm, b) subjected to frequent episodic immigration of upper airway commensals through microaspiration; and c) is prepared to maintain low biomass, to facilitate oxygen and CO2 exchange.1 While most of our understanding of the role of microbes in host immunity comes from studying the gut microbiota, the special conditions present in the lung are key pressures that determine the composition of the lower airway microbiota and its interactions with the host.

Early development of the lung microbiota is a major determinant of lower airway mucosal immunity. There is now evidence that in early life, the lung microbiota affects the maturation of the host immunity, where a diverse microbial community signaled by enrichment with oral commensals contributes to the development of antimicrobial peptides and immunoglobulins.2 Delivery mode, C-section vs. vaginal, affects the composition of the lower airway microbiota in preterm births. Experimental preclinical data support that these changes are key to a host immune shift from a Th2-predominant phenotype to a Th1 phenotype. Germ-free mice models demonstrate that the lower airway microbiota is key to the development of immune tolerance to allergens, mechanisms likely triggered by induction of checkpoint inhibition.3 The upper airways are the gatekeepers of the microbes into the lower airways. Longitudinal studies of the upper airway microbiota have now shown that crosspollination of oral taxa (eg, Neisseria, Streptococcus, Prevotella and Fusobacterium) into the nasopharynx occurs prior and during respiratory tract infections in early childhood.4

In the adult lung, microaspiration commonly occurs and its rate is increased in many inflammatory respiratory diseases.5,6 The exposure of the lower airways to upper airway secretions can be identified using culture-independent techniques by the enrichment of oral anaerobes such as Prevotella, Veillonella and Streptococcus. In healthy individuals, this exposure contributes to a subclinical pro-inflammatory state characterized by increased inflammatory cells with a Th17 phenotype in bronchoalveolar lavage (BAL) and a blunted toll-like receptor (TLR) response of alveolar macrophages.7,8 Therefore, similar to the gut, specific lung microbiomes are associated with Th17 immunity.8 The molecular mechanisms determinant of this association still need to be elucidated, although there are multiple bacterial metabolites found in the lower airways that may exert immunomodulatory effects. For example, short chain fatty acids (SCFAs) are produced by oral anaerobes through fermentation.9 We have described that that high levels of SCFAs can be found in the lower airways associated with the enrichment of the lung microbiota enriched with oral anaerobes.10 Importantly, the levels of these SCFAs in the lower airways may affect the production of cytokines that are key to the innate immune response to pathogens such as IFN-γ and IL-17A.10 Taken together, these data support that the lung microbiota exerts an immune-modulatory role that may affect a subject’s lower airway immune tone and susceptibility to pathogens.

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2 | Viral and Bacterial Coinfections and Asthma

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Viruses such as respiratory syncytial virus (RSV) and rhinovirus (RV) are the major causes of acute wheezing illnesses in the first few years of life. Infections with these viruses are ubiquitous in childhood and many infections are associated with mild or even no respiratory symptoms. Longitudinal studies have demonstrated that more severe lower respiratory illnesses with RSV or RV are associated with an increased risk for developing childhood asthma. These relationships suggest that there are cofactors that influence the severity of virus-induced acute respiratory illness, and that those cofactors associated with more severe illnesses could also modify the subsequent risk of asthma.

Viral factors to consider include the species or subgroup of virus, which can affect viral virulence. For RSV, duplication in the region of the G attachment protein is associated with a greater likelihood of severe wheezing illness, and the severity of RSV-associated illness is related to the subsequent risk for asthma. RV are the pathogens most commonly associated with wheezing illnesses in children over the age of 1 to 2 years. Of the three species of RV, RV-A and RV-C types are more virulent and more often associated with acute wheezing illnesses compared to RV-B. RV-C infections and illnesses may be overrepresented in children with more severe wheezing illnesses, particularly in the first few years of life. When studied in cultures of differentiated airway epithelial cells, RV-A and RV-C replicate faster, cause more cellular damage and invoke a stronger cytokine response compared to RV-B.

Genetics of the host can also affect the clinical response to viral infection. For example, a polymorphism (rs6967330, C529Y) in the RV-C receptor, CDHR3, increases expression of this protein on the surface of airway epithelial cells. As a result, children with this polymorphism are more likely to develop RV-C infections and illnesses. This suggests the possibility that rs6967330 increases the risk of RV-C LRI, and that the resulting damage to airways could lead to remodeling and increased risk of asthma, especially in children who have multiple RV-C illnesses.

The airway microbiome is an important environmental cofactor for acute wheezing illnesses during the preschool years. In preschoolers participating in a birth cohort study in Copenhagen, detection of either pathogenic bacteria or common respiratory viruses in nasal secretions conferred a similar risk for wheezing illnesses. In addition, studies of airway bacteria during RSV infections suggest that more severe illnesses are associated with a combination of viral detection and a pathogen-dominated microbiome. These studies suggest that viruses and bacteria interact in the airway to modify the risk for developing respiratory illnesses.

To test this hypothesis, the temporal relationship between detection of viruses, bacteria and symptoms was studied in a group of over 300

| Figure 1 | Associations between detection of RV and bacterial pathogens with respiratory illness. Odds ratios were calculated for the presence of a symptomatic respiratory illness during infections that were associated with detection of a RV, a bacterial pathogen, or both. Abbreviations: H Flu, Haemophilus influenzae; Morax, Moraxella catarrhalis; and Strep, Streptococcus pneumoniae. Graphs drawn from data in reference 7 |
In the first few years of life, acute viral illnesses are also associated with changes in the airway microbiome and a transient expansion of bacterial pathogens. The combination of RSV with either *H. influenzae* or *S. pneumoniae* is associated with an enhanced inflammatory response, as assessed by transcriptomic analysis of peripheral blood cells. The long-term risk of developing childhood asthma may also be related to early colonization with bacterial pathogens. In the Children’s Asthma Study (CAS) in Perth, febrile wheezing illnesses, those associated with RV-C, and development of a microbiota with *S. pneumoniae* as a dominant organism were all significant risk factors for subsequent asthma. Another important host factor for developing asthma following acute viral wheezing illnesses in early childhood is allergy, and there may be interactions between allergic sensitization, viral illnesses and the microbiome. In CAS, establishment of upper airway microbial communities that are dominated by pathogens was associated with acute wheezing illnesses. In nonallergic children, wheezing illnesses tended to be transient, while children with allergic sensitization were more likely to develop persistent wheeze and early childhood asthma. 

In summary, there is increasing evidence that bacteria and viruses are both strongly related to respiratory illnesses during early life, and in school-aged children with or without asthma. Recent studies have provided insights about the nature of interactions between viruses, bacteria, host genetics and allergic sensitization with respect to asthma. The challenge that lies ahead is to translate these new findings, which are primarily derived from observational studies, into novel interventional strategies for the prevention of acute wheezing illnesses and asthma. Antibiotics are not likely to be the solution, given the increasing bacterial resistance to antimicrobials and concerns about deleterious effects of antibiotics on the microbiome. Further understanding of these relationships could lead to other strategies for the treatment or prevention of acute wheezing illnesses, and reduce the risk of childhood asthma.

**FIGURE 2** Associations between detection of RV and bacterial pathogens with moderate exacerbations of asthma. Odds ratios were calculated for the presence of an exacerbation of asthma during infections that were associated with detection of a RV, a bacterial pathogen, or both. Abbreviations: H Flu, Haemophilus influenzae; Morax, Moraxella catarrhalis; and Strep, Streptococcus pneumoniae. Graphs drawn from data in reference 7

children ages 4 to 12 years, and approximately half of the study subjects had asthma. Weekly samples of nasal secretions were obtained during the peak months for RV infections (April and September) and were analyzed for viral and bacterial respiratory pathogens by PCR. In these studies, detection of a virus was strongly associated with an increase in the detection rates and quantity of *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*. In addition, odds ratios for illnesses were greatest when both viral and bacterial pathogens were detected (Figure 1), and these same trends were also noted for moderate exacerbations of asthma (Figure 2). RV detected during this study were partially sequenced to determine viral type and species. As expected, RV-A and RV-C were most often associated with respiratory illnesses. It was also notable that infections with RV-A and RV-C (but not RV-B) were also significantly associated with greater detection of bacterial pathogens.

Microbiome structure was evaluated in a subset of these illnesses using 16S microbial genetics; bacteria detected during asymptomatic RV infections were compared to those detected during RV infections that progressed to exacerbations of asthma. During asymptomatic infections, detection of certain commensal bacteria (*Dolosigranulum*, *Corynebacterium*) were increased, while exacerbations were associated with reduced *Corynebacterium* and increased *Moraxella*. These findings suggest that the balance between commensal and pathogenic bacteria could influence the severity of airway symptoms and probability of exacerbations in children with asthma.

In CAS, establishment of upper airway microbial communities that are dominated by pathogens was associated with acute wheezing illnesses. In nonallergic children, wheezing illnesses tended to be transient, while children with allergic sensitization were more likely to develop persistent wheeze and early childhood asthma. In summary, there is increasing evidence that bacteria and viruses are both strongly related to respiratory illnesses during early life, and in school-aged children with or without asthma. Recent studies have provided insights about the nature of interactions between viruses, bacteria, host genetics and allergic sensitization with respect to asthma. The challenge that lies ahead is to translate these new findings, which are primarily derived from observational studies, into novel interventional strategies for the prevention of acute wheezing illnesses and asthma. Antibiotics are not likely to be the solution, given the increasing bacterial resistance to antimicrobials and concerns about deleterious effects of antibiotics on the microbiome. Further understanding of these relationships could lead to other strategies for the treatment or prevention of acute wheezing illnesses, and reduce the risk of childhood asthma.

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Bronchiectasis in the 21st Century: Diagnosis and Management

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The unmet need: Bronchiectasis had a declining incidence over the last century. However in the recent 15 years, the global resurgence of bronchiectasis in children and adults has been highlighted.1-3 Despite its increasing prevalence3 and its substantial impact on morbidity4 and mortality,4 bronchiectasis remains relatively under-researched. Critical knowledge gaps,1 especially in children, persist.2 The unmet needs of people with bronchiectasis are huge and there are few randomized controlled trials (RCTs).1,2,5 Indeed, the European Respiratory Society (ERS) deems bronchiectasis unrelated to cystic fibrosis (CF) as one of the most neglected lung diseases in clinical practice.

While the burden of bronchiectasis is known to be high in some settings (eg the prevalence among Indigenous Australians and Alaskan Indian children is 1 in every 63-68 children), it is often unappreciated that it is also an important chronic disease in mainstream settings in affluent countries;6 for example 40% increase in bronchiectasis prevalence over the last 10-years in the United Kingdom (UK).3 In Australasia, bronchiectasis is more common and more severe in Indigenous than nonindigenous patients, where the mortality gap exceeds 20-years.4 The paradigm: A paradigm for bronchiectasis development and its progression is internationally accepted.1,2 This paradigm is based on decades-old and more recent studies using new technology. It is framed around the notion that primary prevention of bronchiectasis is possible and the knowledge that early detection of causal conditions (eg hypogammaglobulinemia) substantially reduces the risk of the future development of bronchiectasis through early initiation of treatment and optimal care. In children, mild (ie when detected early) bronchiectasis is potentially reversible.1,2 Many factors influence progression of the illness, most of which are modifiable and represent potential intervention points. These factors (secondary prevention) include better clinical management and guideline implementation. Thus, prompt diagnosis and optimal management of bronchiectasis is particularly important in childhood, thereby allowing opportunities for its reversal and/or halting disease progression.1,2

Diagnosis: Prompt and accurate detection of bronchiectasis is pivotal when starting treatment to reverse early disease. Diagnosis requires clinical suspicion and objective tests and thus appropriate case ascertainment is important. The clinical findings of children with bronchiectasis, summarized in a recent review,6 varies considerably among global cohorts and would be dependent on disease severity. Chronic cough, the most consistent symptom of bronchiectasis, may be reported only intermittently (35-100%)6 as cough may resolve after treatment.7 Also, cough may be wet rather than productive in children, as young children usually do not expectorate. Symptoms of dyspnea and hemoptysis are generally rare in pediatric cohorts in high-income countries where bronchiectasis is generally diagnosed earlier (and hence milder disease). Cohorts based in low-income countries generally reported a higher prevalence of wheeze (up to 66%), hemoptysis (up to 41%), digital clubbing (up to 41%) compared to high-income countries outside of Indigenous settings.6 Other pointers include failure to thrive and
chest wall deformity (present in 45% and 95% of cohorts respectively),
recurrent protracted bacterial bronchitis and failure of
the wet/productive cough to respond to 4 weeks of antibiotics
(ORadj 20.9, 95%CI, 5.4-81.8). 

Objective diagnosis of bronchiectasis is based upon the pathog-
nomonic radiological finding of an increased broncho-arterial ratio
(BAR) on chest CT scans. 

The widely used BAR diagnostic threshold of 1.0 was derived several decades ago from adult studies
using now outdated CT protocols and applied to all ages, despite
large differences in mean BAR between young children and the
elderly. 

This approach limits the early detection of pediatric
bronchiectasis and the window of opportunity for its reversal.
While we have advocated using pediatric-specific criteria for bronchiectasis
diagnosis since 2008 (instead of adult-derived BAR > 1.0), this is still
not accepted universally and more studies in different cohorts are
required. Nevertheless, there are however robust reasons why a
pediatric derived cut-off are more appropriate than adult-derived.

In recent years, other techniques include MRI with or without
inhaled agents (eg hyperpolarized helium or xenon) that adds
information about gas exchange. 

Although there are reports that
MRI has a good correlation with CT scores, currently, MRI (compared
to chest CT) takes longer, is more expensive, and still nonideal for
assessing small airways morphology, required for diagnosing bronch-
ictasis.

Management: A myriad of heterogenous risk and/or etiological
factors may lead to bronchiectasis in children. 

While these factors vary among settings, they share a common thread of chronic cough
and recurrent acute exacerbations with persistent lower airway
infection/inflammation. Interrupting these processes as early as
possible is necessary to reverse and/or halt disease progression
and further tissue damage.

Effective clinical management reduces short and long term
morbidity associated with bronchiectasis. 

There is increasing evidence that intensive treatment of children who either have bronchiectasis, or who are at risk of developing severe broniec-
tasis, prevents poor lung function in adulthood. New approaches to
managing people with other chronic airway diseases, include
the concept of phenotypes and ‘treatable traits’, which we suggested for
pediatric bronchiectasis recently. These treatable traits overlap with
disease phenotypes, although this is yet to be consolidated in adults
with bronchiectasis and not yet clearly established in children.
Proposed pediatric bronchiectasis ‘pediatric treatable traits’ are
nonexclusive traits and can be subgrouped into ‘infection’, ‘inflam-
mation’, ‘co-morbidities’, ‘underlying disease’ and ‘generic modifiable
factors’. While they may be useful, clinical validation and more
knowledge is needed to understand how these concepts would
improve short-term clinical outcomes and long-term prognosis in
children with bronchiectasis.

Center management goals include: (a) optimizing postnatal lung
growth, (b) preventing premature respiratory decline, (c) optimizing
QoL, (d) minimizing exacerbations and, (e) preventing complications.
Ideally a team approach with incorporation of allied health expertise
(nursing, physiotherapy, nutritionist, social work) is used as this
model improves outcomes of chronic diseases.

While many options are available, there are few with high-level evidence data. Indeed,
with few RCTs in children with bronchiectasis, treatment recom-
mendations are based largely on expert opinion and extrapolation of
studies conducted in CF patients and in adults with bronchiectasis.

The possible dangers of some of these approaches were previously
highlighted.

Much more needs to be done to reduce the burden of
bronchiectasis and improve the lives of children with bronchiectasis
and their families, on all fronts from research, clinical care and
resource allocation. The field is a long way off in all fronts but there is
now more hope with recent RCTs that have focused on bronchiec-
tasis unrelated to CF.

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ABSTRACTS

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Sleep-disordered breathing (SDB) in childhood is an often missed diagnosis of great potential importance to a child’s healthy development, and is quite prevalent in pediatric pulmonary patients. In its earliest forms, SDB can be remarkably subtle in children, however prompt diagnosis may permit interventions before the emergence of important sequelae of this disorder including learning impairments, behavioral dysregulation, and the possible development of metabolic issues. Obstructive sleep apnea syndrome (OSAS) is the end-point of what may be a long cascade of maladaptation of the oropharyngeal airway over the course of infancy and childhood. Too often, it is only at the stage of frank OSAS that children are diagnosed and treatment is initiated. The signs and symptoms of pediatric SDB are almost invariably present much earlier, and can be readily identified by the prepared and astute clinician.

There are several conditions which are known to predispose patients to SDB and OSAS, and which therefore should prompt particular vigilance in the pediatric provider. Two broad categories include: a) prematurity, with a greater risk of SBD attending the most premature (in one study of 400 premature infants, 77% presented OSAS at 4 years of age); and b) syndromes impacting the synchondroses (ie the growth centers, including the intermaxillary suture) which remain active after birth until 13 to 15 years.1-3 Impairment of these centers causes abnormal orofacial development and may impact the bony structures supporting the upper-airway (UA), increasing the risk of UA collapse during sleep. These conditions are numerous and include genetic syndromes (neuromuscular diseases, connective tissue disorders, dental dysgenesis, etc.), and anatomic issues which impair the normal tongue movements against the nasal palate (short frenulum) or which impede nasal breathing.

Early in life, normal nasal breathing may be disrupted by anatomical problems including septal deviation and enlarged adenoids. Later, nasal allergies, chronic reflux, and repetitive upper-airway infections leading to tonsillar enlargement can contribute significantly. A skillfully-elicited patient history, combined with a mindfulness of the family’s broader history of sleep disorders, will guide an appropriately-focused physical examination, which includes an evaluation of the facial and oropharyngeal structure. Examination of the mouth and nose is critical, with particular attention given to the hard palate. The hard palate should have a width of at least 20 mm at birth (conveniently, this is about the width of the tongue depressor), and should widen as orofacial growth progresses over the first 2 years of life. This initial history examination may prompt further evaluation by the pediatric pulmonologist’s subspecialist colleagues, including otolaryngologists, allergists, and pediatric orthodontists.

Following a focused pediatric evaluation, informed by this understanding of oropharyngeal development, a nocturnal polysomnogram (PSG) should be performed, and should include the usual variables, incorporating measures of breathing (including nasal and oral airflow and thermistors, chest and abdominal movement, transcutaneous CO2, oximetry, etc.), electroencephalographic (to permit sleep staging and scoring of microarousals), electrocardiographic measurement, electromyographic measurements for muscle tone and movement, and body position accelerometry. In subtle cases, esophageal manometry (Pes) may be helpful; and in neuromuscular patients this may be augmented by the use of sternocleidomastoid or other accessory EMG leads.4

The core issue in the appropriate interpretation of the pediatric PSG is the recognition of the non-hypoxic SDB phenotype that is typical in children, and which presents much earlier than the classic adult phenomena of hypopneas and obstructions with oxygen desaturation. In particular, two variables are critical in the assessment of pediatric SDB: the percentage of nasal airflow-limitation during total sleep time (conservatively, a maximum of 20% of flow limitation during sleep can be considered acceptable), and the amount of mouth-breathing during sleep (mouth-breathing may be normally seen during around 5% of a patient’s sleep).4 In children, nocturnal hypoxemia due to SDB, in the absence of pulmonary disease, should prompt consideration for a long-un-treated anatomical problem.

Once the results of the clinical and polysomnographic evaluations are available, a decision on therapeutic approach may be considered. Specific treatments are always tailored to the patient’s particular findings: For example, aggressive allergy treatment with desensitization could be considered for significant nasal allergy and congestion. Often, pediatric patients will benefit tremendously from adenotonsillectomy.5 Some patients may require adjunctive surgical interventions including nasal turbinate ablation, septrinoplasty, or frenuloplasty.

We would note that frenuloplasty, with a goal of re-establishing the usual interface of the tongue and the roof of the mouth - key to development and maintenance of the normal palatal arch - is most effective when done within the first month of life. As a consequence, this issue must be anticipated when the parents have a personal history of sleep disordered breathing, narrow palate, or ankyloglossia. After this brief window, frenuloplasty alone is often not sufficient to attenuate the usual progression towards narrowing of the palate with diminishment of nasal breathing and impairment of normal orofacial development. In our practice, we advise that late frenuloplasty be paired with an intensive course of myofunctional therapy (MFT) to improve lingual range of motion and discourage the development of fibrous adhesion.

The biggest barrier to effective MFT is the difficulty of its practice in the very young child, and in older children poor adherence may limit its utility. In infants who are still bottle-fed, use of special orthopedic nipples which induce the infant to make a larger effort when sucking may help in the remodeling of the hard palate and the intermaxillary cartilage, however evidence is still lacking for this therapy despite a compelling proposed mechanism. In those cases where finances permit, the services of a trained myofunctional therapist, adherence to therapy and subsequent outcomes can be quite good, ideally with regular practice of the myofunctional exercises several times per week(Camacho:2017dp). Considering the difficulty of adherence to the consistent practice of MFT, so-called “passive MFT” via special dental devices, which function by
Orthodontic intervention treatment, specifically palatal expansion, is perhaps the most anatomically efficient treatment for the structural issues underlying pediatric sleep-disordered breathing. By widening the palate early through the use of simple maxillary expanders such as the Crozat appliance, the pliable intermaxillary suture may be stimulated, resulting in maxillary bone growth. This is best achieved through a pediatric orthodontist with sleep expertise. Parents must understand well the goals and usual trajectory of the treatment, including the likelihood that expansion will have to be repeated over time. As children grow older and the sutures fuse, often as early as 10 years of age, bone-to-bone expansion can be performed using a combination of minor surgery and orthodontia with trans-palatal expansion. It should be noted that aesthetic orthodontia, with a goal of merely straightening the teeth, rarely has any benefit in the treatment of SDB, and in many cases may exacerbate the issue by further narrowing a space-limited oral airway.

Positive airway pressure therapy (PAP) remains an important treatment approach for select patients. PAP can be deployed at any age, and is often useful as an interim or adjunctive treatment; for example, in-between staged orthodontic treatments. The major problem with PAP is the interface: nasal or full-face masks may negatively impact a child’s developing facial bones, causing midface hypoplasia and retrusion. In our clinic, the shortest time to observed abnormal maxillary retrusion was 8 months following initiation of daily PAP. Though modern interfaces geared towards the pediatric population may mitigate this effect, caution is warranted and any child placed on such treatment should be followed by an attentive orthodontist. Often, continuous positive-airway pressure (CPAP) therapy is not well-tolerated by children and adolescents, and bi-level therapy, which permits a greater degree of control over the delta between inspiratory and expiratory pressures, may be a better option independent of peak pressures. This is the case not only in children with cystic fibrosis, ciliary dysmotility, and other principally obstructive pulmonary diseases, but also in children with neuromuscular disorders or connective tissue disease.

Any child diagnosed with SDB should be followed at close and regular intervals by a sleep specialist. If polysomnographic testing normalizes after intervention, it is reasonable to repeat the PSG every two to 3 years until about age 15. At that time there is generally an enlargement of the soft tissues of the UA, presumably related to sex hormone changes, and an abnormal increase in airway resistance may occur.

The development of sleep-disordered breathing in children is a dynamic and often subtle process, which has its roots in the prenatal period and early infancy. Awareness of the myriad ways this disorder manifests in childhood and adolescence will permit earlier diagnosis and intervention, in many cases preventing the development of a maladaptive oropharyngeal airway and the more severe possible outcomes.

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**5 | Vaccines to Prevent Childhood Pneumonia: Impact on Child Health**

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Vaccines have been amongst the most successful public health interventions to reduce the burden of childhood pneumonia, under-5 mortality and improve child health. However, pneumonia remains the major single cause of mortality in children outside the neonatal period, accounting for approximately 900 000 deaths annually in children under 5 years.\(^1\)\(^2\) Further accumulating evidence suggests that pneumonia early in life may have long term effects on lung health by reducing lung function and setting a trajectory for the development of COPD or asthma.\(^3\) Prevention of pneumonia may therefore be an important strategy not only to improve child survival but also to reduce the prevalence of chronic non-communicable lung diseases in children and adults.

Advances in immunization against common pneumonia pathogens including measles, pertussis, *H. influenzae* type b (Hib) and pneumococcus [pneumococcal conjugate vaccines (PCV)] have resulted in important reductions in pneumonia-associated mortality, severity and incidence and have led to a changing spectrum of pneumonia from other pathogens.\(^4\) It is likely that even further reductions in pneumonia incidence, severity and mortality will occur as uptake and
accessibility to newer vaccines is strengthened. From 2000 to 2010, the incidence of childhood pneumonia decreased by approximately 25%, from 0.29 to 0.22 episodes per child year in low and middle income countries (LMICs). Similarly from 1990 to 2013, pneumonia-associated disability-adjusted life years (DALYs) decreased by 58%, from 186 million to 78 million.

Combined data from six studies of the effectiveness of Hib vaccine found a reduction of 18% in radiological pneumonia, of 6% in severe pneumonia and of 7% in pneumonia-associated mortality. Similarly, for PCV the estimated reduction was 29% in radiologically confirmed pneumonia, 11% in severe pneumonia and 18% in pneumonia-specific mortality. The protective effect of PCV has extended beyond the vaccinated group of children to those in older age groups who have not been vaccinated through reduction in nasopharyngeal carriage of disease-causing serotypes amongst vaccinated children. Consistent with this, PCV has also led to a substantial decline in hospitalization for adult pneumonia by reducing circulating pneumonia causing pneumococci serotypes. Widespread PCV immunization of infants has led to a dramatic decline in the rates of hospitalization for pneumonia in adults, especially the elderly. These reductions have also led to reductions in antibiotic-resistant pneumococcal disease as many resistant serotypes are contained in 13-valent PCV. Replacement disease, with non-vaccine serotypes due to an increase in non-vaccine serotype disease, requires ongoing surveillance as widespread coverage with PCV13 is attained in communities.

PCV has also been associated with reduction in hospitalization for viral-associated pneumonia, suggesting that viral-pneumococcal interactions may result in more severe disease resulting in hospitalization. A post-hoc analysis of the South African PCV9 vaccination study found a 32% lower hospitalization rate for pneumonia episodes associated with respiratory viruses in vaccinated children. This has been supported by data from high income countries, such as the USA where a 41%-50% reduction in influenza virus-attributable pneumonia hospitalization was reported for every 10% increment in childhood PCV immunization in the USA.

Recently there has been a resurgence in pertussis pneumonia in children possibly due to lack of immunization, waning protection following acellular pertussis vaccination and adult cases serving as a reservoir for childhood immunization. Strategies to reduce this may include ensuring all children complete their primary immunization, immunization of pregnant women or booster immunization of adolescents or adults. However, even in low or middle income settings with high coverage for the 13-valent PCV, Hib and pertussis, the incidence of pneumonia remains high especially in the first 6 months of life, and other pathogens must be considered. In areas of high TB prevalence, M. tuberculosis has been associated with acute pneumonia in children, with culture-confirmed disease occurring in approximately 7%-8% of cases. The role of mixed infections is increasingly being appreciated, associated with severe disease. Globally, RSV is a predominant pathogen particularly in infants.

Currently there is substantial progress in developing new strategies to prevent RSV, primarily development of new RSV vaccines as well as of long acting monoclonal antibodies. These include RSV fusion (F) glycoprotein subunit vaccines for maternal immunization, live-attenuated RSV and adenovirus-vectored RSV for infant immunization, and RSV F monoclonal antibody with extended half-life for neonatal or seasonal infant immunization. Several studies are underway.

Immunization of pregnant women to protect against pneumonia in the first 3 months of life is gaining prominence as a potential effective strategy for pathogens such as pertussis, influenza and RSV. A randomized controlled trial of influenza immunization of pregnant women reported a vaccine efficacy of approximately 50% amongst immunized women and similar reductions in infants under 6 months of age for influenza proven infection. A Phase 3 study of RSV subunit vaccine in pregnant women has recently been completed with results imminent.

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The introduction of home Noninvasive Ventilators (NIV) has significantly enhanced respiratory management in children with sleep-related disordered breathing and chronic respiratory failure, and has shown evidence of clinical and psychosocial benefits as well as a substantial increase in survival in some subgroups. The use of NIV in children has significantly increased in recent years.

From its initial introduction into practice as care for patients with neuromuscular disorders in the 1990s, home NIV is now a well-established standard treatment for patients with neuromuscular disorders (NMDs) and associated sleep-related disorders of breathing or diurnal respiratory failure in many countries. NIV has been shown to improve nocturnal hypoxemia, improve hypercapnic ventilatory response, improve sleep quality and architecture, reduce morbidity, improve quality of life and increase longevity.

Apart from the use in patients with upper airway obstructions and NMDs, the use of NIV for several other purposes has gained increasing attention, for example congenital central hypoventilation syndrome (CCHS), bronchiolitis obliterans. Several studies have reported use of NIV in CCHS infants and young children, and NIV decreases the complexity of the home-care program compared with ventilation via tracheostomy. The use of home NIV in children with chronic respiratory insufficiency avoids long-term hospitalization with better qualities of life for children as well as reducing the cost of medical care.

Home NIV can be provided by continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BPAP) or heated humidified high flow (HHHF) or negative pressure ventilator. A negative pressure ventilator is a useful modality that is rarely utilized now because of the cumbersome interface, either a chamber or cuirass or poncho. CPAP or HHHF are primarily indicated for those with obstructive sleep apnea syndrome (OSAS) with or without upper airway obstruction during wakefulness and those with moderate chronic respiratory insufficiency. For those with severe chronic respiratory insufficiency, bi-level pressure support, i.e. expiratory pressure to maintain functional residual capacity and to prevent collapse of the upper airway and inspiratory pressure to provide gas exchange, is often needed. For home NIV to be successful, the following areas need to be addressed: 1) correct settings of pressure and humidifier; 2) suitable interface; 3) establishment of tolerance; 4) ensuring adherence.

Ideally, correct pressure levels are obtained in the sleep laboratory with polysomnography monitoring. If this is not available, auto-CPAP or auto-BPAP is used for those with only OSAS with the following outcome measures: 1) the apnea-hypopnea index as recorded by the machine, 2) the desaturation index from overnight oximetry and 3) the relief of daytime symptoms. Different interfaces are available. The commonest is nasal mask which is appropriate for more than 90% of children in the author’s practice. Other interfaces include oro-nasal mask and nasal pillow. If significant unintended air leak, i.e. total leakage minus the intended leakage for the given pressure and interface, occurs, the site of leakage is often the mouth. If it is confirmed from observation, a chin strap should be provided to close the mouth so as to allow adequate pressure to be administered. A heated humidifier is essential even in countries with high humidity in view of the high air flow provided by the machine to prevent excessive irritation of the airway mucosa, a guaranteed reason for non-adherence.

Conditioning is important to achieve tolerance by the child and this is achieved by a graded step-up of exposure (Table 1). The conditioning usually takes 2 to 3 sessions of training by an experienced pediatric nurse. After NIV is started at home, a proactive approach to look for problems is important. Hence, the respiratory nurse should speak with the parents by phone or other means 1 day, 1 week and 1 month after the first night of NIV to look for symptoms of intolerance, for example skin erythema, excessive tearing, lack of improvement of symptoms. Data should be downloaded from the NIV machine after 1 week of usage. Adherence, AHI, leakage and pressure-limited ventilation should be analyzed by the attending pediatrician who will adjust the settings to achieve optimal ventilator support for the patient. Having established a good adherence to home NIV, the child and parents should be seen in a home NIV clinic by the respiratory pediatrician and the respiratory nurse every three to 6 months for fine adjustment of support level and complications of long term NIV such as mid-face hypoplasia. The aforementioned steps should be set out in a structured program with detailed methodology.

Evidence has shown that the chronic use of tight-fitting masks may affect facial growth resulting in mid-face hypoplasia. This finding seems more likely when the child is started on NIV before the age of 8 years and has weak facial muscles. Hence, it is advisable to alternate the interface between nasal mask and nasal pillow. Furthermore, the interface should not be too tight. One way to look for excessive tightness is monitoring the unintended leakage. The harness should be loosened up if the unintended leakage is less than 5 L/min. Facial and oral muscle exercise training as suggested in orofacial myofunctional therapy is recommended for children who commence NIV from infancy. The other option is the use of reverse headgear designed to relieve the pressure on the mid-face with support from the forehead and the chin. Regular monitoring of...
mid-face growth is important to allow timely intervention by Noninvasive methods.

Provision of a successful ventilation support at home requires a close collaboration of pediatric respirologists, pediatric respiratory nurses and home ventilator service providers with a structured program that sets out the objectives and the detailed methodology to achieve the stated objectives. With a successful home NIV program, children could enjoy home life even if they have chronic respiratory insufficiency/failure.

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7 Management of Pre-School Wheeze

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Worldwide, admissions for pre-school wheeze are a significant health burden. Morbidity and even mortality are common, and treatment strategies are ineffective compared with school age, atopic eosinophilic asthma.

Is the diagnosis correct? The first step is a thorough history and examination; many preschoolers will correctly be managed without any investigations. The term ‘wheeze’ is used to describe numerous noises, not just a polyphonic, whistling expiratory noise, and it is essential to determine what the family are describing: a video-questionnaire may help. After history and examination, the child is placed in one of four categories (1) normal child +/- parental anxiety – and normal child is the hardest diagnosis of all to make; (2) a major underlying illness, such as tuberculosis or cystic fibrosis (differential diagnosis will depend on your geographical area); (3) one of the ‘asthmas’; and again the phenotype may vary across the world, and (4) minor morbidity such as allergic rhinitis or gastroesophageal reflux which may mimic or exacerbate the asthmas. The next steps depend on the category into which the child is placed.

If history and physical examination suggests that the child has one of the ‘asthmas’, the second aim of the history is to determine if the infant has pure episodic viral wheeze or multiple trigger wheeze. The child’s category may change over time and with treatment, and categorization does depend on accurate symptom perception by the parents, but if symptoms are truly intermittent, then intermittent therapy is appropriate.

Management of chronic symptoms: The first step, before any prescription is written, is to ensure the environment is optimal, reducing as far as possible indoor pollution (tobacco, e-cigarettes,
biomass fuels; we all need to be aware of what our local issues in terms of indoor and outdoor are. It is also essential that pediatricians be advocates for clean air for children, because we cannot get clean air without engaging politicians.

Minor intermittent symptoms may legitimately be treated with short-acting inhaled β-2 agonists or anticholinergics via a mask and spacer. It is well known that inhaled corticosteroids (ICS) if instituted early do not reduce the risk of progression to school age, atopic eosinophilic asthma, so treatment can be purely symptomatic. If symptom severity and frequency is such that this approach is not effective, then regular daily therapy should be considered.

The biggest recent advance has been the first attempt to introduce personalized medicine into the treatment of pre-school wheeze. The Lancet commission highlighted that the term asthma should be used as the start, not the end of the patient journey; and in the pre-school years, the question should be not ‘at what age can I diagnose asthma?’ but ‘Does this child have either or both of the treatable airway traits of eosinophilic airway inflammation or bronchodilator responsive variable airflow obstruction?’. The INFANT investigators attempted to answer the first question in a three-way, cross-over comparison of regular ICS, intermittent ICS, and regular leukotriene receptor antagonists. Regular ICS was the preferred therapy, but only in those with a peripheral blood eosinophil count > 300/μl and aeroallergen sensitization. It should be noted that the blood eosinophil count analyses were post-hoc, and so need confirmation, and in a developed world setting. Really importantly, the significance of a raised blood eosinophil count may be very different in an area with a high parasite burden. However, it would seem reasonable to withhold ICS from pre-school children with a normal peripheral blood eosinophil count in any context.

However, in many contexts, a more pragmatic approach of a blind therapeutic trial of ICS may have to be undertaken. In that case, a three-step protocol is wise. Step 1 is to institute ICS at a dose of no higher than beclomethasone 200 μg twice daily using an appropriate spacer. A high dose is chosen for the trial, on the basis that if a lower dose were to be chosen, time might be wasted by escalating to a higher dose, before concluding that the symptoms are steroid resistant. Response is (arbitrarily) assessed at 6 to 8 weeks, and, whatever the child’s symptoms at that point, treatment is stopped. If there is no response, there is no point continuing with an ineffective therapy. If symptoms have remitted, it is at this stage unclear whether this is spontaneous or as a result of treatment. This is resolved by a period of observation; if the child relapses on stopping treatment, then ICS therapy is re-instituted at the lowest dose needed to control symptoms. This strategy means that children will not be wrongly labeled as asthmatic and committed to long-term therapy because of transient symptoms.

Prevention of acute attacks: This is an area of need; attacks are associated with greatly impaired quality of life and adverse future lung function trajectories. We know that ICS are not effective at reducing acute attacks of pre-school wheeze, largely because, unlike in school age asthma where ICS are very effective in reducing attack frequency, there is no background of type 2 inflammation. All we can currently do is modify risk by ensuring annual influenza immunization, optimizing the environment and ensuring there is a treatment plan in place.

Treatment of acute attacks: Unlike in school age asthma, oral prednisolone is not indicated in acute, pre-school wheeze unless the attack is very severe. If the child is well enough to stay in the community, prednisolone is not needed, nor is it necessary for the vast majority of pre-schoolers admitted to hospital. I reserve prednisolone for pre-schoolers who are deteriorating to the point of high dependency care or have a history of severe attacks. In terms of intermittent ICS, very high doses (1.5 mg/day fluticasone equivalent) may reduce severity of attacks, but with a burden of side-effects, and I would not go higher than fluticasone equivalent 150 mcg bd, again discontinuing this strategy if it is ineffective. Montelukast, a cysteinyl leukotriene antagonist, was initially thought to be an effective treatment for acute pre-school wheeze, but unfortunately recent very large studies failed to show any benefit for either intermittent or continuous montelukast therapy in this age-group, and this therapy cannot be recommended. Two studies of azithromycin in children with either acute wheeze or troublesome respiratory symptoms showed evidence of benefit, but unfortunately a third study failed to show benefit. There is also the concern of bacterial macrolide resistance if they are widely prescribed. On current evidence, it would be reasonable to treat pre-schoolers with a history of really severe attacks of wheeze with azithromycin when they are in the throes of another such attack to try to prevent progression to the need for Intensive Care, but also not to persist with this strategy if it is ineffective.

The future? We currently rely on phenotyping by clinical history, for the most part. We recently studied the relationship between symptom patterns and bronchoalveolar lavage inflammation and microbiome. Worryingly, there was no correlation between clinical and pathological phenotypes. Instead, cluster analysis showed that there was a dysbiotic, Moraxella-rich cluster which was associated with airway neutrophilia, and a second, mixed-microbiota cluster with macrophages and lymphocytes in the lavage. This leads to the intriguing speculation that at least some pre-school wheezers may respond to antibiotics targeted against Moraxella, although this approach cannot be recommended without further data.

It is known that respiratory epithelial function is abnormal in children with asthma, for example reduced interferon secretion in response to viruses, although whether this is the primary abnormality in asthma, or secondary to repeated cycles of infection and treatment, is unclear. We are currently 3 years into a five-year study which will determine the developmental biology of epithelial and immune development, and how this relates to the microbiome. The aim is to determine the endotypes leading from apparently normal baby at birth to pre-school wheeze to atopic, allergic asthma, and hence determine biomarkers of risk and ultimately, to intervene...
to reverse this process. However, this will not be achieved without better knowledge of the relevant pathways. However, the differences in the prevalence of wheeze and atopy in genetically almost identical populations who have very different exposures, shows that reduction in risk is absolutely possible.

Summary and Conclusions: The current state of knowledge of preschool wheeze is woeful. We do not know how to prevent it, we do not know how to predict those who are at high risk of going on to develop atopic, eosinophilic asthma at school age, and we have no treatment strategies to apply even if we could predict a high risk group accurately. We do not know the endotypes of the disease, and we have very few effective treatment strategies, and indeed our therapeutic efforts are primitive. This is a rich area for future research; we must do better, both for the sake of preventing present symptoms and also improving long-term lung disease.

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8 Cell Sheet Engineering for Clinical Applications

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Introduction: Our research has been focused on cell sheet preparation, manipulation and transplantation to treat difficult diseases. For our goal, we first developed unique tissue culture dishes in which their inner芙蓉表面积 was modified and equipped with the temperature-responsive polymer poly(N-isopropylacrylamide) (PIPAAm). The “intelligent surface” of these dishes possessed the hydrophobicity similar to regular tissue culture polystyrene dishes at 37°C. However, the surface reversibly became hydrophilic at a lower temperature (lower than 32°C) and spontaneously released the cultured cells as a single layer without the need for trypsin or EDTA, thus leaving the cell layer with the extracellular matrix (ECM) intact. All the cultured confluent cells were harvested as a single contiguous cell sheet from
the temperature-responsive culture dishes and readily applied to other biological and nonbiological surfaces due to the ECM.\textsuperscript{1,2}

As shown in Figure 1, the harvested cell sheet from the intelligent surface maintains both cell surface proteins and cell to cell binding; on the contrary, when enzymes are used to harvest cultured cells, adhesive proteins and surface proteins are disrupted. In case of enzyme treatment, the function and surface protein structure of harvested cells are dramatically decreased.

**Cell Sheet Harvesting and Clinical Applications:** Cell sheet applications are categorized based on the manner of therapeutic actions as shown in Figure 2. The A type is a substitution of injured tissue with cell sheet (Figure 2).

After patients have lost stem cells from the transparent corneal epithelium due to alkali injury, opaque conjunctiva starts to cover the surface instead of corneal epithelium, leading to a loss of the patient’s eyesight. To treat stem cell-deficient corneal disease, one effective therapy is cornea transplantation. However, cornea transplantation is limited by the number of available donors. We developed autologous oral mucosal cell sheets from small-sized tissue specimens, and our collaborator, K. Nishida, transplanted them to these patients as a cell sheet patch following surgical conjunctiva removal.\textsuperscript{3} Transplantation of oral mucosal cell sheets recovered transparency comparable to human corneal epithelium and improved vision capabilities.

Although endoscopic submucosal dissection for esophageal epithelial cancer is effective, ablation of a large area often induces stenosis. Ohki et al\textsuperscript{4} transplanted autologous oral mucosal cell sheets to the ablation area of the esophagus. Remarkable suppression of stenosis and rapid healing of the surface of the esophagus was observed. Ten patients have been treated at the Tokyo Women’s Medical University Hospital. In addition, collaborative clinical studies have been conducted for the treatment of 10 patients at the Nagasaki University Hospital\textsuperscript{5} and for 10 patients with Barrett’s esophagus at the Karolinska Institute in Sweden.\textsuperscript{6}

Periodontal ligament (PL) cells from wisdom teeth were utilized for making PL cell sheets to treat periodontitis patients.\textsuperscript{7} Autologous PL cell sheet transplantation successfully treated ten patients, demonstrating stabilization at the tissue-teeth interface and regeneration of the surrounding bone. From 2018, T. Iwata has initiated allogenic PL cell sheet therapy in the Tokyo Women’s Medical University Hospital.

M. Sato et al have succeeded in treating osteoarthritis of eight patients’ knees using three-layered autologous chondrocyte sheets.\textsuperscript{8} Positive staining of collagen II and Safranin O on transplanted cell sheet cartilage tissues was confirmed. The evidence clearly showed that engineered cell sheet cartilage tissues form a hyaline structure such as that of native cartilage. They have initiated allogenic cell sheet therapy since 2017.

When a pearl tumor near the tympanic membrane is removed by surgery, unfavorable adhesion often occurs. H. Kojima et al have succeeded to prevent tympanic membrane adhesion by transplantation of autologous nasal mucosal cell sheets to the wall of the middle ear chamber.\textsuperscript{9}

In the case of B type cell sheet therapy (Figure 2), Y. Sawa et al have treated severe heart failure patients using myoblast sheets. In 2007, they implanted a left ventricular assist device (LVAD) for a patient suffering from cardiomyopathy. They failed to find a heart donor for the patient for one and half years before the patient decided to accept autologous cell sheet tissue engineering therapy. Myoblast sheets from the patient’s own muscle tissue were fabricated in a clean room and transplanted to the heart wall directly. Constant and long-term release of cytokines, HGF, FGF, VEGF and other factors from the transplanted cell sheets improved heart functions by recruiting stem cells from blood circulation which induced microcapillarized-heart tissue growth. After 3 months, the LVAD was removed and 7 months later the patient had recovered to the point of release from constant primary care. Since then, Y. Sawa et al have treated more than 40 patients and discussed the safety and efficacy of autologous myoblast sheet regenerative therapy. Terumo Co. has completed clinical trials and achieved conditional approval for market in Japan from the Ministry of Health, Labor and Welfare, Japan, in 2015.
For B type treatment, the advantage of cell sheets is the ability to transplant to the target site while maintaining high viability of the cells. From this perspective, chronic and genetic diseases of the liver, pancreas, and kidney are expected to be treatable by cell sheet tissue engineering technology.

As cell sheets easily form layered structures, three dimensional layered tissues are designed using cell sheets, as shown in Type C. We have succeeded in preparing synchronized beating tissues made from multi-layered cardiomyocytes.

Conclusions: A temperature-responsive cell culture surface is developed as a platform of cell sheet tissue engineering. The temperature-responsive cell culture surface enables the creation of transplantable 2D and 3D cell sheet tissues. Cell sheet-based tissue engineering has been successfully applied for several treatments in clinical settings. In the next generations of cell sheet-based tissue engineering, the creation of 3D engineered organs becomes the foremost issue (Figure 2). To achieve this, mass production of human parenchymal cells and vascularization within 3D tissues are required. Utility of bioreactors for the differentiation of induced pluripotent stem (iPS) cells into parenchymal cells such as human cardiomyocytes is expected to be a promising solution. The induction of vascularization within 3D thick tissues has been achieved with a combination of bioreactor and growth factor culture. Inevitably, the integration of various technologies will lead to the creation of functional 3D organs.

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9 | Gene-Environment Interactions at the Beginning of Asthma

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The identification in two genome-wide association studies (GWAS) by Moffatt et al1,2 of the so-called ORMDL3 asthma locus in chromosome 17q21, which has now been replicated by several other GWAS, including a large, multiancestry study,3 is a major scientific accomplishment and is certain to shed new light on the pathogenesis of the disease. It has now been established that the 17q21 region may contain two or three separate loci3 that are independently associated with asthma, with one closer to the ORMDL3 gene in the 3’ end of the region showing a stronger association with asthma, whereas a second one in the 5’ end showing no specific age relation. Little was known initially about any of the genes (eg, ORMDL3 and GSDMB in the 3’ end) showing single nucleotide polymorphisms (SNPs) that are strongly associated with childhood asthma. A study by Caliskan et al4 contributed important insights into the potential mechanisms that explain the association between SNPs in the 5’ end of the locus, and asthma. The study showed that, in two birth cohorts in the US and Denmark, one of these SNPs (rs7216389 in ORMDL3) was strongly associated with the risk of having wheezing illnesses attributable to the human rhinovirus (HRV) during the first 3 years of life. This same SNP was associated with an increased risk for asthma during the school years but only among subjects who had HRV-related wheezing in early life. These results strongly suggest a gene-by-rhinovirus interaction in the determination of asthma

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risk by this locus. The authors did show increased expression of several genes in this locus among carriers of the risk allele for rs7216389, and showed that peripheral blood mononuclear cells stimulated with HRV showed increased expression of these same genes when compared with unstimulated cells. However, there was no association between rs7216389 and the relative increase in expression of these genes in stimulated and unstimulated cells. Recent in-vitro studies using A549 human lung epithelial cells showed that silencing of the ORMDL3 gene strongly reduced expression of the HRV receptor ICAM1. These results suggest that ORMDL3 may be involved in the regulation of the receptor system for HRV. It is thus plausible to surmise the pathway through which HRV may predispose for the development of asthma: risk alleles in the ORMDL3 locus increase the severity of HRV wheezing in early life and, by this mechanism, predispose for the development of airway remodeling and airflow limitation, which are major risk factors for subsequent asthma.

Although these developments open encouraging new avenues of research, major issues remain unresolved. A major conundrum is the fact that the prevalence of asthma increased markedly in the last decades and until 2010, with apparent stabilization thereafter, whereas HRV infections have always been very common in early life, and the risk alleles for asthma in the "ORMDL3" locus are also very common in the population. It is difficult to accept that two risk factors, one genetic and one environmental, with consistent and interacting associations with childhood asthma, could have played no role in determining the "asthma epidemic". Work performed in rural communities in Europe sheds new light on this puzzle. Loss et al followed 983 children from birth up to age 6 years. They replicated the interaction between rs7216389 and wheezing illnesses, in their case in the first year of life, as determinants of asthma at the age of 6 years. They also showed however, that the at-risk alleles for early wheezing illnesses and asthma were protective against wheezing illnesses in the first year of life in children more heavily exposed to animal sheds, as compared to those unexposed. These findings provide the tantalizing hypothesis that decreased exposure to environmental microbial products during the last decades may have eliminated the protection of against the ill effects of HRV infection in early life in carriers of risk alleles for SNPs in the ORMDL3 locus. This locus would thus be subject to a double interaction; in the absence of the blocking effects of microbial exposure (as in the studies by Caliskan et al in urban areas), carriers of the at-risk alleles show increased susceptibility to acute lower respiratory illnesses due to HRV and increased risk for subsequent asthma. Carriers of the non-risk alleles show no such susceptibility, and the presence or absence of microbial exposure is likely irrelevant as determinant of risk for asthma. This scenario is still hypothetical, and the molecular mechanisms involved need to be fully elucidated. However, they offer the potential for an allele-specific prevention strategy of asthma: it is plausible to surmise that live bacteria, or their products, may be specifically administered to young children whose risk for asthma is defined by the presence of the risk alleles for SNPs in the ORMDL3 locus.

These intricate gene-by-environment interactions involving the most highly replicated locus for asthma in the whole genome point to the complexity of the genetic determination of asthma and, most likely, of all complex diseases. It is quite likely that, had asthma GWAS been done mostly in farming populations, the strong associations identified in chromosome 17q21 in urban populations might not have been present or might not have been replicated as consistently. Multidisciplinary approaches, with expertise in genetic susceptibility and environmental exposures that increase risk and protect against asthma, and of the molecular mechanisms that underlie these interactions, will be essential to advance in the quest to prevent childhood asthma before it ever starts.

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Background: Hereditary interstitial lung disease (HILD) is a disease entity caused by a genetic disorder including a congenital form of pulmonary alveolar proteinosis (PAP)(CPAP) diagnosed based on bronchoalveolar lavage (BAL) and/or lung histology, interstitial pneumonitis (IP) based on lung histology.1 Almost all patients with alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) show lethal pulmonary hypertension. Patients with HILD often show a severe and progressive oxygenation disorder at birth or in early childhood. However, some patients show respiratory symptoms for the first time as adults. Widespread ground glass opacification (GGO) and individually irregular consolidation on the dependent side or geographic opacification on high-resolution computed tomography (CT) are helpful for suspicion of HILD. Known genetic abnormalities include mutations in SFTPB for surfactant protein (SP)-B deficiency, SFTPC for SP-C abnormality, ABCA3 for ATP-binding cassette A3 (ABCA3) deficiency, and NKX2.1 for thyroid transcription factor-1 (TTF-1) dysfunction among infants with PAP or IP, and FOXF1 among infants with ACDMPV. Mutations in genes encoding colony-stimulating factor (GM-CSF) receptors (CSF2RA and CSF2RB) are also associated with CPAP in infants and adults.2 Mutations in GATA2 are associated with monocytopenia and mycobacterial infection (MonoMAC) syndrome, which shows a broad spectrum of clinical manifestations, including PAP.3

Methods: We launched a system to aid Japanese neonatologists and pediatricians to search for genetic causes of unexplained respiratory failure in February 2011.4,5 Up to October 2018, we performed sequencing analyses of SFTPB, SFTPC, ABCA3, FOXF1, NKX2.1, GATA2, CSF2RA and CSF2RB with DNA specimens from 171 patients. This study was approved by the local ethics committees and all analyses were performed with written informed consent from parents. We could not find causative variations in some patients with pathologically-proven PAP or IP. We performed whole exome sequencing analysis (WES) in a family including three affected siblings by CPAP with hypogammaglobulinemia without mutations in known causative genes.

Results: Causative genetic variations were detected in 33 patients, 7 CPCP cases, 13 IP cases and 13 ACDMPV cases. The variations were found in SFTPC (12 cases), ABCA3 (5 cases), NKX2.1 (3 cases), and FOXF1 (8 cases of mutations and 5 cases of copy number variations). We found no pathogenic variations in SFTPB, GATA2, CSF2RA or CSF2RB. One child PAP patient had autoantibodies against GM-CSF. As a result of WES analysis, we detected a potentially causative variation of OAS1 (c.227 C > T, p.Ala76Val) in three affected siblings in a family.5 Deep sequence analysis with next-generation sequencing indicated 3.81% mosaicism of this variation in DNA from their mother’s peripheral blood leukocytes, suggesting that PAP observed in this family could be inherited as an autosomal dominant trait from the mother. We identified two additional de novo heterozygous missense variations of OAS1 in two unrelated sporadic affected individuals also manifesting infantile-onset PAP with hypogammaglobulinemia (c.326 G > A, p.Cys109Tyr and c.592 C > G, p.Leu198Val). PAP in the two sporadic affected individuals resolved after hematopoietic stem cell transplantation, indicating that OAS1 dysfunction was associated with impaired surfactant catabolism due to the defects in alveolar macrophages.

Conclusion: Distribution of causative genetic variations for HILD in Japanese children is considered different from that in Western countries. HILD due to variations with autosomal recessive traits is relatively rare in Japan. OAS1 dysfunction due to OAS1 mutation might be a novel type of primary immune deficiency.

REFERENCES


2 | Value of Imaging

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Radiology plays a vital role in the diagnosis and management of pediatric interstitial lung disease (ILD). While chest radiographs (CXR) are insensitive and nonspecific, chest computed tomography (CT) is highly sensitive and recommended as the initial modality for the diagnosis of ILD in children. ILD is highly unlikely in the setting of a normal CT scan, and an abnormal CT scan may permit a specific diagnosis or guide further diagnostic testing.

Magnetic resonance (MR) imaging does not involve exposure to ionizing radiation, unlike CT, and shows high sensitivity and agreement with CT for the finding of consolidation. Hyperpolarized gas MR can be used to assess regional lung ventilation, and MR elastography can provide information on regional lung stiffness. However, MR is insensitive for detection of common findings in ILD such as ground-glass opacities and septal thickening. This limitation, along with the need for sedation in young children, currently limits MR to primarily an investigational role in the evaluation of pediatric ILD.

Disorders in which a specific diagnosis can be made without biopsy on the basis of chest CT findings in the appropriate clinical context include bronchiolitis obliterans (BO) and neuroendocrine cell hyperplasia of infancy (NEHI)/persistent tachypnea of infancy (PTI), with the former characterized by bronchiectasis and mosaic attenuation with air trapping and the latter characterized by hyperinflation with ground-glass opacities of the right middle lobe, lingula, paramediastinal and infrahilar regions. A presumptive diagnosis of pleuroparenchymal fibroelastosis (PPFE) can also be made in the appropriate clinical context on the basis of characteristic CT findings (upper lobe predominant peripheral septal and pleural thickening, platythorax), helping avoid pneumothorax and refractory air leak from an unnecessary biopsy in this disorder. Certain other disorders can be strongly suspected on the basis of CT findings, including Langerhans cell histiocytosis (multiple irregularly-shaped cysts and nodules), hypersensitivity pneumonitis (multiple centrilobular opacities with air trapping), and lung disease related to surfactant mutations (diffuse ground-glass opacities, crazy-paving, cysts with chronicity) or filamin A gene mutations (hyperinflation, atelectasis, airway malacia, ascending aorta dilation), thereby directing confirmatory testing and often averting the need for a lung biopsy in these conditions. On the contrary, clinical presentation and CT findings compatible with pulmonary hemorrhage may indicate the need for a lung biopsy to distinguish pulmonary capillaritis from idiopathic pulmonary hemosiderosis, since the former often requires prolonged immunosuppression to avoid fibrosis. In cases of possible pulmonary interstitial glycogenosis (PIG), the diagnostic performance of CT is not well-defined, and the risk of confirmatory biopsy must be weighed against the adverse effects of empirical steroids if a presumptive diagnosis is made on the basis of clinical presentation and CT findings.

When defined as providing a diagnosis, clinically important new finding, alteration of management plan, or exclusion of lung disease, the diagnostic yield of CT for pediatric ILD is reported to be in the range of 20%-25%, although the yield is likely compromised by suboptimal imaging technique and lack of widespread awareness of disease entities and pediatric ILD classification schemes. An international web-based peer review system to improve diagnostic yield found altered diagnoses in a small portion of cases, with discrepancies more often from the initial diagnoses being too general than from them being incorrect. In the future, artificial intelligence applications may improve the classification and diagnosis of pediatric ILD, although the rarity of these disorders is an impediment to developing such applications.

In addition to establishing a specific pediatric ILD diagnosis or restricted differential diagnosis, imaging can serve to demonstrate disease natural history, assess disease activity and severity, evaluate response to therapy, and detect progression of clinically-occult disease. Radiological findings parallel clinical improvement in NEHI, while pulmonary hypertension may persist despite radiographic improvement in bronchopulmonary dysplasia (BPD) and other alveolar growth disorders. Lucencies resembling “cysts” or “emphysema” seen on CT in BPD and other alveolar growth disorders are related to enlarged simplified alveoli with diminished vascularity and correlate with the level of respiratory support needed. CT is useful for showing response to treatment with steroids or other immunosuppressants in eosinophilic pneumonia, organizing pneumonia, and pulmonary capillaritis. CT is valuable for early detection of ILD in connective tissue diseases such as juvenile systemic sclerosis in which ILD is an adverse prognostic factor and may advance without symptoms or abnormal pulmonary function tests (PFTs).

In summary, chest CT remains the primary imaging technique for evaluating pediatric ILD. CT is very valuable for making specific diagnoses and guiding other diagnostic procedures to avoid lung biopsy. CT is also useful for grading disease severity, assessing response to therapy, and monitoring clinically-occult disease.

REFERENCES

3 | Management and Prognosis

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Interstitial lung disease in children (chILD) comprises a disparate group of > 200 different conditions with a total prevalence of < 1 in 100,000 children. Hence to make progress, international collaboration is essential. Also, across the globe there may be different patterns of ILD related to different environmental exposures and genetic backgrounds, so it is important not to extrapolate between countries (discussed in more detail below). European protocols for the investigation and management of chILD were published in 2015.1 Subsequently, new investigations have come to the fore as novel entities have been discovered, and we have new insights into the early onset growth and developmental disorders. The European guidelines will be reviewed and updated in this presentation, principally with an increased focus on a specific genetic or environmental diagnosis in chILD. This review will also highlight new insights into very early chILD and new data on prognosis.

Imaging: The starting point of the pathway was the confirmation of the presence of chILD with HRCT. The initial HRCT may be diagnostic of a specific 'box', for example hypersensitivity pneumonitis (which prompts a search in the environment; the importance of a precise environmental diagnosis is obvious; disease progression may be halted or reversed if the toxin is removed, eg humidifier disinfectant, pigeons, or budgerigars) and specific gene mutations. Another ‘box’ is the classical cobblestone appearance of pulmonary alveolar proteinosis (PAP); this pattern leads to a search for specific genetic disorders, as well as GM-CSF auto-antibodies. Finally, a truly specific diagnosis may be reached, such as Langerhans cell histiocytosis. Ancillary imaging may also be helpful if HRCT scanning of the lungs is inconclusive; imaging of other organs may be diagnostic. The classic example is the nodular heterotopia on cerebral MRI seen in FNLA mutations.2 Another example is thyroid imaging in NKX2.1 mutations (brain-lung-thyroid disease).

Blood tests: The next step in the pathway was to try to make a diagnosis through blood tests. Since the pathway was written, an increasing number of entities have been described, and clearly testing must be targeted. However, in the appropriate context, for example the multisystem interferonopathy SAVI,3 a genetic test will be diagnostic and obviate further testing.

Bronchoscopy: This test finds its greatest use if an infective mimic of chILD is suspected, or to diagnose pulmonary hemorrhage. There have been no significant developments in the role of bronchoscopy since the pathway was published.

Lung Biopsy: The 2015 pathway finished with lung biopsy and often a largely morphological, umbrella diagnosis. Increasingly, the focus is reaching a specific genetic or environmental diagnosis rather than leave diagnostic efforts when an umbrella, pattern-recognition description has been attained. Some genetic diagnoses may already lead to specific treatments. Thus a lung biopsy showing follicular bronchiolitis, lymphoid interstitial pneumonia, cellular bronchiolitis or NSIP, or lymphoproliferative disease may be the first presentation of one of the > 350 primary immunodeficiencies, some of which may be curable by bone marrow transplantation.

Towards a more specific diagnosis: There is increasing reason to make a precise genetic diagnosis. The situation is complex – the same gene mutation can cause different patterns of chILD, and the same histological abnormalities by many different genes. The classical example of the former is Surfactant Protein C, which causes chronic pneumonitis of infancy when presenting early, but the same mutation in the same kindred can present in middle age with usual interstitial pneumonia, a condition not seen in children.4 GATA-2 mutations may cause a PAP-like picture or a vasculitic disease. Despite these complexities, the pursuit of a genetic cause of chILD is important; chILD caused by mutations in TMEM173 and LRBA can be treated with the monoclonals Tofacitinib and Abatacept respectively. Identifying genes responsible for chILD offers the possibility of gene-specific treatment, for example Ataluren for disease caused by premature termination codons.

The International breadth of chILD: It is really important that each country research the nature of their indigenous chILD. Different prevalences of consanguineous marriage and different environmental exposures means it is unsafe to extrapolate between countries. So in an adult study, hypersensitivity pneumonitis related to air coolers in the home was a very common cause of ILD.5 Exogenous lipid...
pneumonia shows marked geographical variations in prevalence, related to local maternal differences in the use of oily medicines given to infants. International collaboration is vital in terms of diagnostic review of these complex cases, but it should be easy to send imaging and biopsy slides to overseas centers. There is a big need for talented young researchers to determine the different patterns of chILD globally.

New controversies in early onset chILD: In the original Gail Deutsch classification, neuroendocrine cell hyperplasia of infancy (NEHI) and pulmonary interstitial glycosenosis (PIG) were termed specific conditions, and the alveolar capillary dysplasia-congenital alveolar dysplasia spectrum (ACD-CAD) included as a cause of very early onset chILD, usually with a fatal prognosis. The alveolar growth disorders are also of early onset. It is increasingly being appreciated that these are not discrete entities. NEHI (bombesin positive) and PIG (glycogen positive) cells are seen in the normal developing fetal lung, and the evidence is consistent with the hypothesis that these conditions are in fact part of a spectrum of pulmonary dysmaturity syndromes, respectively of airway (NEHI cells), mesenchymal (PIG cells) and vascular elements (ACD-CAD), rather than discrete conditions. Presentation is usually with early onset of respiratory distress. Correctly, mild cases of this clinical syndrome never undergo lung biopsy, and for these the clinical description ‘persistent tachypnea of infancy’ has been proposed. In terms of pathology, two independent series have shown that that NEHI cells decline with age, and are not specific to NEHI. Furthermore, specific genetic disorders (TTF-1 and FOXP mutations) which affect pulmonary maturation lead to a histological picture indistinguishable from NEHI. PIG and ACD-CAD are also associated with pulmonary growth disorders, and manifestations of PIG and NEHI may be present in the same child. Hence, contrary to current classifications, NEHI, PIG, and ACD-CAD should be considered as overlapping manifestations of pulmonary dysmaturaton, frequently associated with disorders of alveolar growth, rather than as separate conditions. Identification of one of these patterns should be the start, not the end of the diagnostic journey, and underlying particular genetic causes should be sought. Undoubtedly more genes which cause pulmonary dysmaturaton syndromes await discovery.

Prognosis of chILD: The rarity of these conditions makes it unwise to prognosticate so dogmatically. The chILD-EU prospective, observational, cohort study of newly diagnosed chILD over a one-year follow-up period recruited 127 children, median age 0.9 (interquartile range 0.3, 7.9) years. Common symptoms at presentation were dyspnea (68%, 69/102), tachypnea (75%, 77/103) and low oxygen saturation (SpO2) median 92% (88, 96). Death (N = 20, 16%) was commoner in those < 6 months of age with SpO2 < 94% at presentation. Survivors improved multiple clinical parameters within 3-12 weeks of diagnosis and starting treatment. This was a group of all comers, and there are few data in the literature about specific conditions [Cunningham S. submitted for publication]. The biggest series of ABCA3 mutations showed that all those with two severe mutations presented in the neonatal period and were dead or transplanted within a year. Those with only one or no severe mutations generally had a much better prognosis. In a much smaller series, NEHI patients with prolonged oxygen dependency were found to have underlying NFK2.1 mutations. Patients with PIG tended to do well, with the exception of those born preterm.

Summary and Conclusions: The increasing thrust of investigation of chILD is to go from morphological to genetic diagnoses. The next step will be to find gene specific treatments, and test them in model systems, so we can move away from nonspecific therapies such as corticosteroids.

REFERENCES

Factors that can promote exacerbations of childhood asthma include pollutants (as a source of oxidative stress), allergy and exposure to allergens, and viral and bacterial pathogens. Each of these environmental stimuli alone contributes to the risk of an exacerbation. However, most exacerbations are likely to involve exposure to multiple environmental factors. These concepts raise important mechanistic questions about how these factors interact to promote the acute pathological features of exacerbations. In addition, these interactions may suggest novel strategies for the treatment and prevention of exacerbations.

Allergy is a strong predictor of acute wheezing illnesses and is positively related to the risk of exacerbations and children with asthma. For example, a case control study conducted in Costa Rica studied 287 children who presented to an emergency department. These included 96 with acute wheezing and 65 with stable asthma as well as 126 control children who did not have asthma. PCR was used to detect acute rhinovirus (RV) infection, and each child was evaluated for the presence of wheezing, total and allergen specific IgE antibody, and exhaled nitric oxide. The probability of acute wheeze was strongly related to RV detection and to titers of IgE antibody that was specific for dust mite. For children who tested negative for RV, there was a modest positive relationship between mite-specific IgE and the probability of current wheeze. For children who tested positive for virus, there was a robust relationship between mite-specific IgE and the probability of wheeze.

Studies demonstrating a close relationship between allergy viral infection and acute wheezing illnesses suggest the possibility that allergy might interfere with the antiviral response and therefore promote more severe infections involving the lower airway. In fact, several mechanisms have been identified for allergic inflammation to inhibit antiviral responses, and this theory has been tested in two large clinical trials of urban children with moderate-severe allergic asthma. In the first study, a one-year treatment regimen with omalizumab significantly reduced exacerbations of asthma, and it was notable that the expected fall and spring increases in exacerbations during peak viral respiratory seasons were blunted. A second study examined the effects of seasonal omalizumab that was added to standard guidelines-based asthma care in an attempt to reduce fall exacerbations, which are predominantly caused by RV infection. This study confirmed that omalizumab can prevent the fall increase in exacerbations that occurs during the peak RV season. In addition, virological analysis of weekly samples of nasal secretions in this same population documented that omalizumab treatment reduced the detection of RV and shortened the duration of viral colds. These interventional trials have established that inhibiting IgE is related to improvement in antiviral responses and reduction in virus-induced respiratory illness and exacerbations of asthma.

There is abundant clinical evidence that viruses and bacteria can team up to cause respiratory infection such as otitis media, sinusitis and pneumonia. More recent data suggest that both types of pathogens contribute to respiratory illnesses and exacerbations of asthma. Viruses are typically the initiating event for respiratory illnesses, and can compromise the barrier function of the epithelium and increase the expression of cell surface receptors that promote bacterial invasion. A study of 309 school-aged children (approximately half with asthma) collected weekly nasal mucus samples during the September and April cold seasons, and then tested for common viral and bacterial respiratory pathogens. Children were at greatest risk of experiencing respiratory illness symptoms if both a RV and a bacterial pathogen (Moraxella catarrhalis, Haemophilus influenzae or Streptococcus pneumoniae) were detected. The same trends were identified for the subset of children with asthma; exacerbations were most common when both a virus and one of these bacterial pathogens were detected. Furthermore, detection of RV-A or RV-C, which are more virulent species, was associated with an increased risk of respiratory illness and an increased risk of detecting a bacterial pathogen.

A nested case-control study was conducted to determine whether there were differences in airway microbiome between children who presented with asymptomatic RV infections and those who presented with RV-induced exacerbation of asthma. During asymptomatic infections, there were several changes in nasal bacterial relative abundance. Commensal organisms such as Dolosigranulum and Corynebacterium were increased in relative abundance. In contrast, infections that lead to exacerbations of asthma had a reduction in Corynebacterium. Moraxella was increased in infections with or without symptoms. When considered together, the results of these studies support the idea that there are interactions between respiratory viruses and bacterial pathogens and commensals, and that both types of pathogens contribute to the risk and severity of upper and lower airway symptoms.

Pollutants that induce oxidative stress such as ozone and environmental tobacco smoke are also potent inducers of asthma symptoms and exacerbations. Recent studies have identified interactions between the response to oxidant stress and antiviral responses. Oxidative stress induces NRF2, which is a transcription factor that induces the synthesis of proteins that neutralize reactive oxygen species. In contrast, viral infections are detected by multiple intercellular innate immune sensors and activation of this network leads to induction of interferon responses, interferon-associated proteins. In studies involving primary cultures of airway epithelial cells, inhibition of NRF2 using SI RNA led to a reduction in RV replication and an enhanced antiviral transcriptional response. The investigators next tested whether cigarette smoke extract (as a source of oxidative stress) would inhibit the antiviral response. In fact, adding 2% cigarette smoke extract to the tissue culture medium...
increased RV replication and inhibited the antiviral response. These findings suggest that while airway epithelial cells have effective programs for dealing with oxidative stress and with respiratory viruses, excessive oxidative stress may inhibit antivirus programs and provide a mechanism for oxidative pollutants to enhance viral replication and increase the risk of virus-induced exacerbations of asthma.

Most exacerbations of asthma are initiated by viral infections and currently there are no effective antiviral agents. There is increasing evidence that pollutants, viral infections and airway bacteria can all influence the risk for virus-induced exacerbations of asthma, and the airway responses to these factors are interactive. Studies to understand the mechanisms of these interactions may lead to new therapeutic approaches to prevention or treatment of exacerbations of asthma. Notably, in the absence of effective antivirals, controlling allergic inflammation with anti-inflammatory medications and reducing exposure to environmental pollutants and tobacco smoke can reduce exacerbations. Finally, in addition to targeting respiratory viruses, there is increasing evidence that bacteria may also play a causative role. While use of antibiotics may be problematic due to the increasing prevalence of antibiotic resistance and adverse effects on commensal bacteria, there is active and renewed interest in development of vaccines or probiotics for use in children and adults with asthma.

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2. | Anticholinergic for Asthma Treatment in Children and Adolescents

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Introduction: Asthma, a prevalent disease affecting millions of individuals, is associated with a significant morbidity and a high economic and medical burden. Despite receiving guideline treatments, many patients remain symptomatic and have suboptimal lung function. There is therefore an unmet need for additional therapies to improve asthma control. In the last years, there has been a renewed interest in the use of anticholinergics for asthma treatment. Indeed, several studies have assessed the potential benefits and safety of the once-daily (OD) long-acting anticholinergic tiotropium bromide for the treatment of uncontrolled moderate-to-severe asthma in adults and adolescents. According to the current GINA guidelines, tiotropium bromide administered by Soft Mist inhaler may be used as OD maintenance bronchodilator treatment for patients aged >12 years with symptomatic asthma despite receiving medium-high dose inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA). Major benefits detected are: a) modest improvement of lung function and b) increased time to severe exacerbations requiring oral corticosteroids. Tiotropium has been shown to be safe and well tolerated in these patient populations. However, given the high prevalence of asthma and wheezing in childhood, there is a great interest on the possible use of tiotropium in preschoolers and in school-age children, patients not included in the current indications.
Acetylcholine and muscarinic receptors: Long-acting anticholinergic agents are well-established drugs for the treatment of chronic obstructive pulmonary disease. However, through interaction with muscarinic receptors, acetylcholine also plays an important pathogenic role in asthma. Five subtypes of muscarinic receptors (M1-M5) have been identified, but only M1, M2 and M3 have been detected in the lung and airways in humans. M1 receptors appear to be expressed chiefly in the peripheral lung tissue, i.e., in small airways with a diameter < 2 mm and in the alveolar walls, whereas M2 and M3 receptors represent the major populations in larger airways. Regulation of airway tone, airway smooth muscle contraction, mucus secretion and vasodilatation occurs mainly through interaction of acetylcholine with the M3 receptors. Indeed, M3 receptors are expressed by airway smooth muscles, mucus glands, ciliated epithelial cells, fibroblasts, mast cells and vessels. In contrast, M2 muscarinic receptors, located in the postganglionic cholinergic nerves, limit neurotransmission by downregulating acetylcholine release from parasympathetic nerves with a negative feedback loop in signal transduction. Enhanced acetylcholine activity due to loss of M2 receptor function has been described in some patients with asthma and in animal models of airway hyperreactivity.

M2 receptors are also the predominant muscarinic receptor subtype expressed in cardiac muscle and loss of their function may also adversely impact ventricular function, with development of severe and even fatal cardiac arrhythmia. Although acetylcholine is not considered a regulator of airway inflammation, accumulating evidence demonstrate the expression of muscarinic receptors by inflammatory cells, including T-and B-lymphocytes (M1-M5), mast cells (M1), neutrophils (M1/M2/M3) and eosinophils (M1). On these cells, muscarinic receptor activation appears to be involved in cell proliferation and pro-inflammatory mediator release. Acetylcholine is not sufficient to induce airway smooth muscle cell proliferation; however it may enhance smooth muscle responses to epidermal growth factor and platelet-derived growth factor in these cells.

Tiotropium bromide: Tiotropium is a potent and selective long-lasting muscarinic antagonist that slowly dissociates from M1 and M3 receptors and rapidly from the auto-inhibitory M2 receptors. The long duration of binding to M1 and M3 receptors results in prolonged bronchodilation, allowing OD dosing. After inhalation of a single dose of the drug, the onset of action is slow with peak of bronchodilation occurring after 3-3 hours. Top plasma levels are reached in 5 minutes, with a subsequent rapid decline in less than 1 hour to very low levels, and a terminal half-life of 3-6 days. These pharmacokinetic characteristics are independent from the dose. Factors that may increase systemic exposure are: a) chronic use; b) impaired renal function; c) increasing age; d) concomitant assumption of cytochrome P450 poor metabolizers. In addition to the long duration of the bronchodilatory action, tiotropium has been shown to have anti-inflammatory and inhibitory effects on airway remodeling in animal models of asthma. Collectively, these data suggest that tiotropium may have other therapeutic benefits in asthma beyond its long-lasting bronchodilatory activity.

Tiotropium in adolescents: OD tiotropium, as add-on to ICS with or without other maintenance therapies, has been shown to be an efficacious bronchodilator in adults with mild, moderate and severe asthma. Tiotropium has also been investigated in adolescents (12-17 years of age) with poorly controlled asthma: the primary endpoint was "peak FEV1 response", i.e. change from baseline within 3 hours post-dose (FEV13h), and the secondary endpoints included "trough FEV1 response", i.e. change from baseline pre-dose FEV1, and changes in "Asthma Control Questionnaire (ACQ-7) score". In a Phase II study, 105 adolescents were randomized to receive 4-week OD tiotropium (5 μg, 2.5 μg or 1.25 μg) or placebo, as add-on therapy to medium-dose ICS, with or without leukotriene receptor antagonists (LTRA). Improvements were seen in "peak FEV13h response", statistically significant only with the 5 μg dose. Differences in "trough FEV1 response" at the end of each treatment period were also greater with tiotropium, but statistically significant only with 5 μg and 1.25 μg doses. At the end of the 4-week treatment periods, adjusted mean "ACQ-7 scores" improved similarly in all treatment groups, tiotropium and placebo. In a subsequent larger Phase III trial, adolescents with poorly controlled asthma received tiotropium (5 μg or 2.5 μg) or placebo over 48 weeks, as add-on therapy to ICS with or without an LTRA. Statistically significant improvements were observed in "peak FEV13h response" with both tiotropium doses, and in "trough FEV1 response", but only with tiotropium 5 μg. The ACQ-7 responder rates at week 24 were higher in the tiotropium groups than in the placebo group but the differences were not statistically significant. In an additional Phase III study, 392 patients received tiotropium 5 μg or 2.5 μg or placebo over 12 weeks, as add-on to high-dose ICS, plus one or more controllers (LABA or LTRA), or as add-on to medium-dose ICS, plus two or more controllers (eg LABA, LTRA, or sustained-release theophylline). A significant improvement in "peak FEV13h response" was observed at week 12, but only with tiotropium 2.5 μg. Positive trends in assessments of asthma control were observed in all treatment arms, with a reduction in rescue medication use and an improvement in ACQ scores observed; however, differences with tiotropium, compared with placebo, were not statistically significant. Interpretation of these data was somewhat difficult due to the short trial period combined with a large placebo effect, with lung function improvements from baseline observed in the placebo arm. Trends for improvements in lung function, safety and tolerability with tiotropium were comparable with those of placebo, and consistent with the existing data in adults with severe asthma.

Tiotropium in school-age children: A systematic review was performed to assess the efficacy and safety of OD tiotropium 2.5 μg and 5 μg in children, aged 3-11 years, with moderate-to-severe symptomatic asthma, as an add-on to ICS plus one or more controller medications. Three randomized, placebo-controlled trials were included, evaluating the results of 3-12 week treatment periods. Primary outcomes were "peak FEV13h response" and "trough FEV1 response" measured at the end of the dosing interval. The results on more than 900 patients demonstrated that tiotropium was associated with significant improvements in "peak FEV13h response"...
response" and "trough FEV₁ response", compared with placebo. At 5 μg dose, a non-statistically significant trend toward a greater bronchodilation, in comparison with 2.5 μg dose, was detected. In addition, tiotropium significantly increased the rate of ACQ-7 responders, compared with placebo (82.2% vs. 75.4%) and significantly decreased the number of patients with at least one exacerbation in comparison with placebo (29.1% vs. 39.8%). There were no significant differences with placebo in rescue medication use, withdrawals and adverse events.

**Tiotropium in preschoolers:** In a multicenter study, in 102 children younger than 5 years with at least a 6-month history of persistent asthmatic symptoms and a need for ICS, received for 12-weeks OD tiotropium 2.5 μg, tiotropium 5 μg, or placebo as an add-on to ICS with or without additional controller medication. Mean daytime asthma symptom scores were not significantly different between groups, but tiotropium showed the potential to reduce asthma exacerbation risk compared with placebo. Tolerability of tiotropium was similar to that of placebo.

### CONCLUSIONS

Additional well powered trials are needed to further assess the safety and efficacy of tiotropium in adolescents and children with persistent asthma. In addition, well powered, long-term and longitudinal studies are also needed to evaluate whether tiotropium, as add-on to guidelines-based therapy, is effective in attenuating seasonal asthma exacerbations and to examine the effects on long-term outcomes of asthma in childhood and, possibly, on airway remodeling.

### REFERENCES


### CHRONIC SUPPURATIVE LUNG DISEASE AND PNEUMONIA

**1. Protracted Bacterial Bronchitis and Links with Bronchiectasis – PRO/CON Debate**

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PBB is clinically defined as (a) the presence of isolated chronic (> 4 weeks) wet/productive cough, (b) resolution of cough with antibiotic treatment and (c) absence of pointers suggestive of an alternative specific cause of cough. While the original description¹ included a criteria that required findings from bronchoalveolar lavage (BAL), it was later adapted for clinical use in the same year as undertaking BAL routinely in a child with chronic wet or productive cough is unwarranted and not feasible. PBB has been officially recognized in chronic cough guidelines of many countries and a European Respiratory Society (ERS) taskforce document has also been produced.² Currently, suggestions for classifying PBB are PBB-clinical, PBB-micro, PBB-extended and recurrent PBB.³

Children with PBB are typically very young (median age ~2 years) and may have parent-reported wheeze. The reported 'wheeze' may actually be a rattle (reflective of airway secretions) and not a true wheeze.⁴ However, children with PBB may have co-existent asthma, although in a prospective cohort study, median peripheral blood eosinophils, total IgE and RAST testing for common aeroallergens in children with PBB were similar to controls.⁵

The chest X-rays of children with PBB may be reported as ‘normal’ but usually show peribronchiolar changes. In many children, co-existent trachea-bronchomalacia⁶ is present although we found no significant difference in the frequency of trachea-bronchomalacia
between children with PBB and ‘non-PBB controls’ (children with respiratory symptoms but did not have PBB).3,5

Common respiratory pathogens found in the bronchoalveolar lavage (BAL) of children with PBB are *H. influenza* (mostly non-typeable), *S. pneumoniae* and *M. catarrhalis*. In the original description of PBB,1 children who had the classical respiratory viruses detected by PCR were excluded, so as to obtain a ‘clean group’. In PBB, the child’s cough resolves only after a prolonged course (usually 2 weeks) of appropriate antibiotics7 with resultant improved cough-specific and generic health-related quality of life measures.3 Some children required up to 4 weeks of antibiotics. Anecdotal experience suggests that when shorter courses of antibiotics are used, the cough subsides but does not resolve and/or resolve but recurs very quickly. Reasons for this are unknown but one postulate is that longer courses of antibiotics are required to overcome the bacteria associated with formation of biofilms, demonstrated in the BAL of children without cystic fibrosis or *Pseudomonas aeruginosa* infection.3

Some children with PBB have recurrent episodes (> 3/y) and some progress to bronchiectasis.8 Thus, children with PBB should be clinically reviewed. Predictors of disease progression are recurrence (> 3/y) and presence of non-typeable *H. influenzae* in the BAL.8 Further, while chronic wet/productive cough in children often signify PBB, wet cough could also be the marker of other conditions.

Readers are referred to recent publications for reasons outlining how and why PBB is closely linked with bronchiectasis or a continuum.3,9 This was first proposed a decade ago4 and recent studies support this, as recently summarized.3,10 The clear reason why the motion for the strong link between PBB and bronchiectasis should be supported is that Prof. Bush has coauthored a review regarding the continuum with chronic endobronchitis being the common thread.10

This paradigm is based on decades-old and more recent studies using new technology. It is framed around the notion that primary prevention of bronchiectasis is possible and the knowledge that early detection of causal conditions (eg hypogammaglobulinemia) substantially reduces the risk of the future development of bronchiectasis through early initiation of treatment and optimal care. In children, mild (ie when detected early) bronchiectasis is potentially reversible.9,10 Many factors influence progression of the illness, most of which are modifiable and represent potential intervention points. These factors (secondary prevention) include better clinical management and guideline implementation. The paradigm emphasizes that prompt diagnosis and optimal management of bronchiectasis is particularly important in childhood with opportunities for its reversal of bronchiectasis and/or halting disease progression.9,10

REFERENCES

1.2. PBB – A Precursor to Bronchiectasis? (Con)

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The suggestion that we should consider protracted bacterial bronchitis (PBB) to be a precursor of bronchiectasis requires three propositions to be proven:
1. PBB and bronchiectasis are discrete and separate entities
2. There is progression from the discrete entity PBB to the discrete entity bronchiectasis
3. This has some clinical relevance to the way we treat children

As has been argued elsewhere,1,2 PBB and bronchiectasis are descriptive labels, not diagnoses. The label is the start, not the finish of the child’s diagnostic journey. Just as renal failure, whatever the underlying cause, leads to elevation in serum creatinine, so host defense failure manifests with chronic infection, neutrophilic inflammation and airway tissue destruction, whatever the underlying cause. The clinical manifestations are also the same: a wet, productive sounding cough, in older children sputum expectoration, wheeze due to narrowing of the airway lumen due to secretions, breathlessness, and sometimes general ill health. Thus, both labels should lead to an identical work up, assessing all aspects of host defense, including for example assessment of the innate and adaptive immune systems, exclusion of cystic fibrosis and primary ciliary dyskinesia, and evaluation for aspiration syndromes. If the disease appears to be localized, anatomical causes of a breakdown in host defenses, such as airway compression or endobronchial foreign body,
should be excluded. The arbitrary label 'bronchiectasis' was initially applied when airway dilatation had become irreversible; this is clinically not useful, since although irreversible can be implied, by definition only reversibility, not irreversibility, can be proven. Indeed, we know that airway dilatation which had been thought to be irreversible can reverse, and this led to the addition of another arbitrary term 'pre-bronchiectasis' to the literature. Bronchial size is related to the accompanying artery, which assumes that the arterial diameter is normal (which it may not be if there is local hypoxic vasoconstriction). Bronchial caliber varies developmentally and with lung volumes, making it a very difficult measurement to make reliably. And yet, on the basis of an arbitrary and highly variable ration, we talk about bronchiectasis, pre-bronchiectasis and PBB, the only distinguishing feature of this last being a normal airway caliber.

The airway pathobiology in PBB and bronchiectasis has recently been reviewed, and although there are differences in degree (interestingly, PBB was characterized by more severe neutrophilic inflammation than bronchiectasis [9]), essentially pathophysiologicaly, they are the same disease with the same inflammatory and tissue destructive pathways. Hence logically enough, the treatment is the same – antibiotics, airway clearance by various techniques, mucolytics as appropirate, and general respiratory health measures such as immunizations (including annually against influenza), the avoidance of exposure to tobacco, vaping and other indoor and outdoor pollutants, and exercise. No-one would wait until some arbitrary threshold in an almost impossibly difficult ratio had been attained.

So returning to my three propositions: there is no evidence that PBB and bronchiectasis are discrete conditions, they are part of a spectrum of chronic suppurative lung disease (CSLD). The CSLD label is a far better one, because every child falling under this umbrella term needs the same diagnostic work-up and treatment. CSLD can be described as being cured by a single or multiple courses of antibiotics, or persistent despite antibiotics. The rate of progression depends on the underlying cause, with cystic fibrosis being an exemplar of a disease that deteriorates relentlessly and rapidly if untreated. In summary, it is impossible to progress from one entity that does not exist to another entity that does not exist! Dividing CSLD into discrete arbitrary blocks is as useful as trying to divide up the river Thames into segments. The Thames is a single great river, and CSLD is a single useful label.

The two questions most usefully asked in research and clinical medicine are 'so what?' and 'what for?' I can find no satisfactory answer to them when it comes to arguments about whether PBB and bronchiectasis are separate entities! However, and most importantly, Dr Chang and myself would both be in agreement that a chronic wet, productive sounding cough is a real red flag, which must emerge from the debate. This is the most important message which must emerge from the debate.

REFERENCES

2 Atypical Pneumonia in Children: Etiology and Management

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Introduction: Community-acquired pneumonia (CAP) is a common cause of morbidity and mortality in children. The term “atypical pneumonia” originates from clinical features that differ from typical CAP symptoms and initially involve mild symptoms that progress to pneumonia with varying severities and extrapolmonary manifestations that do not respond to β-lactam antibiotics. In general, atypical pathogens can include all pathogens other than typical bacteria. However, in narrow terms, Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila are considered as atypical pneumonia pathogens. They are all intracellular organisms that lack a cell wall. Therefore, they do not respond to β-lactam antibiotics but show good responses to
Macrolides, tetracyclines (TCs), or fluoroquinolones (FQs). While _M. pneumoniae_ and _C. pneumoniae_ manifest as mild, slowly progressing, and often self-limiting diseases, _L. pneumophila_ pneumonia presents as an abrupt onset of high fever and cough, which rapidly progresses to pleuritic chest pain, respiratory difficulty, and fatal outcomes if not treated in time. There is an age-specific distribution of atypical pneumonia, where _M. pneumoniae_ is more common in children aged > 3 years, _C. pneumoniae_ is more frequent in infants, and _L. pneumophila_ is very rare in children aged < 19 years.\(^3\)

_M. pneumoniae_ accounts for 7%–40% of CAP in children aged 3-15 years and has an outbreak every 3-4 years worldwide. _C. pneumoniae_ comprises 2%–19% of CAP cases in children. Diagnostic methods and criteria of _C. pneumoniae_ are not standardized; thus, its true incidence can be underestimated. _L. pneumophila_ is a rare pathogen of CAP in children, accounting for less than 1%.\(^3\)

Macrolides are the treatment of choice for atypical pneumonia because of their low minimum inhibitory concentration (MIC) and safety profiles in children. However, the recent rising incidence of macrolide-resistant mycoplasma pneumonia (MRMP) is becoming a world-wide problem, especially in Korea, Japan, and China. Point mutations of the 23S rRNA genes (mostly at sites 2063, 2064, and 2617) inhibit the binding of macrolides to _M. pneumoniae_.\(^4\) The increasing prevalence of MRMP may be attributed to the extensive use of macrolides because MRMP incidences have decreased in accordance with the reduced use of macrolides.\(^5\) FQs or TCs are alternative antibiotics for patients with macrolide resistance; however, these drugs have safety issues in children, due to serious adverse reactions. The Korean Food and Drug Administration recommends the use of FQs and TCs in children aged > 18 years and 12 years, respectively.\(^6\) Macrolide resistance among _L. pneumophila_ and _C. pneumoniae_ infections has been rarely reported; however, _L. pneumophila_ with FQ-resistant mutations has been reported recently.\(^6\)

Whether macrolides should be used as a first-line empirical therapy in children with CAP remains debated. The guidelines for the use of antibiotics in children with lower respiratory tract infections that are published by Korea Centers for Disease Control and Prevention recommend using macrolides only when atypical pneumonia is suspected or confirmed.\(^7\) However, real-world macrolide prescriptions have not been in accordance with this guideline. It may not be too late to begin macrolide treatment when atypical pathogens are confirmed in immunocompetent children with mild-to-moderate pneumonia. Contrary to _L. pneumophila_ pneumonia, pneumonia due to _M. pneumoniae_ and _C. pneumoniae_ do not rapidly progress nor are life-threatening, but usually progress slowly and present self-limiting and benign courses. However, patients with fulminant MRMP and severe complications have been reported. _L. pneumophila_ spreads from contaminated water, such as water from cooling towers, and has been rarely observed in children. Legionellosis incidences in Korean children aged < 19 years have been reported to occur at a rate of 0.02/100,000 individuals.\(^8\) The extensive use of macrolides has increased the incidences of resistance strains, including _M. pneumoniae_ and _S. pneumoniae_. MRMP disease severity does not differ significantly from macrolide-sensitive mycoplasma pneumonia.\(^9\) Clinical resistance to macrolides can be attributed to an excessive production of pro-inflammatory cytokines, regardless of of mutation. Several studies have shown the clinical effectiveness of corticosteroids for complicated MRMP that did not require a change in antibiotics.\(^10\)

This review assesses the epidemiology, pathogenesis, diagnosis, and treatment of atypical pneumonia caused by _M. pneumoniae_, _C. pneumoniae_, and _L. pneumophila_ in children.

**REFERENCES**


**5 | ASTHMA AND PRESCHOOL WHEEZING DISORDERS – UPDATE**

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School-aged children with asthma who remain with persistent poor control, or frequent exacerbations, despite being prescribed maximal therapy, have Problematic severe asthma. Maximal therapy for children is defined in the ATS/ERS guidelines for the management of severe asthma as at least 800 mcg/day budesonide (or equivalent) plus a long-acting beta2 agonist and current or previous failed trial of leukotriene receptor antagonist and/or oral theophylline. Importantly, patients with seemingly severe asthma may have other, modifiable causes of poor asthma control. It is therefore essential to undertake a step-wise approach to diagnosis and management of Problematic severe asthma to ensure poor control is not because of a wrong diagnosis, and that a potentially easily remediable factor is not wrongly treated with expensive biologics. It is important that children on maximal maintenance treatment and poor control are not automatically labeled as having severe asthma, there is a sub-group with Difficult to treat Asthma (DA), in whom underlying modifiable factors explain persistent symptoms and poor control. After modifiable factors have been optimized and addressed, there remains a small group of children with good adherence and persistent poor control, these are patients with true severe therapy resistant asthma (STRA).

Confirming an asthma diagnosis

History and examination: Asthma is characterized by symptoms including wheeze, cough, breathlessness and chest tightness, all of which may fluctuate over time. An essential component is to obtain objective confirmation of symptoms either as documented doctor-observed symptoms, or by administration of an objective questionnaire. A key issue that often leads to misdiagnosis in children is the mistaken assumption that all noisy breathing equates to wheeze and therefore asthma. Therefore, an accurate record of documented wheeze and symptoms consistent with asthma is critical to prevent inappropriate diagnosis, but equally importantly, inappropriate treatment.

Incorporating objective tests to make a diagnosis of asthma: is this necessary? The importance of a correct diagnosis for the individual is necessary. Incorporating objective tests to make a diagnosis of asthma: is this diagnosis, but equally importantly, inappropriate treatment. Symptom consistent with asthma is critical to prevent inappropriate asthma. Therefore, an accurate record of documented wheeze and symptoms consistent with asthma is critical to prevent inappropriate diagnosis, but equally importantly, inappropriate treatment.

Assessments of adherence to medication: The most common modifiable factor underlying DA is poor adherence to maintenance therapy, encompassing at least 45%-55% of all patients (adults and children). Good adherence is defined as the administration of > 80% of prescribed doses of ICS. The British Thoracic Society (BTS) Guidelines state all patients with asthma must have an annual adherence assessment, and the proposed gold standard method is using an electronic monitoring device, however other options include checking prescription pick up/refill. For children with problematic severe asthma, an objective assessment of adherence is an absolute requirement before consideration of therapy escalation. An observational prospective cohort study assessed spirometry with bronchodilator reversibility, FeNO, asthma control test (ACT) scores and quality of life scores before and a median of 92 days after an electronic monitoring device was given to children (median age 12.4 years). Suboptimal adherence (< 80%) was demonstrated in 58%. Children with good adherence were split into those with improved control (need encouragement to maintain adherence), or those with persistent poor control (STRA). Among children with poor adherence, there was a sub-group whose control improved (likely over-treated), and a second sub-group with persistent poor control. The latter are of particular concern as they are at high risk of asthma death and require an adherence intervention such as directly observed therapy in school, or this may be a group for whom biologics administered in
hospital may be the only safe option, even though, in truth, their disease is not necessarily treatment refractory. The prevalence of true STRA was only 18% of the entire cohort and the majority had DA emphasizing the importance of the time and resources spent in identifying modifiable factors before therapy escalation.

**Minimizing exacerbating environmental exposures:** Environmental exposures that may result in persistent poor control include exposure to aero-allergens to which the child is sensitized (house dust mite, pet dander, moulds), ambient air pollution and tobacco smoke. Objective confirmation of smoke exposure by measuring urinary or salivary cotinine levels helps ensure the family seek cessation advice. Minimizing aero-allergen exposure in sensitized children is essential as there is a known relationship between exposure and increased disease severity. There is little the individual can do to reduce exposure to air pollution, although advice includes remaining indoors, closing windows and avoiding physical activity outside when pollution levels are high. However, the impact of these measures in improving asthma control is difficult to quantify and government policy to reduce emissions is likely to be more effective as has been seen with legislation to reduce exposure to environmental tobacco smoke.

**Identification of co-morbidities:** Breathing pattern disorders including vocal cord dysfunction and hyperventilation may contribute to DA and are often present with anxiety and psychosocial exacerbators. Ideally, all children with Problematic severe asthma should have a physiotherapy assessment to allow detection and management of dysfunctional breathing, and clinical psychology assessment. The complex interplay of factors contributing to DA means the multi-disciplinary team evaluation may need to be undertaken during an in-patient stay. This approach showed improvement in asthma control from 18% to 69% in children with DA. Moreover, immediate and sustained improvement in objective measures including spirometry, exhaled nitric oxide and exacerbations was demonstrated in 24/26 children following a 2-week in-patient assessment. Alarming features prompting in-patient assessment include excess use of short acting bronchodilator, discrepancy between symptom reporting and objective markers of disease severity, and safeguarding concerns.

**Summary:** A step-wise approach to diagnosis and management of school-aged children with Problematic severe asthma, undertaken in specialist centers, is essential To identify those with DA. Before therapy escalation, detailed MDT assessments that allow identification and correction of reversible factors contributing to poor asthma control are needed. Recent studies suggest only 20%-30% of all children with Problematic severe asthma have true STRA while the majority have DA, highlighting the importance of the MDT in management. The most common reversible factor is poor adherence to maintenance inhaled corticosteroids and objective adherence monitoring must be undertaken as part of the assessment.

**References**


These findings pointed to events occurring in childhood and potentially in utero as major determinants of the risk for COPD in adult life. Using data from the Tucson Children’s Respiratory Study (TCRS), our group extended the assessment of lung trajectories to the childhood years. We used latent class analysis and found that such two such classes could be clearly differentiated when assessing FEV1 and FEV1/FVC ratio from the age of 13-the fourth decade of life. Risk factors for a “persistently low lung function” trajectory were low maximal flows at functional residual capacity in the first year of life and at age 6 years, maternal asthma, and early life lower respiratory illness caused by respiratory syncytial virus (RSV-LRI). A larger study from Tasmanian included participants that reached 53 years of age and identified six FEV1 trajectories. Of particular interest was a group of subjects that started adult life with low lung function but also became smokers in adult life: this group showed accelerated FEV1 decline in adult life and 46% of these subjects had COPD by age 53 years. In a third report from the United Kingdom and Australia, four FEV1 trajectories were identified in subjects followed from early childhood up to age 24 years. The authors created an allele score based on the most significant genetic variants associated with FEV1 in genome-wide association studies. The results were disappointing: association between the trajectories identified and the allelic score were very weak, suggesting that the genetic factors that determine FEV1 in adult studies are not the same as those underlying early lung function growth. Taken together, these studies suggest that there are potentially preventable risk factors that determine lower lung function trajectories from childhood to adult life and that may increase the risk for COPD in adult life.

Our group has also uncovered a parallel mechanism through which childhood events may increase the risk of COPD. This mechanism was first suggested by studies done also in Tucson by Burrows and coworkers. They observed that smokers who recalled having had “respiratory trouble before the age of 16 years” were more likely to have COPD than smokers without such a history. They acknowledged that their findings could be biased by preferential recall, but suggested the possibility of an interaction between early life history of respiratory disease and smoking as determinants of chronic airflow limitation. We leveraged on the work by Burrows, et al. and found that adult participants in TCRS who had RSV-LRI in early life and smoked were more likely to be diagnosed with asthma and have increased variability of peak flow than those who had neither of these risk factors or just one but not the other. It is plausible to surmise that physicians who examine young smokers in their twenties with respiratory symptoms such as wheezing or persistent cough attach the label of asthma to these subjects. Most likely, these subjects are having the first manifestations of airway damage and chronic inflammation that may give way to the more severe symptoms associated with COPD during later decades. We will continue following these participants in the TCRS to determine if these symptoms derive into incipient deficits in lung function. There are two possible explanations for the RSV-LRI-by-smoking interaction: a) RSV-LRI in early life may prime the airways for increased susceptibility to smoking in adult life; b) RSV-LRI is a marker for an immune response that, on the one hand, predisposes for severe responses to RSV infection and, on the other, increases susceptibility to tobacco smoke. As part of our ongoing assessment of TCRS participants, we are inducing sputum and assessing gene expression patterns in smokers with or without a history of RSV-LRI. We will also measure lung function in these same two groups at age 36 years. We expect these studies to be the first to yield critical information on the molecular events that link early life lower respiratory illnesses with the subsequent development of COPD.

REFERENCES

3 | Rural Protection against Asthma – Insights for Primary Prevention

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Asthma is one of the most common chronic disorders affecting children and adults. Despite improved understanding of the pathophysiology of asthma, the exact etiologies are still largely unknown. Many epidemiological studies have shown that prevalence
of childhood asthma has increased in many countries over the last few decades \(^1,^2\) and comparative studies have shown that asthma is rather uncommon in rural or developing regions. \(^3,^4\) The reduction of exposure to beneficial microbes has been thought to be the most important protection factor. This has led to a great research interest in studying the role of microbial exposure in the pathogenesis of childhood asthma.

The findings from comparative studies of rural and urban populations were very consistent. Furthermore, there was a marked difference in asthma prevalence in populations with similar genetic or ethnic backgrounds living in rural and urban environments. \(^5,^6\) Among the ISAAC centers from China, Hong Kong is one of the most developed and Westernized cities. The prevalence of asthma is much higher in Hong Kong than in other mainland cities. Studies in central Europe suggested that exposure to livestock farming and consumption of farm milk appeared to be the most important protective factors. \(^6\) Subsequent studies further revealed that exposure to endotoxin and increased diversity of microbes were important protective factors. \(^7\) A mouse model of asthma also showed that early exposure to farm dust extracts might have a preventive effect. \(^8\) The current "established" risk factors for the development of asthma such as allergen exposure clearly cannot explain the international and intra-regional variations in asthma prevalence. These epidemiology studies have shown that we need to rethink the possible pathogenesis of asthma. Recent research has moved away from studying of allergens to risk factors that may program the initial susceptibility to asthma.

The comparison of Amish and Hutterite populations provided a unique opportunity to evaluate the protective factors and the underlying mechanisms of protection. \(^9\) Endotoxin levels in the home environment were found to be much higher in Amish homes when compared to those of Hutterite homes. Analyses of peripheral blood mononuclear cell compositions and gene expressions suggested an enrichment of innate immunity among Amish children in response to microbial exposure in early life could explain the protection. In contrary to studies in Europe or North America, the farms in China are primarily agricultural in nature. Large farm animals are uncommon in Chinese farms. Studies conducted in northern China confirmed that both agricultural and livestock farms confer protection against asthma. \(^10\) For children from rural China living in homes engaged in agricultural farming, their gene expression of different inflammatory genes were suppressed as compared to children from urban areas. Taken together, early exposure in a rural environment confers protection against asthma and allergies are likely to be mediated via through early microbial exposure and immune modulation resulting in gradual maturation of the immune system. Such maturation will result in a low propensity to develop an allergic response toward innocuous environmental stimuli or allergens. Clear understanding of what types of microbes and what underlying mechanisms are involved will be crucial in the development of primary preventive strategies in the future.

REFERENCES


6 | TECHNOLOGY ADVANCES IN MANAGEMENT OF LUNG DISEASE

1 | Noninvasive Assessments of Airway Inflammation and Infection in Asthma and Wheezing Disorders

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Airway inflammation is a key pathological feature of asthma and wheezing disorders in children. It is becoming increasingly apparent that objective assessments of airway inflammation to
identify a specific phenotype and treatable trait are important to enable targeted treatment for the individual patient. Moreover, evidence that infections and microbial dysbiosis during acute attacks and periods of disease stability may contribute to symptoms means assessments of airway infection are also important to allow targeted therapy. Although the gold standard is bronchoscopic sample collection from the lower airways for both inflammation and infection, this is not a feasible option in all children as it is an invasive test that can only be undertaken in those with very severe disease, and cannot be repeated to allow longitudinal assessments. Noninvasive techniques are therefore important and being increasingly used. The techniques currently available for use in children and their clinical application will be discussed.

**Induced sputum**

**Utility of induced sputum to assess lower airway inflammation:** Sputum induction using nebulized hypertonic saline undertaken during stable disease can be performed safely in school-age children with severe asthma and preschool children with recurrent wheezing. Samples of good quality for assessments of inflammation are obtained from school-aged children in between 75%-80% of cases and show a good correlation with inflammation in broncho-alveolar lavage. In practice, the use of sputum eosinophils to make an asthma diagnosis is challenging because of the time and expertise required for both the induction, processing and analysis of the sample. For this reason, the utility of less invasive biomarkers that may reflect airway eosinophilia are preferred. The utility of induced sputum inflammation is predominantly recommended for patients thought to have severe disease. As preschool children are unable to spontaneously expectorate, the technique used to obtain induced sputum has to be modified to incorporate chest physiotherapy and oropharyngeal suction. However, this adjustment means a more proximal airway sample is obtained which is only representative of lower airway inflammation in approximately 40% of cases. Therefore, this technique cannot be recommended to assess lower airway cytology in preschool wheezers.

**Induced sputum to assess infection:** The advantages of induced sputum as a reflection of lower airway bacterial and viral infection have been shown in children with recurrent infections of all ages from 6 months and above, and specifically, for preschool children with recurrent wheezing, in whom infection may play an important role in driving disease. There was a 62% agreement in bacterial infection detected by traditional culture techniques between broncho-alveolar lavage and induced sputum from preschool children with recurrent wheeze and infections, suggesting this technique should be adopted in the first instance to avoid the need for invasive tests such as bronchoscopy. Similar findings have been reported for preschool children with cystic fibrosis. It is likely that molecular techniques that allow assessments of the airway microbiome may be important in identifying phenotypes of preschool wheeze and patients that may benefit from targeted antibiotic therapy, use of induced sputum is therefore an attractive option to enable targeted therapy, but the accuracy of induced sputum in reflecting the lower airway microbiome assessed in broncho-alveolar lavage needs to be determined.

**Nasal samples to assess infection:** Numerous studies in infants and preschool wheezers have used nasopharyngeal swabs or aspirates to detect bacterial or viral infection. What remains unclear, however, is the relationship between the nasal and lower airway microbial profile. A recent study has shown very little correlation between nasal swabs and the lower airway microbiome, although throat swabs allowed distinctions between different chronic lung diseases, the differences between broncho-alveolar lavage and throat swabs were too large to allow throat swabs alone to be used for clinical decision making. A possible use of throat swabs in the individual patient may be to look for longitudinal changes following an intervention, or over time. At present, it is difficult to conclude that nasal and throat swabs can be used as a Noninvasive surrogate for broncho-alveolar lavage samples.

**Exhaled nitric oxide (FeNO):** Online FeNO measurements at a flow rate of 50 ml/second are recommended to aid asthma diagnosis in school-aged children if there is diagnostic uncertainty after lung function tests and assessments of reversible airflow obstruction have been made. A systematic review of the utility of exhaled nitric oxide for the diagnosis of asthma in children has shown that the measure may be informative when used in conjunction with other tests, but importantly, that the cut-off for normal should be lower in children than adults. Several factors of relevance to children have been shown to influence levels of exhaled nitric oxide, including age, height, gender, race and passive smoke exposure. Another key issue for children, even if only considering those aged 5 and above, is their technique and ability to perform an adequate maneuver that allows maintenance of a sustained exhalation flow rate and an acceptable recording. With these numerous factors that affect values of exhaled nitric oxide in children, the American Thoracic Society (ATS) guidelines suggest values in children below 20ppb are very unlikely to be associated with eosinophilic airway inflammation, whilst those above 50ppb suggest airway eosinophilia and a response to corticosteroids. A significant factor that must be considered for children when interpreting values of exhaled nitric oxide is the influence of atopy. Allergic sensitization alone, without any clinical manifestation of atopic disease or asthma, is strongly associated with elevated levels of exhaled nitric oxide. On balance, although an assessment of exhaled nitric oxide may be helpful in supporting a diagnosis of asthma in children, given the challenges associated with technical ability to perform the test and the numerous factors that may either elevate or lower the value, its use currently can only be justified in specialist centers, where the equipment is used frequently and technical expertise in obtaining measurements are reliable, where children with diagnostic uncertainty are seen, results are interpreted with the knowledge of the influencing factors.

There is currently no evidence in children that routine measurements of FeNO are helpful for monitoring disease and making adjustments to asthma therapy. Measurements in younger preschool children are very challenging and require the use of offline techniques. However, there are no data showing direct relationships
between FeNO and airway eosinophilia in preschool children, therefore its use in the clinic cannot be recommended.

**Blood eosinophils and neutrophils:** A blood test is easier and can routinely be performed in all clinical settings, thus making the utility of peripheral, rather than airway eosinophils, more attractive to help make a diagnosis of asthma for both adults and children.

In children, several factors need to be considered before the interpretation of a blood eosinophil count. Firstly, the cut-off for normal values changes with age. The range for blood eosinophils in healthy children aged between 6 months and 13 years is between 500 to 700 cells/mcl. Thus, using cut-offs of > 300/mcl as suggested in numerous adult studies may be inappropriate. Another factor that must be considered is the presence of atopic disease without asthma which may result in elevated blood eosinophils without airway eosinophilia. Therefore, if blood eosinophils are relied upon as a biomarker in a child with eczema and wheeze, disentangling the reason for peripheral eosinophilia is difficult and may lead to a false positive diagnosis. Another issue is the impact of steroid treatment on peripheral eosinophil count. If a child is steroid naive, an elevated blood eosinophil count may truly represent airway eosinophilia, but for children on inhaled corticosteroids, the peripheral eosinophil count may be low or normal, while an airway eosinophilia may persist, this is especially true for children with severe asthma. On balance, in school-age children with asthma, given the number of potential caveats that may give a result that does not truly reflect airway eosinophils and without a cut-off for the upper limit of normal yet being established, there is currently little evidence to support the use of blood eosinophils as a diagnostic marker for asthma.

The utility of blood eosinophils as a promising biomarker in preschool children with wheezing to predict response to inhaled corticosteroids has been better evaluated. There is evidence of a positive relationship between blood and broncho-alveolar lavage eosinophils in preschool children. Moreover, preschool children with aero-allergen sensitization and elevated blood eosinophils were differential responders to maintenance inhaled corticosteroids. This suggests two Noninvasive tests, an assessment of allergic sensitization using skin prick tests and a peripheral blood eosinophil count may be helpful in directing treatment for preschool wheezers. The role of respiratory infection (both viral and bacterial) and neutrophilic airway inflammation in mediating symptoms in preschool wheeze is being increasingly recognized in this age group, but Noninvasive biomarkers that distinguish children with predominant eosinophilic and allergic airways disease compared to those with infection-driven disease are currently lacking. Unlike blood eosinophils, there is currently little evidence that blood neutrophils are useful in detecting airway neutrophilia in preschool wheeze.

**Summary:** Noninvasive assessments of airway inflammation, including FeNO, blood eosinophils and sputum eosinophils can be undertaken in children and need to be incorporated into routine clinical practice to help identify treatable traits for children of all changes to allow treatment that is directed to objective phenotypes. Optimal cut-offs for blood eosinophils remain uncertain in children and studies that incorporate this as a biomarker of response to treatment are needed to better define utility in children. The possibility of utilizing aero-allergen sensitization and blood eosinophil values to identify preschool wheezers most likely to respond to inhaled corticosteroids needs also to be prospectively tested. Finally, the potential use of exhaled breath volatile organic compounds to identify lower airway inflammation and infection is an exciting development that needs to be tested in children with airway diseases.

**REFERENCES**


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**2. Will Long Distance and Remote Assessment ever Work?**

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Asthma is one of the most common chronic disorders affecting children and adults. Despite the availability of different effective treatments and evidence-based guidelines to facilitate optimal asthma control, a large proportion of patients in different parts of the world still cannot achieve control resulting in excessive morbidity and mortality. There are many reasons responsible for poor control in different patients. These include under-estimation of disease severity of the patients, under-treatment by patients or their physicians, poor inhalation technique, mismatch of asthma phenotypes and treatment. Poor adherence is probably the most important reason explaining the poor control in many patients. There is a variety of modern digital technologies available to facilitate better adherence and improving the skills of inhalation techniques of asthmatic patients. Some of these technologies can also provide real time information for the clinician to make appropriate adjustments of medications when needed. Such technologies range from simple text messaging to interactive mobile applications which provide long distance monitoring of patients. The use of interactive websites has been shown to be useful in improving asthma control in children. The more primitive methods of using phone calls and text messaging have also been used to improve medication adherence and RCTs have also been performed. The combinations of using an electronic monitoring device and smart phone applications have been developed in parallel to the advances in the development of modern information exchange between patients and their clinicians. Many clinical trials have demonstrated that the use of such application could improve adherence of asthma medication leading to improved asthma control. Patients can also input their daily symptoms using their smart phone and such information can be transmitted to their physicians to facilitate adjustment of medication remotely by their physicians. One can envision the addition of atmospheric data and pollution data to even further refine the adjustment of treatment to obtain the best possible control for individual patients in the near future.

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3 | Exercise Tests in Children

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Introduction For all animals, life is a series of activities or exercises that range from rest to grooming oneself to playing with others. Hence, it could well be appreciated that one’s quality of life is closely related to one’s ability to perform various exercises. For the pediatrician, precise assessment of the cardiorespiratory and metabolic responses to exercise can be a helpful tool in understanding the symptoms of exercise intolerance, in assessing its impact and in recommending specific programs of physical activities. This review is aimed at providing basic information about exercise tests in general and its use in children in particular.

Basic physiology of exercise

Exercise requires muscle contraction which is made possible by the availability of ATP. ATP production is derived from aerobic and anaerobic metabolism of glucose, sometimes fat and rarely protein. Aerobic metabolism, which consumes oxygen, is preferred because of its higher efficiency in terms of production of ATP. This oxygen consumption, VO2, is matched to oxygen delivery, DO2, is a product of cardiac output and arterial/mixed venous oxygen content difference, i.e. DO2 = Q x Hb x (SaO2-SvO2) x 1.34. Aerobic metabolism requires oxy-hemoglobin which is pumped by the heart after the deoxy-hemoglobin is oxygenated in the lung. At rest, oxygen consumption is around 3.5 ml/kg/min. This rises to 30 ml/kg/min in healthy athletic children with strenuous exercise. Anaerobic threshold refers to the highest level of exercise without inducing a sustained increase in lactic acidosis.

Level of exercise (or work capacity) (Fig. 1)
Level of exercise is divided into five grades from very light to very heavy exercise.

**Measurement of exercise capacity:** Exercise capacity is expressed as one of the following indices: 1) oxygen consumption, (2) watts, (3) kilopond meters per minute (kpm), kp referring to the force acting on the mass of 1 kg at the normal acceleration of gravity. Oxygen consumption serves as a physiological index of the rate of energy expenditure.

In adults, oxygen consumption at rest is around 200 to 250 ml per minute. Oxygen consumption increases by approximately 12 ml per minute per watt. Maximal oxygen uptake (VO2max) refers to the level of oxygen consumption of a subject beyond which higher workload does not result in increased oxygen consumption. VO2max can be measured by a cardiopulmonary exercise test (CPET). After VO2max is reached, the additional workload is met by energy produced from anaerobic metabolism. Cardiac output is the limiting factor for VO2max in normal subjects. Most of the increase in cardiac output derives from the increase in heart rate. Cardiac output is approximately 5 liters plus the VO2 times 5 (Q = 5 L + VO2 x 5). A fit and healthy young adult of 70 kg should be able to maintain a VO2max of about 3 L/min. VO2max is commonly used in exercise physiology as a measure of cardiorespiratory fitness. The VO2max is achieved by a combination of increase in cardiac output (up to 5 times), increased oxygen extraction by tissue (up to 3 times), and ventilation (up to 8 times). During heavy exercise, the total work exceeds the capacity of aerobic work. The deficit is made up by anaerobic metabolism, of which the principal product is lactic acid. Lactic acid begins to cause distress at levels above 11 mmol/L, ten times the normal resting level. Lactate accumulation seems to be the limiting factor for sustained distress at levels above 11 mmol/L, ten times the normal resting level.

Cardiac output is the limiting factor for VO2max in normal subjects. Most of the increase in cardiac output derives from the increase in heart rate. Cardiac output is approximately 5 liters plus the VO2 times 5 (Q = 5 L + VO2 x 5). A fit and healthy young adult of 70 kg should be able to maintain a VO2max of about 3 L/min. VO2max is commonly used in exercise physiology as a measure of cardiorespiratory fitness. The VO2max is achieved by a combination of increase in cardiac output (up to 5 times), increased oxygen extraction by tissue (up to 3 times), and ventilation (up to 8 times). During heavy exercise, the total work exceeds the capacity of aerobic work. The deficit is made up by anaerobic metabolism, of which the principal product is lactic acid. Lactic acid begins to cause distress at levels above 11 mmol/L, ten times the normal resting level. Lactate accumulation seems to be the limiting factor for sustained heavy work whilst in moderate to severe exercise, the limiting factor of exercise is degree of shortness of breath (SOB) or dyspnea. SOB is a subjective feeling of "high" proportion of the maximal breathing capacity (MBC). MBC is defined as the maximal minute volume of ventilation that the subject can maintain for 15 seconds. MBC is obtained by asking the subject to breathe in and out of a spirometer without the need for removal of carbon dioxide. Dyspnea ensues when ventilation reaches a third of MBC. In normal subjects, 60% of MBC can normally be maintained with difficulty for 15 minutes.

In children with moderate to severe lung diseases, the VO2max is limited by their decreased MBC. In addition to their reduced ventilatory reserves, patients with lung diseases have increased ventilatory requirements for a given level of exercise because of increased physiological dead space. Moreover, the physiological dead space does not decrease with exercise in those with lung diseases in contrast to healthy individuals.

**Age-related exercise capacity:** Adjusted for size, younger children are able to produce less power than older subjects. VO2max increases in roughly direct proportion with body weight. Compared with adults, children have a faster recovery of heart rate and ventilation after high intensity exercise. The reason behind the difference in recovery is not well known. It may be related to differences in production of lactate, hydrogen ion and catecholamine during exercise.

Indications for exercise tests in children There are three indications to study individuals while they exercise. First, an exercise test can quantify the degree of cardio-respiratory endurance by assessment of an individual's oxygen consumption during maximal exercise (VO2max). Comparison of VO2max with age- and sex-matched controls is informative for assessing an individual's cardio-respiratory endurance. It could also serve as a monitor of disease progression. Second, to elucidate the etiologies for the observed exercise intolerance. Analysis of the results of the exercise tests helps indicate whether the limiting factor is a pulmonary problem, a cardiac problem or lack of conditioning of muscles or poor volition. Third, responses to various treatments (eg inhaled steroid in asthma) can be assessed.

Choice of exercise tests

Exercise tests can be classified by complexity. Simple tests entail little or no equipment. These include time standardized walk, for example 6 minute walk or 3 minutes step test, grip test for muscle strength. Moderately complex tests entail some equipment. These include measurement of FEV-1 and FVC, plotting of flow/volume loop and measurement of oxygen consumption and heart rate. A complex test like VO2max entails measurement of oxygen consumption, carbon dioxide production, cardiac output and various derived values. This complex test is expensive and time consuming. Subject to availability, choice of the appropriate test for children depends on the specific question being asked and the aspect of exercise tolerance that is of interest.

The child undergoing an exercise test should be placed in an environment with little distraction. A child also requires gentle, continuous verbal encouragement during the test. VO2max requires gas exchange analysis, which is of two general types: continuous measurement (breath-by-breath) and discrete measurement (requiring mixing chambers of the exhaled gas). Both systems can yield useful and accurate information on cardio-respiratory responses to exercise. The usual progressive exercise protocol lasts between 10 and 15 minutes and usually about the last half of the test is performed at work rates that are above the subject's lactate or anaerobic threshold. It must be realized that maximal exercise tests are not representative of patterns of physical activities actually encountered in children. It was shown that children were engaged in

<table>
<thead>
<tr>
<th>Level</th>
<th>%VO2max</th>
<th>%HRmax</th>
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<tr>
<td>Very light</td>
<td>&lt;30</td>
<td>3-35</td>
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<tr>
<td>Light</td>
<td>30-49</td>
<td>25-59</td>
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<tr>
<td>Moderate</td>
<td>50-74</td>
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<td>Heavy</td>
<td>75-84</td>
<td>80-89</td>
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<td>Very heavy</td>
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**FIGURE 1** Level of exercise
low-and medium-intensity activities in 77% of the time and high-intensity activity 3.1% of the time from 8 AM to 8 PM. Normal results of maximal exercise tests are obtained from studies performed in large samples of healthy children. These values are profoundly effort-dependent, and healthy subjects are routinely cajoled and prodded to continue exercising in the high-intensity range To achieve data of optimal quality. In contrast, patients with known or even suspected abnormalities are not encouraged as vigorously as are healthy subjects. Lactic acidosis and respiratory or cardiac insufficiency can accompany high work rates, and this causes reasonable concern regarding the safety of high-intensity exercise testing in individuals with heart or lung disease. Hence, it is important to have a qualified medical staff with appropriate equipment for emergency treatment by the patient's side. His/her main tasks would be to stop the test if the child is clinically unstable and to respond to any complications, for example asthma attack, arrhythmia. Subsequently, published "normal" maximal values may not be reliable for children with suspected impairment, for whom a progressive submaximal test is more appropriate.

The complication rate was 1.79% in one series of 1,730 studies. It included chest pain, dizziness or syncope and decreased blood pressure. Hazardous arrhythmias occurred in only 0.46% of subjects. No mortality was recorded.

In conclusion, exercise tests in children are very helpful for children who complained of discomfort during exercise. CPET is one of the exercise tests that is helpful to quantify cardio-respiratory health.

REFERENCES
Step 2 is to recognize anomalies suggesting complications of OSDB, such as behavioral or cognitive problems, attention deficit hyperactive disorder, excessive daytime sleepiness, systemic or pulmonary hypertension, nocturnal enuresis, failure to thrive, metabolic syndrome or decreased quality of life. 

Step 3 is to recognize conditions associated with persistence of OSDB without treatment, such as adenotonsillar hypertrophy, obesity, neuromuscular disorders, genetic disorders, craniofacial anomalies or male sex.

Following clinical evaluation, and given that the literature most often uses the apnea-hypopnea index (AHI) to describe OSDB severity, the ERS Task Force stated that the next step should be the performance of an attended, overnight polysomnography (PSG). The latter allows the severity of OSDB to be quantified and obstructive sleep apnea syndrome (OSAS) to be diagnosed. It also helps in deciding which children must be treated vs. those that can be carefully followed. Using the PSG results, the ERS Task Force statement recognized the existence of two definitions for OSAS in children, both requiring the presence of OSDB symptoms: 1) obstructive AHI ≥ 2 episodes·h⁻¹ or obstructive apnea index ≥ 1 episode·h⁻¹; 2) AHI ≥ 1 episode·h⁻¹ (including both obstructive and central events). In addition, the presence of an AHI > 5 episodes·h⁻¹ implies that OSDB is unlikely to resolve spontaneously and that the child is at special risk for morbidity. The ERS Task Force stated that no alternatives can fully replace overnight PSG in children with OSDB. When an attended, overnight polysomnography or cardiorespiratory polygraphy is not available, several options can however predict OSAS. These include ambulatory polysomnography or cardiorespiratory polygraphy, or nocturnal oximetry. Finally, both the Pediatric Sleep Questionnaire and the Sleep Clinical Record (2) have been shown to be of some value to predict OSAS.

As per the ERS Task Force statement, the above diagnostic procedures typically lead to a step-by-step treatment of the anomalies recognized as risk factors for OSDB in children. Reevaluation after each intervention is mandatory to detect residual significant OSDB and to determine the need for further treatment.¹

Alternatives to overnight, attended polysomnography: The recognition of the gap between the high number of children with symptomatic OSDB and the poor availability of overnight PSG worldwide has led to the search for alternative tools. While home cardiorespiratory polygraphy is used in many centers in lieu of PSG in children with high-pretest probability for OSA, it is still not available for the majority of OSDB children. In addition, the American Academy of Sleep Medicine has endorsed the following position statement: “Use of a home sleep apnea test is not recommended for the diagnosis of OSA in children”.³ On the other hand, home-based nocturnal oximetry presents the distinct advantage that it is widely available. The McGill score is commonly used to prioritize OSDB children for adenotonsillectomy⁴ and a score > 1 can be used to identify OSDB children who need to be monitored overnight postoperatively.⁵ Moreover, results from a study on the automatic analysis of home nocturnal oximetry have shown its reliability and accuracy, suggesting that it “could be an essential approach To develop abbreviated diagnostic tools for childhood OSA”.⁶ Further results on a patient database from 17 centers worldwide strongly suggest that neural network-based automated analyses of oximetry recordings accurately identify OSA severity among OSDB children.⁷ Finally, it has been recently shown that a 3% desaturation index ≥ 3.5/h can be used to recognize OSDB children with hypoxemia responsive to adenotonsillectomy.⁸ Overall, nocturnal oximetry increasingly appears as a valuable alternative to overnight polysomnography to help decide which OSDB children need to be treated and when. It is however important to stress that the accuracy of nocturnal oximetry has mostly been validated in OSDB children without co-morbidity.

Drug-induced sleep endoscopy: (DISE) is intended to mimic sleep by using an anesthetic drug such as dexmedetomidine, which has little impact on upper airway muscle functioning. DISE is useful to thoroughly assess the upper airways and identify the site(s) of obstruction, such as late-onset laryngomalacia and enlarged lingual tonsils. It is consequently used to guide ENT surgery.⁸ The jury is still out on the best time to perform DISE, either systematically before adenotonsillectomy, or as a second step when significant OSDB is still present after adenotonsillectomy.

Nasal continuous positive airway pressure (CPAP): Nasal CPAP is increasingly used in OSDB children, when optimal surgical and medical treatment is not sufficient to cure the disease. Current guidelines recommend performing CPAP titration during an attended, overnight PSG. Given the poor availability of the latter, successful outpatient initiation of nasal CPAP has been reported in OSDB children, using auto-titrating devices for children weighing more than 30 kg.⁹

Diagnosis and management of young children aged less than 2 years with OSDB: A statement from an ERS Task Force on the subject has been published in 2017.¹⁰ Similar to children aged more than 2 years, a step-by-step approach was proposed, based on a review of the literature until December 2016 as well as the current practice of the Task Force members. The main differences with the Task Force statement for children aged 2 to 18 years are as follows. The diagnosis of OSDB is more often considered in infants with stridor during wakefulness or in the context of craniofacial anomalies (eg Pierre Robin sequence), genetic disorders, neuromuscular disorders (eg cerebral palsy, spinal muscular atrophy), pulmonary hypertension, delayed somatic growth or apparent life-threatening event. Tonsillar hypertrophy is rare at this age. Upper airway imaging (eg, for craniosynostosis) is more often performed, as well as upper airway endoscopy. While the latter is often performed during wakefulness, DISE has also been shown to be valuable.⁸ Finally, although nocturnal PSG should preferentially be used to diagnose OSAS, nocturnal oximetry is often used as an alternative test to predict OSAS.

REFERENCES
3  |  Early Interventions to Change the Trajectory of Childhood Sleep Disordered Breathing

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The pharynx is a collapsible tube with no rigid supports. It is critically involved in many functions from the earliest moments of life, including sucking, swallowing, vocalization, phonation, and later, speech. Pharyngeal anatomy, in addition to the nose, is also involved in the upper airway support of breathing during wakefulness as well as sleep, and in the context of change inherent in different sleep states. The size and dynamics of the upper airway [UA] have an impact on airflow. Sleep itself is associated with a fundamental modification of pharyngeal muscle tone and reflex responses, and leads to functional narrowing and increased upper airway resistance in normal individuals.

Certain conditions have the potential to make the pediatric UA more susceptible to collapse during sleep, and these act directly on the main factors responsible for the size of UA: development of anatomic support of UA; and neurological control of muscles constituting UA. Patency of the UA is also determined by airway tissue size, and almost all attention has been has been focused on this latter factor (such as in the case of enlarged adenoids and/or tonsils), rather than the fundamental determinants of collapsibility. In fact, any abnormality of one of these two factors described above which determine the functional size of the UA – anatomical development and neuromuscular control – will have a negative impact on airflow.

Several factors have been identified which impact normal development of anatomical structures supporting UA. These include:

Prematurity: During fetal life, starting at 18 weeks gestation, critically important “training” of sucking and swallowing actions allows development of appropriate reflexes involving the tongue and muscular support of the UA. Premature—even modestly premature—infants under 37 weeks gestational age may have both generalized hypotonia which does not spare the tongue and UA muscles, and abnormal training of sucking and swallowing reflexes. This effect is likely to be augmented at lower gestational age.

Abnormal stimulation of 2 orofacial growth centers active after birth: Important orofacial growth centers, including the intermaxillary cartilage, which is responsible for osteochondral maxilla ossification; and the dento-alveolar ligaments, which suspend roots of permanent teeth and are responsible for maxillary and mandibular growth, remain active until mid-puberty, around 13-15 years of age. Normally there is a continuous stimulation of these centers via actions of nasal breathing, sucking, swallowing, mastication, and phonation. Several known defects will impact normal development from birth on, leading to clinically narrow hard palate and abnormal maxillary or maxillo-mandibular growth. Some are genetically associated, ranging from, for example, well-recognized diseases of neuromuscular dysfunction (Duchenne, Myotonic Dystrophy, Charcot-Marie-Tooth); and connective tissue disorders (Marfan Syndrome, Ehlers-Danlos syndromes, and other hyperlaxity syndromes); to the less-well-recognized syndrome of short lingual frenulum (or more rarely, short labial frenulum). Other common and very much under-recognized syndromes contributing to poor stimulation of the orofacial growth centers include: dental agenesis when two or more permanent teeth are missing/undeveloped; and ongoing nasal obstruction. Nasal obstruction itself is interesting as a manifestation of a multitude of potential underlying defects, including significant nasal septum deviation, enlarged adenoids from an early age, early nasal allergic or nonallergic inflammation, and enlarged tonsils, particularly if not addressed early in life.

Clinically, when any one of these problems are suspected or detected, a thorough history and physical examination should ensue, including a systematic clinical evaluation of the nasal and oral airways, looking for resultant anatomical features: a narrow palate, maxillary and/or mandibular underdevelopment, dental crowding or bite abnormalities (open or crossbite), the presence of speech and swallow abnormalities, chronic oral breathing, all of which indicate factors which may impede normal orofacial development. It is also important to obtain a careful family history, as not infrequently, family members are affected...
too but are unaware of the manifest impact of poor sleep and abnormal breathing in themselves or relatives.

If such features are present, clinical evaluation should lead to nocturnal polysomnography - PSG-with an accepted montage evaluating sleep. PSG testing should be of at least 7 hours and must be done with simultaneous video recording allowing important behavioral observation.

We are well past the era of simply analyzing the PSG for classic apnea and hypopnea.

It is important to systematically measure and communicate indicators of non-hypoxic abnormal breathing during sleep. As mentioned, the UA is controlled by reflexes that have a much higher response threshold during sleep and may be less functional at times, particularly during REM sleep. If the UA is compromised in some way, a number of physiologic responses may occur (increased inspiratory effort; increased respiratory rate, etc), but the common-pathway, primary defense will be an "arousal response" that will disrupt sleep but will lead to airway re-opening and reduced resistance.

The response threshold is thought to vary based on genetic factors, but also depend on features of sleep itself, including whether recent sleep curtailment exists (exogenous sleep restriction), and also importantly the amount of sleep disruption and sleep fragmentation to which one has been exposed. The longer the exposure to abnormal breathing during sleep and ensuing sleep fragmentation, the more blunted the arousal response may become, until finally leading to overt obstructive hypopnea and, especially when such abnormalities are stacked together, emergence of discrete oxygen desaturation. The presence of repetitive oxygen desaturation in the typically developing child without overt cardiopulmonary disease – including obesity -is a truly late event, and in many cases indicates that the syndrome was not picked up at its earliest manifestations.

From infancy on, poor sleep has an impact. For one thing, sleep disruption and ensuring behavioral change during wake may be seen as "pseudo-colic" in the infant with repetitive awakenings and crying in addition to sleep restriction and fragmentation; in older children, behavioral manifestations have been very well reported, and are correlated with features of abnormal breathing other than AHI. The early recognition of abnormal breathing is critical. Great value must be given to identifiable, early indicators of abnormal breathing on PSG. These include mouth breathing during sleep: Humans are strongly preferential nasal breathers in the absence of pathology, and restoration of normal breathing during sleep, when airway resistance is naturally higher than wake, is probably a good indicator of a return to normal breathing route overall. In normal individuals, mouth breathing occurs about 5% of sleep time [range 0 to 10%]; any increase indicates abnormal breathing during sleep.

Once detected, efforts must be made to remedy abnormal influences on structure or function of the upper airway as early as possible. In the case of prematurity, this means transitioning to breast feeding as soon as possible, as needed with guidance from a therapist specialized to assist in this transition. During fetal life, Hooker reflexes are present which are very similar to the primitive reflexes present at birth in normal infants (The reflex protusion of lips and tongue when lips are stimulated, with direction of tongue toward the point of stimulation, and induction of a suck-swallow reflex). This reflex may be used to start transition to readiness in the non-breastfeeding premature infant, and when infant suck strength and swallow coordination are sufficient, bottle feeding can be initiated using a special nipple and progressively increase resistance. In this way, there may be a role for myotherapy at the earliest stages of life. In young children outside of the neonatal period, it is equally important to recognize, and then address -if possible-precipitating factors related to breathing disruption in sleep.

In the case of short frenulum, clipping of frenulum is only possible during the 1st month of life; after this timeframe, a frenulum disinsertion is needed. It is equally important in this situation to undergo myofunctional therapy to maximize gain from the procedure; but this is not always easy to achieve, since exercises are required daily, which may be difficult in many instances. Passive myofunctional therapy with an oral device has been reported, but numbers are low and more work is needed in this area. Orthodontic approaches have also aimed to stimulate the intermaxillary growth center in the very young. This can be successful and can begin as early as 1 year of age with a Crozat expander.

Whatever the early methods used, after detection of maladaptive influences on UA growth and function, appropriate follow-up must ensue. This is the role of the sleep specialist.

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CHALLENGING CASES
The four abstracts selected for this session and presented orally by their first author are cited below. You can read them in the "POSTERS" section, category # 14
O-87 Repetitive Respiratory Wheezing Due to Pulmonary Artery Sling.
Chang Tai Yeh – Kaohsiung, Taiwan
Aerodigestive Dysbiosis in Children

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With the advent of next generation sequencing (NGS), we now recognize that the lower airways harbor a complex microbial community. This community is influenced by the environment as well as by the host conditions. Changes in the lower airway microbial community structure and composition are associated with host immune tone, disease states and acquisition of pathogens. For a long time, we have recognized the presence of an infection by a pathogen. Now that we are starting to accept that the lower airways are not sterile, we need to identify changes in the lower airway microbial structure and composition that may lead to changes in host immunity and pathogen susceptibility. Investigators have adopted the term dysbiosis as a way to describe in broad terms changes in mucosal microbiota that occur in different pathogenic conditions. Even more obscure is the use of this term when referring to the lung microbiota.

In early life, the lung microbiota develops under the influence of the environmental microbial exposure. For example, preterm babies born by C-section have a lower airway microbiota enriched with Staphylococcus, a common skin commensal, whereas preterm babies born via vaginal delivery have their lower airway microbiota enriched with Ureaplasma, a common vaginal commensal.1 These early dysbiotic signatures delay the maturation of the innate immune system in the lower airways, which requires the development of a more diverse lower airway microbiota. The main source of this diverse microbiota is the upper airways.

Microaspiration of oral secretions commonly occur leading to one form of dysbiosis, under which the lower airways are enriched with oral commensals, which we termed pneumotypeSPT for presence of supraglottic predominant taxa.2,3 This form of dysbiosis is frequently found in health, is consistent with prior observations that microaspiration frequently occurs even in healthy subjects,4,5 and its prevalence is likely increased in many airway inflammatory diseases. In children with increased risk of aspiration, finding oral commensals in the lower airways is associated with inflammatory markers.6 The mechanisms by which this form of dysbiosis leads to specific host immune response are not clear. Some of these are likely mediated by pathogen-associated molecular patterns. Although oral commensals are not considered pathogens in the upper airways, they do express small molecules that can bind to pattern recognition receptors such as toll-like receptors. Further, this lower airway microbiota signature can also affect the lower airway metabolic environment with presence of metabolites with significant immunomodulatory effects.3 An example is the presence in the lower airways of short chain fatty acids, which are end-products of fermentation of anaerobes such as oral commensals and cannot be produced by mammalian cells. These molecules can affect T cell responses to pathogens.7

A different type of dysbiosis occurs during infections with pathogens. In this scenario, one would expect that the lower airway microbiota would be enriched and dominated by the pathogen. This situation has been described in the lower airways of children with chronic cough colonized with Haemophilus.4 However, in many other situations, pathogens are present in low abundance and coexisting with a very diverse microbiota. An example of this situation occurs during infections with non-tuberculous mycobacterium, where these pathogens are rarely found in high abundance.8 Importantly, some of the non-pathogenic microbes seem to have a stronger association with levels of inflammatory markers in the lower airways than the pathogen itself. This therefore suggests that other dysbiotic signatures beyond the presence of the pathogen might be contributing to the disease process.

In conclusion, we are now starting to identify dysbiotic signatures in the lower airways by evaluating either host inflammatory profiles present or colonization with pathogens. These signatures will be key to uncover mechanisms by which the lower airway microbiota contributes to the disease process.

REFERENCES
Neonatology for the Pediatric Pulmonologist: Imaging Beyond BPD

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Bronchopulmonary dysplasia (BPD) is a chronic lung disorder most common in low birth weight premature infants. Originally described in 1967, the characteristic clinical and radiographic features of BPD have evolved over time with increased viability of very premature infants and changes in therapy, including exogenous surfactant administration and less aggressive positive pressure ventilation and oxygen supplementation. So-called "new" BPD, although first described over 20 years ago, is primarily related to acinar underdevelopment with alveolar enlargement and simplification, and is subsumed under the category of alveolar growth disorders in the standard classification scheme for pediatric diffuse lung disease.

While BPD associated with prematurity is the most common alveolar growth disorder, alveolar growth abnormality is also the characteristic feature of certain other neonatal lung disorders. These include Wilson-Mikity syndrome, occurring in low birth weight infants with slowly progressing respiratory distress in the first few weeks of life despite minimal respiratory support at birth, and pulmonary hypoplasia related to limited intrathoracic space in utero. These conditions are also associated with congenital cardiovascular disease, lung malformation, or skeletal dysplasia. Alveolar growth abnormality is also seen in association with congenital cardiovascular disease, trisomy 21, and as an idiopathic condition.

Patients with an alveolar growth abnormality typically present with neonatal respiratory distress, and either improve or worsen depending on the extent of catch-up growth of the alveoli and whether or not pulmonary hypertension ensues. The chest radiographic (CXR) and computed tomography (CT) findings in infants with BPD and other alveolar growth abnormalities range from nearly normal to markedly abnormal, with distorted pulmonary lobules, peribronchial reticular opacities, ground-glass opacities, and luencies resembling emphysema or "cysts." The luencies are attributable to enlarged alveoli with reduced alveolar septation and vascularization, and quantitative CT scoring based on these findings correlates with the clinical severity, level of respiratory support, and risk of rehospitalization.

Overdistention of the airways and airspaces, especially in the setting of positive pressure ventilation and noncompliant lungs, can result in pulmonary interstitial emphysema (PIE), air leak and cardiorespiratory compromise. To avoid these complications, it is important not to confuse PIE with the "cysts" commonly observed in alveolar growth disorders.

Pulmonary interstitial glycogenosis (PIG), previously known as infantile cellular interstitial pneumonitis, should be suspected in neonates and young infants with respiratory distress out of proportion to their gestational age. PIG is characterized by infiltration of the pulmonary interstitium by glycogen-laden lipofibroblasts, resulting in restrictive lung disease with impaired gas diffusion. PIG is associated with alveolar growth abnormality, pulmonary hypertension and congenital cardiovascular disease, and the ultimate clinical outcome primarily depends upon the severity of these comorbidities. CT findings reported in PIG include ground-glass opacities and cysts, but these are nonspecific and possibly attributable to the underlying alveolar growth abnormality, and definitive diagnosis is not possible without biopsy. Corticosteroid therapy may hasten the resolution of PIG, possibly due to acceleration of lung maturation, but should be used judiciously since this disorder is self-limited and typically resolves by late infancy.

A genetic disorder of surfactant metabolism should be considered in the setting of unexplained severe respiratory distress syndrome (RDS) in a late preterm or term neonate. Usual histological findings are pulmonary alveolar proteinosis with diffuse alveolar epithelial hyperplasia and foamy macrophages without hyaline membrane formation. Neonates unable to produce surfactant protein B (SP-B) due to disease-causing biallelic inherited autosomal recessive SP-B gene mutations typically develop severe RDS within hours of birth, and diffuse hazy granular pulmonary opacification similar to RDS of prematurity is shown on CXR. In contrast to RDS of prematurity, infants with genetic SP-B deficiency progress to respiratory failure that is unresponsive to exogenous surfactant administration. Without lung transplantation, most die within a few months after birth. Acute severe RDS in neonates or chronic diffuse lung disease in older infants can be associated with spontaneous or inherited autosomal dominant surfactant protein C (SP-C) gene mutations or biallelic autosomal recessive ATP binding cassette A3 (ABCA3) gene mutations.

Monoallelic ABCA3 mutations are present in 3%-4% of infants of European descent and are overrepresented in infants of > 33 weeks gestational age with RDS. CXRs of infants with disease-causing SP-C or ABCA3 gene mutations demonstrate hazy granular pulmonary opacities, while CT scans show ground-glass opacities, consolidation, septal thickening, or crazy-paving. NK2 homeobox 1 (NKK2-1), also known as thyroid transcription factor-1 (TTF-1), is expressed in the lung, thyroid, and forebrain, and regulates transcription of the genes for surfactant proteins and Clara cell secretory protein. Disease-causing sporadic or inherited autosomal dominant NKK2-1 gene mutations or deletions lead to maldevelopment of the basal ganglia and thyroid and decreased production of surfactant proteins, resulting in "brain-lung-thyroid syndrome."
characterized by congenital hypothyroidism, hypotonia, chorea, and lung disease. Clinical manifestations of the lung disease are varied, with neonatal RDS being the presenting pulmonary phenotype in most cases.

Recognition of clinical and imaging findings suggestive of a genetic disorder of surfactant metabolism is crucial for guiding genetic testing and possibly avoiding lung biopsy. Lung biopsy may still be appropriate if genetic testing is non-diagnostic or if awaiting the results of genetic testing would unduly delay the diagnosis in patients with rapidly progressive disease requiring lung transplantation for survival. Occasional cases are encountered in which imaging and pathological features are suggestive of a surfactant disorder but genetic testing for known disease-causing mutations is negative. These cases are likely related to uncharacterized genetic defects of surfactant metabolism, especially those with a family history of unexplained childhood-onset diffuse lung disease.

Although very rare, the diffuse developmental disorders of the lung are associated with markedly impaired alveolar gas exchange, resulting in respiratory failure and severe pulmonary hypertension within days of birth in the absence of the usual causative conditions of prematurity, meconium aspiration, congenital heart disease, perinatal asphyxia, or sepsis. Acinar dysplasia is characterized by developmental arrest of the lungs in the pseudoglandular or early canalicular phase, resulting in a paucity of alveolar spaces, while congenital alveolar dysplasia is characterized by arrest in the late canalicular/early saccular phase, resulting in incomplete alveolarization. Alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD/MPV) is characterized by reduced alveolar capillary density, pulmonary lobular maldevelopment, and anastomotic bronchial veins (previously mischaracterized as misaligned pulmonary veins) with intrapulmonary right-to-left shunting that bypasses the alveolar capillary bed. ACD/MPV is also associated with malformations of the cardiovascular system, gastrointestinal or urinary tracts, and some cases are related to sporadic or familial autosomal dominant FOX1 gene mutations. Although the initial CXRs may be unimpressive, follow-up CXRs may show progressive hazy opacification of the lungs, resembling the findings of RDS of prematurity or genetic surfactant disorders. Air leak is common and likely related to barotrauma. Death usually ensues within a few weeks, unless the lung involvement is patchy rather than diffuse, or extracorporeal membrane oxygenation (ECMO) is available as a bridge to lung transplantation.

Pulmonary lymphangiectasia is characterized by dilation of lymphatics draining the interstitial and subpleural spaces and can be a primary disorder or secondary to lymphatic congestion from conditions such as congestive heart failure or obstructed pulmonary veins. The primary form is typically congenital and may be accompanied by nonimmune hydrops fetalis, congenital chylothorax, or generalized lymphedema. Primary pulmonary lymphangiectasia classically presents in a late preterm or term neonate with severe respiratory distress and diffuse hazy opacification of the lungs on CXR resembling the findings of RDS of prematurity or a genetic surfactant disorder. CT reveals septal thickening, bronchovascular bundle thickening, patchy ground-glass opacities, and pleural effusion. Treatment of primary pulmonary lymphangiectasia is generally supportive, and prognosis is poor.

Primary ciliary dyskinesia (PCD) is a genetic disorder characterized by dysfunctional ciliary function. Multiple genes have been linked to PCD, but known disease-causing mutations account for only about 60% of PCD cases. Cilia lining the respiratory tract play an important role in clearing amniotic fluid from the neonatal lungs. Neonatal respiratory distress occurs in up to 70 to 75% of patients with PCD, although this is often misattributed to transient tachypnea of the newborn or neonatal pneumonia, and the diagnosis of PCD is frequently delayed until later childhood or adulthood following evaluation for recurrent respiratory tract infections. Situs inversus or heterotaxy occurs in half of PCD cases, related to randomization of left-right axis asymmetry from embryonic nodal cilia dysfunction. Recognition of clinical or imaging features suggestive of PCD should prompt confirmation of diagnosis with genetic testing, ciliary beat analysis or electron microscopy.

In summary, alveolar growth disorders are the most common cause of chronic diffuse lung disease of neonatal onset, with BPD being by far the most prevalent, although other conditions manifesting alveolar growth abnormalities are often underrecognized and include Wilson-Mikity syndrome, pulmonary hypoplasia, trisomy 21, and congenital cardiovascular disease. Lucencies or ‘cysts’ on imaging serve as a marker of the severity of the alveolar growth disorders, and the additional presence of ground-glass opacities suggest possible superimposed PIG. The finding of diffuse pulmonary opacities in a late preterm or term neonate with unexplained severe RDS should prompt evaluation for a genetic surfactant disorder, diffuse developmental disorder, or lymphangiectasia.

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Iatrogenesis is more common in neonatal intensive care units (NICUs) because the infants are vulnerable and exposed to prolonged intensive care. Sixty percent of extremely low-birthweight infants are exposed to iatrogenesis. The risk factors for iatrogenesis in NICUs include prematurity, mechanical or Noninvasive ventilation, central lines, and prolonged length of stay. This led to the notion in modern Neonatology that “less is more.” Kugelman et al1 reviewed how this is implemented in the delivery room, with prenatal steroids, delayed cord clamping, oxygen supplementation and suctioning of the upper airways during deliveries with meconium-stained fluid. Minimal handling is then described in the NICU by using Noninvasive respiratory support and surfactant administration, and in using modalities that may allow continuous Noninvasive monitoring of CO2. “Kangaroo Care” and Newborn Individualized Developmental Care and Assessment Program (NIDCAP). Whether “less is more,” or not enough, is to be seen in future studies.

While trying to use Noninvasive ventilation to decrease the need for intubation, we have to be aware of iatrogenesis related to NIV. Binasal prongs are the most effective interface for nasal continuous positive pressure (CPAP) delivery; however, their use is associated with pressure-related nasal injury. Imbulana et al2 published a systematic review concluding that nasal injury is common in preterm infants born < 30 weeks’ gestational age receiving CPAP via binasal prongs and showed that nasal masks and nasal barrier dressings may reduce nasal injury secondary to CPAP. Nasal high flow causes less nasal injury than CPAP. A recent meta-analysis showed that nasal mask may be as effective as binasal prongs for providing nasal respiratory support.3

An interesting study regarding Noninvasive ventilation was published by Songstad NT et al4 The authors assessed whether using retrospective consent affected recruitment, participant characteristics, and outcomes within a randomized controlled trial. They conducted a secondary analysis of a randomized trial, which compared nasal high flow (nHF) with nasal CPAP for primary respiratory support in preterm infants. In Era 1, all infants were consented prospectively; in Era 2, retrospective consent was available. The use of retrospective consent resulted in greater recruitment and differences in risk factors between eras (more intrapartum antibiotic use, less full courses of antenatal steroids and pre-randomization CPAP). The main outcome was also affected: in Era 1, nHF failure (15 of 56, 27%) and CPAP failure (14 of 55, 26%) rates were similar, P = 0.9. In Era 2, failure rates differed: 24 of 85 (28%) nHF infants versus 13 of 86 (15%) CPAP infants, P = 0.04. Using retrospective consent altered the study sample, which may be more representative of the whole population. This may improve scientific validity but requires further ethical evaluation.

In line with the less invasive approach, a recent randomized clinical trial was performed on the effect of needle aspiration of pneumothorax on subsequent chest drain insertion in newborns.5 Infants were randomly assigned to drainage using needle aspiration (NA, n = 33) or chest drain (CD, n = 37) insertion, stratified by center and gestation at birth (<32 vs. >32 weeks). Fewer infants assigned to NA had a CD inserted within 6 hours (55% [18 of 33] vs. 100% [37 of 37]; relative risk, 0.55; 95% CI, 0.40–0.75) and during hospitalization (70% [23 of 33] vs. 100% [37 of 37]; relative risk, 0.70, 95% CI, 0.56–0.87. The authors concluded that needle aspiration reduced the rate of CD insertion in symptomatic newborns with pneumothorax diagnosed on chest radiography.

On the other hand, less may not always be more as suggested by the following two examples. The first example deals with the recent Neonatal Resuscitation Program (NRP) recommendation against routine endotracheal suctioning of meconium-stained nonvigorous newborns but suggested resuscitation with positive pressure ventilation. The purpose of the study by Chiruvolu A et al6 was to study the effects of this change in management. In this multicenter cohort study, 130 nonvigorous newborns born during 1 year before implementing the new NRP guidelines (retrospective group) were compared with 101 infants born after these recommendations (prospective group). Significantly higher proportions of newborns were admitted to the NICU for respiratory issues in the prospective group compared with the retrospective group (40% vs. 22%) with an odds ratio (OR) of 2.2 (95% confidence interval [CI]: 1.2–3.9).

Similarly, a significantly higher proportion of infants needed oxygen therapy (37% vs. 19%) with an OR of 2.5 (95% CI: 1.2–4.5), mechanical ventilation (19% vs. 9%) with an OR of 2.6 (95% CI: 1.1–5.8) and surfactant therapy (10% vs. 2%) with an OR of 5.8 (95% CI: 1.5–21.8). The authors concluded that the recent NRP guideline change was not associated with an increased incidence of meconium aspiration syndrome but was associated with an increased incidence of NICU admissions for respiratory issues.
The second example comes from targeting oxygen saturation in extremely premature infants. In a prospectively designed meta-analysis of individual participant data from 4965 infants in 5 randomized clinical trials, there was no significant difference in the primary composite outcome of death or major disability between those treated with lower vs. higher oxygen saturations (53.5% vs. 51.6%, respectively). However, lower oxygen targets were associated with increased death and necrotizing enterocolitis. The rate of retinopathy of prematurity treatment was reduced. A recent study found that lower saturation of infants kept on low oxygen saturation targeting was associated with a higher rate of pulmonary hypertension. This might be the reason for the higher death rate in this group, although this assumption was not tested.

To minimize invasive ventilation and prevent bronchopulmonary dysplasia (BPD), the role of corticosteroids that are considered to be not harmful to the neurodevelopmental system is under assessment. Onland et al. evaluated the effect of systemic hydrocortisone, initiated between 7 and 14 days after birth, on death or BPD among very preterm infants (< 30 weeks’ gestational age) receiving mechanical ventilation. This was a double-blind, placebo-controlled randomized trial conducted in 19 NICUs in the Netherlands and Belgium. Infants were randomly assigned to receive a 22-day course of systemic hydrocortisone (n = 182) or placebo (n = 190). Death or BPD occurred in 70.7% infants randomized to hydrocortisone and in 73.7% of infants randomized to placebo (adjusted risk difference, −3.6% [95% CI, −12.7% to 5.4%]; P = 0.54). Death at 36 weeks’ postmenstrual age occurred in 15.5% with hydrocortisone vs. 23.7% with placebo; risk difference, −8.2% [95% CI, −16.2% to −0.1%]; P = 0.048) and a nonsignificant difference was found in BPD (55.2% with hydrocortisone vs. 50.0% with placebo; risk difference, 5.2% [95% CI, −4.9% to 15.2%]; P = 0.31). The authors concluded that among mechanically ventilated very preterm infants, administration of hydrocortisone between 7 and 14 days after birth, compared with placebo, did not improve the composite outcome of death or BPD at 36 weeks’ postmenstrual age.

Finally, Go M et al. compared the respiratory compliance in late preterm infants (340–346 weeks) who received antenatal steroids (n = 25) vs. matched late preterm infants (n = 25) who did not receive antenatal steroids. This was a single-center prospective cohort study. The treated infants had a significantly increased respiratory compliance/kg (adjusted 95% CI, 0.03-0.49; P = 0.016) and fewer required continuous positive airway pressure (P = 0.007) or > 24 hours of supplemental oxygen (P = 0.046). The authors concluded that respiratory compliance was significantly increased in this cohort of late preterm infants who received antenatal steroids compared with matched infants who did not receive antenatal steroids. Although not randomized, these data provide physiological support for the possible beneficial effects of antenatal steroids in late preterm infants.
Preterm infants with respiratory distress syndrome (RDS) have low pulmonary compliance and high thoracic-cage compliance. Thus, to avoid loss of lung volume and atelectasis, they need gentle support of functional residual capacity (FRC) and surfactant replacement. The aim of the respiratory treatment of RDS is to oxygenate and ventilate the premature infants while preventing death, bronchopulmonary dysplasia (BPD), and neurological morbidity.\textsuperscript{1, 2} Even a few breaths by positive pressure ventilation were found to be harmful to the lungs. Furthermore, endotracheal ventilation was found to be associated with cerebral palsy and low mental developmental index. Thus, to achieve the goals of respiratory support, we try to avoid endotracheal ventilation by using Noninvasive ventilation (NIV). This strategy is part of the notion of modern Neonatology that “less is more.”\textsuperscript{2}

NIV may be used in the initial treatment of RDS with the aim to decrease the rate of endotracheal ventilation.\textsuperscript{3} Allowing nasal respiratory support as a safe and efficient alternative to endotracheal ventilation and surfactant in the most premature infants was the result of a thorough evaluation by two large RCTs. Morley et al.\textsuperscript{3} randomly assigned 610 infants who were born at 23-28 weeks gestation to nasal continuous positive airway pressure (NCPAP) or intubation and ventilation at 5 minutes after birth. They concluded that early NCPAP did not significantly reduce the rate of death or BPD, as compared with intubation. The SUPPORT trial\textsuperscript{4} was a randomized, multicenter trial, involving infants who were born at 24.0 to 27.6 weeks gestation. Infants were randomly assigned to intubation and surfactant treatment (within 1 hour after birth) or to NCPAP treatment initiated in the delivery room. A total of 1,316 infants were enrolled in the study. This study supported consideration of NCPAP as an alternative to intubation and surfactant in preterm infants. The primary outcome (death or BPD) rates did not differ significantly between the two groups. However, infants in the NCPAP group required less frequent intubation or postnatal corticosteroids for BPD (P < 0.001), required fewer days of mechanical ventilation (P = 0.03), and were more likely to survive and be free from mechanical ventilation by day 7 (P = 0.01). These studies made it possible to consider NCPAP as an alternative to intubation and surfactant in extremely preterm infants and revealed a small but significant benefit in long-term outcomes.

Attempts to enhance NCPAP to achieve a better outcome for nasal respiratory support led to the use of nasal intermittent positive pressure ventilation (NIPPV). A recent meta-analysis\textsuperscript{5} including ten trials, enrolling a total of 1061 infants, showed significantly reduced risk of meeting respiratory failure criteria (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.53-0.82) and needing intubation (typical RR 0.78, 95% CI, 0.63-0.94) among infants treated with early NIPPV compared with early NCPAP. The meta-analysis did not demonstrate a reduction in the risk of BPD among infants randomized to NIPPV (typical RR 0.78, 95% CI, 0.53-1.06). The authors concluded that early NIPPV does appear to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation and endotracheal tube ventilation among preterm infants with RDS. For the initial therapy of RDS, high-flow nasal cannula (HFNC) compared with NCPAP in 564 infants with gestational age ≥ 28 weeks was associated with significantly higher rates of treatment failure within 72 hours. “Rescue” NCPAP use resulted in similar intubation rates in the two treatment groups.\textsuperscript{6}

NIV is used also for preventing extubation failure in premature infants.\textsuperscript{2} For post-extubation, a meta-analysis showed that synchronized NIPPV reduced the incidence of extubation failure and the need for re-intubation within 48 hours–1 week more effectively than NCPAP; however, the rate of BPD or mortality was not changed. The number needed to treat was 3 infants.\textsuperscript{7} It is possible that the additive effect of NIPPV compared to NCPAP is related to synchronization. Neurally adjusted ventilation assist (NAVA) might answer this question. NAVA is a new mode of synchronized NIPPV, which utilizes changes in the electrical activity of the diaphragm (Edi) to trigger the ventilator. There are currently no large RCT comparing NIV-NAVA to non-synchronized NIPPV. High-flow nasal cannula post-extubation in 303 infants < 32 weeks’ gestation was found to be non-inferior to the use of NCPAP, with treatment failure occurring in 34% of the infants in the nasal-cannula group and in 25% of the infants in the NCPAP group.\textsuperscript{8} Almost half the infants in whom treatment with HFNC failed were successfully treated with NCPAP without re-intubation. These results could be partially explained by a recent study showing that in prematurely born infants, synchronized NIPPV compared with HFNC post-extubation reduced the work of breathing and thoracoabdominal asynchrony.\textsuperscript{9} Yet, it should be considered that the incidence of nasal trauma was found to be significantly lower in the nasal-cannula group compared with the CPAP group (P = 0.01).\textsuperscript{8}

To summarize, much effort is invested in the Noninvasive ventilation approach. The outcomes of that approach in the long run are still to be investigated. A recent study did not find benefits, concluding that despite substantial increases in the use of less invasive ventilation after birth, there was no significant decline in oxygen dependence at 36 weeks and no significant improvement in lung function in childhood over time.\textsuperscript{10} The results of that study could have different interpretations. The recent cohorts in that study, 1997 and 2005, showed no significant difference in the rate of endotracheal ventilation. It has been shown that even short exposure to endotracheal positive pressure ventilation is harmful. Thus, it is possible to conclude from the study that every effort should be made to minimize the use of endotracheal ventilation by using more Noninvasive ventilation. At the same time, there was a striking decrease in the use of postnatal glucocorticoids between these cohorts, from 46% in 1993-23% in 2005. The differences between these periods could explain the surprising results found by Doyle et al.\textsuperscript{10} To overcome the possible effect of the decreased use of glucocorticoids, it is possible that we should consider other policies.
of using postnatal glucocorticoids that do not adversely affect neurodevelopmental outcome. These could include inhaled glucocorticoids, low-dose hydrocortisone, or intratracheal glucocorticoids with surfactant.

Considering the complex nature of BPD, a comprehensive approach will be needed to reduce its rate. Beyond understanding the biological and physiological rationale of such an approach, studying it in RCTs seems to be an impossible mission with the current knowledge due to ethical constraints.

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2 | Long-term Respiratory Outcomes of Premature Infants

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Preterm birth: Recent data suggest preterm birth is on the rise, worldwide. Some long-term birth cohorts from Brazil point in this direction and the consequences on children’s respiratory health outcomes are quite significant.¹ Recent studies estimate that 11.3-13.8% of births are premature.² Considering that there are 2.7 million births per year in Brazil, it can be estimated that over 70,000 preemies are born below 32 weeks of gestation, with 25,000 under 28 weeks. These are significant numbers that should impact gravely on any health system.

Large advances in the management of premature infants, such as prenatal use of systemic corticosteroids, availability of surfactants, and less aggressive ventilatory support have provided significant result improvements in the infants’ lung function. However, these newborns are exposed to the extraterrestrial environment very early in the saccular phase of lung development.³ Even with minimally invasive ventilation techniques, there remain negative consequences in the subsequent growth of the airways and the vascular bed of the lungs.³ These negative functional consequences mainly include a variable obstructive spirometric pattern and gas exchange surface reduction (by lung diffusion capacity testing, DLCO), resulting in increased respiratory morbidity, increased ventilatory vulnerability to viral infections, and limitation of physical exercise.

Lung Development: Premature birth significantly affects the normal lung development process, particularly in the alveolar stage, favoring a pulmonary structure with larger and smaller alveoli and a reduction in the number of pulmonary microcapillaries.⁴ Consequently, there is a reduction in alveolar surface available for gas exchange. Another consequence of this “rarefication” of the pulmonary parenchyma is the reduction in the elastic recoil of the lung, which is the main force that gives support to the small airways. The reduction in elastic recoil favors airway collapse during expiration, similar to what is observed in adults with pulmonary emphysema; this leads to reduction in expiratory flows, air trapping, and increase in functional residual capacity. These changes appear clinically and radiologically as pulmonary hyperinflation; clinically there is poor response to treatment with bronchodilators.⁴

Long-term outcome: In adolescents and adults diagnosed with bronchopulmonary dysplasia (DBP), the association of reduction of the airway exchange surface and reduction in expiratory flow will cause a significant decrease in respiratory reserve. This average reduction in cardiopulmonary capacity has not been uniformly documented; it can be completely asymptomatic in relatively sedentary individuals,⁵ but it can also be a limiting factor in the practice of competitive physical activities, which require, in addition to maximal alveolar ventilation, intense gas exchange.
The reduction in maximal expiratory flows is a common finding in premature infants, and it is detectable even in asymptomatic late premature infants.\(^6\) In extreme preterm infants, ventilatory obstruction is the most notable functional abnormality, observed from the first months of life to adulthood.\(^7\) This reduction in ventilatory reserve is the main cause of hospitalization in preterm infants in the first 2 years of life, generally precipitated by respiratory syncytial virus (RSV) infections.\(^8\) The obstructive pattern is most pronounced in premature infants with a diagnosis of BPD: 83% of premature infants diagnosed with BPD will persist with significant spirometric abnormalities throughout a good part of the first decade of life. Clinical and functional data obtained at 11 years of age in preterm infants born less than 26 weeks of gestation (EPIcure study) show that 26% had a diagnosis of asthma and 56% had obstructive changes in baseline spirometry.\(^5\) A review of spirometric studies in BPD survivors shows that ventricular abnormalities persist in most individuals, even in those who received surfactant at birth.\(^2\)

A systematic review on the relation of pulmonary function with prematurity showed that functional deficits are proportional to prematurity, with an average percentage deficit in FEV1 of 7.2% and 19.9%, respectively, in premature infants with and without BPD.\(^9\) It is also important to mention that the mean deficits of pulmonary function in preterm infants have been declining in the last 30 years, most likely due to advances in perinatal care.\(^9\) Several studies have also shown an increase in the prevalence of bronchial hyperreactivity and bronchodilator response in children and adolescents born prematurely compared to full-term infants.\(^5\) The presence of partial or total reversibility of obstruction observed in pulmonary function tests supports the use of bronchodilators in preterm infants, especially if this spirometric reversibility is associated with improvement of respiratory symptoms and control of exacerbations. These patients are generally treated, both in adolescence and in adulthood, with antiasthma medications, especially inhaled corticosteroids for the prevention of recurrent wheezing. A clear benefit has not been definitively demonstrated and its use should be indicated with caution.\(^10\) Exhaled nitric oxide measurement (a marker of lower airway inflammation) is low in premature infants, suggesting that the predominant change is structural rather than inflammatory. Changes resulting from extreme prematurity prevent these subjects from reaching their peak pulmonary function, which usually occurs between 25 and 30 years of age and, therefore, functional decline begins at a lower level, increasing the risk of chronic obstructive pulmonary disease later in life.\(^2\,\(^9\)

**Conclusions:** Premature birth modifies the natural process of lung growth, and perinatal events and medical interventions can add further damage. With time, premature infants with no/minimal neonatal respiratory compromise should be quite healthy, with a trend towards normalization of pulmonary function over the years. However, for the most extreme preterm infants, structural changes are permanent, but outcomes are variable. Many will continue with chronic respiratory symptoms, recurrent wheezing, obstructive ventilation, and reduced cardiopulmonary capacity. The therapeutic options both to prevent further losses of lung capacity or recurrent significant respiratory events are quite limited. Asthma drugs are the only available options and they will work in only a fraction of these individuals. New research looking at novel options for treating these children differently than asthmatics is deemed necessary.

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**11 | CONGENITAL CENTRAL HYPOVENTILATION SYNDROME: FAMILY AND PHYSICIANS PERSPECTIVE**

**GENETIC DIAGNOSIS AND CHARACTERISTICS OF CCHS**

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Congenital central hypoventilation syndrome (CCHS) is characterized by failure of the automatic control of breathing during sleep.
Hypoventilation develops mainly during sleep, and it presents during both wakefulness and sleep in severe cases. CCHS is a neurocrystopathy (a failure of the migration or differentiation of neural crest-derived precursor cells) and is frequently complicated with Hirschsprung disease (HSCR), dysregulation of the autonomic nervous system, and neuroblastoma. The incidence was estimated to be 1 per 200,000 live births in France.2

CCHS is caused by the mutation of PHOX2B, a gene located on the 4p12 that encodes a transcriptional factor with 2 polyalanine chains consisting of 9 and 20 polyalanines and 1 homeobox (3-6). More than 90% of patients have polyalanine repeat expansion mutations (PARMs) in the polyalanine tract of 20 residues (24-33 polyalanines), and less than 10% of patients have non-polyalanine mutations (NPARMs) such as frameshift or point mutation. This disease is caused by a heterozygosis and dominant inheritance. Disease severity in the patients carrying PARMs increases with increasing expansion of the alanine repeats. The patients carrying long PARMs or most NPARMs present with a severe phenotype. Patients with 24 or 25 PARMs have mild symptoms, and exhibit hypoventilation during the neonatal period or after the neonatal period and occasionally have no symptoms.3 The patients carrying 26 or more PARMs or most NPARMs present with a severe phenotype in the neonatal period. HSCR, the most frequently complicated disease, was recognized in patients with 26 or more PARMs and NPARMs, but not in patients with 24 or 25 PARMs. Tumors of neural crest origin occur more frequently in individuals with NPARMs than those with PARMs.4 Sinus arrest was reported in some cases with 26 or more PARMs, but not in patients with 25 PARMs.7

We examined the genotype-phenotype relationship in Japanese CCHS patients and estimated the incidence of CCHS in Japan.6 Subjects were 92 Japanese patients with PHOX2B mutation; 19 cases carried 25 PARMs; 67 cases carried 26 or more PARMs and 6 had NPARMs. The estimated incidence was greater than one case per 148,000 births.

In the 19 cases carrying 25 PARMs, the male-to-female ratio was 3; no cases had Hirschsprung disease; 12 cases developed hypoventilation during the neonatal period and 7 cases developed after the neonatal period. There was no gender difference in the patients with 26 or more PARMs and NPARMs. All 73 cases carrying 26 or more PARMs and NPARMs developed hypoventilation during the neonatal period, 31 of them were complicated with HSCR, and 6 of them received ventilation support during awake and sleep.

We examined the prognosis of development in 83 patients (19 cases with 25PARMs, 64 cases with 26 or more PARMs or NPARMs) by a questionnaire survey and found mental retardation in 25 patients (30%).9 There was no significant difference between the prognosis and their genotypes; however, 8 patients with 25 PARMs (42%) had mental retardation.8 Charnay, et al. (10) studied 31 CCHS patients who received respiratory control from the newborn period and found that the patients with 25 PARMs had a favorable prognosis, while the patients with 26 or 27 PARMs had mild mental retardation. They mentioned that the severity of neurological prognosis was proportional to the expansion of the polyalanine repeat. Compared to Charnay’s report, Japanese CCHS patients had an unfavorable prognosis. We did not find a relationship between developmental prognosis and ventilator support under tracheotomy or age of tracheotomy. However, we found a favorable prognosis in those patients who received ventilation support from day 0. Unfavorable prognosis in the Japanese CCHS patients might be associated with inappropriate ventilator support before the tracheotomy. In addition, the patients with 25 PARMs were not able to receive appropriate ventilation support following a definitive diagnosis owing to subtle and or irregular hypoventilation. Appropriate ventilator support following early clinical and molecular diagnosis is very important to improve the neurological sequelae of CCHS.

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We have performed the CCHS respiratory dock in 28 patients. This accounts for 1/4 of patients in Japan and 1/2 of pre-school patients. The median age in months at the time of dock was 24 (range 2–75). The gene mutation types were 23-27, 30, 31, 33 PARMs and Non-PARMs.

**Respiratory center**

1) VRCO₂(VRCO₂) evaluates the ventilatory response of the respiratory center. VRCO₂ is a value obtained from the relationship between EtCO₂ and Minutes Volume (MV) using the physiological response of the respiratory center. VRCO₂ is calculated by the formula: \( \Delta MV/\Delta EtCO₂/Body \text{ weight (mL/min/kg/mmHg).} \) The VRCO₂ of CCHS is much lower than normal infants³.

2) Edi monitoring

Edi is a electrical signal which the respiratory center outputs through the phrenic nerve and increases in response to inspiratory effort such as CO₂ retention. The electrodes of the Edi catheter are placed at the esophago-gastric junction to detect Edi. In CCHS, the Edi level decreases during sleep, which means that the patient is hypoventilated. Furthermore, the Edi peak did not increase even though the EtCO₂ increased during hypoventilation, which reflects the pathology of CCHS itself⁴.

**Respiratory tract**

1) laryngo-bronchoscopy

A thin flexible fiberscope is used for observation of the airway. If the patient has a tracheostomy, observation via tracheostomy is added. In CCHS, tracheomalacia is an important complication. We diagnosed tracheomalacia in 60% of all patients. Although many of them represented severe hypoxic spells such as dying spell, diagnosis of tracheomalacia was not made before the CCHS respiratory dock. There is a trend whereby the neurological prognosis of patients with tracheomalacia is worse than patients without tracheomalacia.

**Ventilation**

1) Wakefulness without ventilator

We found hypoventilation during wakefulness in about 60% of all patients and there were patients with all gene mutations except for 25 PARMs. As with tracheomalacia, many patients were diagnosed for the first time in CCHS respiratory dock. The VRCO₂ of patients with hypoventilation during wakefulness was lower than those of patients without hypoventilation during wakefulness. It was also suggested that the neurological prognosis of patients with hypoventilation during wakefulness is worse than patients without hypoventilation during wakefulness.

2) Sleep without ventilator

Although all patients presented hypoventilation during sleep without a ventilator, trends of SpO₂ differed with each case. We classified patients in 3 groups by trends in SpO₂. A group with an average SpO₂ of 90%, a group with an average SpO₂ of 80%, and a group with a SpO₂ of less than 70%. There was a correlation between VRCO₂ and the average SpO₂.

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**CCHS Respiratory Dock:**

The image of CCHS respiratory dock is shown in Figure 1, which consists of the three essential elements. The first is the respiratory center which generates inspiration. The respiratory center is evaluated by using the Ventilatory response to CO₂ (VRCO₂) and the electrical activity of diaphragm (Edi) monitoring. Next, we evaluate the respiratory tract for airway lesions and lung function, where laryngo-bronchoscopy is the main examination tool. The last element is ventilation, where we assess whether or not the patient is maintained at an appropriate O₂ and CO₂ level. We continuously monitor the SpO₂ and TCPCO₂ (EtCO₂). In CCHS, we must check ventilation under 3 conditions, during wakefulness without ventilator, and sleep with and without ventilator.

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**Introduction:**

The incidence rate of CCHS is 1/100,000 to 200,000, and the number of institutions which had experiences of CCHS cases represented only 4.5% of the total institutions for pediatric training in Japan¹. Because of its rarity, there is no established respiratory care program and the patients are managed in inconsistent ways depending on each physician. This has led to some problems. For example, it is reported that patients with 25 PARMs in Japan tend to be managed by NIPPV from birth regardless of the severity of hypoventilation. As a result, the neurological prognosis of patients with tracheomalacia is worse than patients without tracheomalacia.2

We designed a program which evaluates the respiratory status of CCHS comprehensively and named it ‘CCHS respiratory dock’. This word is Japanese-English. Dock refers to a dockyard, the building where ships are repaired, and ‘dock’ is used as a word for medical checkup in Japan. Therefore, we named our program ‘CCHS respiratory dock’ and our aim is to spread it use throughout our country.

**CCHS respiratory dock:**

The image of CCHS respiratory dock is shown in Figure 1, which consists of the three essential elements. The first is the respiratory center which generates inspiration. The respiratory center is evaluated by using the Ventilatory response to CO₂ (VRCO₂) and the electrical activity of diaphragm (Edi) monitoring. Next, we evaluate the respiratory tract for airway lesions and lung function, where laryngo-bronchoscopy is the main examination tool. The last element is ventilation, where we assess whether or not the patient is maintained at an appropriate O₂ and CO₂ level. We continuously monitor the SpO₂ and TCPCO₂ (EtCO₂). In CCHS, we must check ventilation under 3 conditions, during wakefulness without ventilator, and sleep with and without ventilator.

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My presentation follows Dr. Sasaki and Dr. Yamada, and explains the 7 reasons why parents can't take their eyes off CCHS children*

About 82 families participate in the Japanese CCHS family group.

The hazardous symptoms (cases) of CCHS children in their daily life are often reported from the families. But it is hard to be recognized by pediatricians at the hospital.

CCHS is the inability to control breathing that varies in severity, they can't sense breathlessness, and affects the central and autonomic nervous system, which causes fatal symptoms.

CCHS children use a ventilator when sleeping, and in severe cases in wakefulness as well.

Many children can be removed off the ventilator during wakefulness. However, that is when parents have to be careful about the symptoms.

1) Patients forget to breathe when they concentrate on watching TV, playing video games, and studying, etc.

2) Patients, especially infants and children, sleep anytime, anywhere, so parents can't leave them alone without a ventilator.

3) Patients who don't have a tracheostomy are able to swim. They continue to dive until they pass out.

4) Hypoventilation gets worse when they are up in the mountains and when flying in an airplane.

5) Hypoventilation gets worse when they get the flu or are infected by virus. Fever does not rise even in the flu. They cannot control their body temperature.

6) Performing sports intensively makes patients hold their breath, and trigger heavy hypoventilation.

7) Managing the ventilator and complications of CCHS renders home medical care much more difficult. For example, Hirschsprung disease, tracheomalacia, hypoglycemia.

These facts are explained with visual materials.

My role as a director of the CCHS family network Japan is to share all family members' experience and knowledge and to develop their capacity as highly experienced parents in advanced home medical care, and to encourage parents and CCHS children to participate in society. Also, I encourage them to capture any moment by visual means, not only happy times, but also when the hazardous symptoms appear. Parents should feedback the symptoms with visual materials to their pediatricians such that the pediatricians may understand more about the disease, because CCHS is rare.

13  |  TB – UPDATE AND ADVANCES

1  |  Advances in TB Diagnostics and Biomarkers

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Accurate diagnosis of childhood TB remains challenging due to paucibacillary disease, a nonspecific clinical presentation and difficulties with obtaining and testing samples in children. Recently however, there have been several diagnostic advances to improve the accuracy of diagnosis of pulmonary TB (PTB) in children. These include advances in specimen collection, in microbiological testing and in identification of potential biomarkers that may be associated with TB disease. In addition, measurements of host response, primarily blood RNA expression patterns, have shown promise for identifying children with PTB compared to those with other respiratory diseases.

Improved methods for specimen collection have provided better samples for testing for microbiological confirmation. The use of respiratory specimens, predominantly induced sputum (IS) and to a lesser extent nasopharyngeal specimens, have enabled microbiological diagnosis in up to 50% of children clinically diagnosed and treated.
for TB. Induced sputum is safe, can be done in children of all ages, and is feasible in ambulatory and hospitalized settings; however, for optimal yield, a second specimen is needed in children, as this provides an incremental yield, on either culture or molecular methods. Microbiological testing on non-respiratory specimens such as stool, blood or urine provides a lower yield than from sputum for PTB.

Rapid molecular diagnostic tests, particularly Gene Xpert (Xpert MTB/RIF) and more recently Xpert ULTRA, have improved the ability for rapid diagnosis with simultaneous detection of resistance to rifampicin. The World Health Organization recommended that Xpert replace smear as the first line investigation in children living in areas of high HIV prevalence or where drug resistant TB is a concern. A meta-analysis found a pooled sensitivity and specificity for Xpert MTB/RIF on a single IS of 65% and 98% respectively, compared to culture in children with PTB with a similar performance on gastric lavage. However, several studies have reported an incremental yield with repeated IS specimens, with the sensitivity of Xpert done on 2 sequential IS specimens as high as 76%. Nasopharyngeal aspirates (NPAs) are more easily obtained than IS; Xpert on 2 NPAs had a sensitivity of 65%. While most studies have focused on hospitalized children, Xpert on two IS was useful for diagnosis in children with suspected PTB presenting with mild disease at primary care health facilities, although the microbiological yield (both by culture and Xpert) were lower than that obtained in hospitalized children. Xpert on stool specimens may offer a promising strategy, particularly in HIV-infected children, but the sensitivity remains much lower than that from induced sputum and further studies are needed.

Xpert MTB/RIF Ultra (ULTRA) is a new diagnostic test for TB on the GeneXpert platform, with a substantially lower limit of detection and improved sensitivity than Xpert in studies in adults. In the first published study, the sensitivity and specificity of a single Ultra performed on one IS in children with suspected PTB was 77% and 97% respectively compared to culture; this was similar to the accuracy of Xpert testing on IS. Combinations of respiratory specimens may provide a novel, potentially useful strategy that can be adapted to different settings and that can identify most children with culture-confirmed PTB; the best combination was 2 NPAs and a single IS which, with Ultra testing, provided a sensitivity of 87% for culture-confirmed cases.

Other new diagnostic tests include urine lipoarabinomannan (LAM), the T cell activation marker (TAM-TB) test, host genome expression profiles and protein biomarkers. LAM has low sensitivity and specificity in children including HIV-infected children, making it unsuitable for diagnosis. An improved version, FujiLAM is currently under evaluation. The TAM-TB test is a novel immunodiagnostic test that can distinguish active disease from infection, relying on predominance of an effector memory cell phenotype. In a Tanzanian study, TAM-TB assay showed good diagnostic performance in children; larger studies are underway. A host RNA signature associated with TB disease in children has been identified; further work to evaluate and develop this as an available diagnostic test is also underway.

REFERENCES

2 | Non-Tuberculous Mycobacteria (NTM)

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Non-tuberculous mycobacteria (NTM) are species other than those belonging to the Mycobacterium tuberculosis complex and do not cause leprosy. NTM are generally free-living organisms that are ubiquitous in the environment. Humans are frequently in contact with NTM, as the bacteria live in the soil as well as natural and engineered water systems. There have been more than 140 NTM species identified to-date. Most NTM species are non-pathogenic,
but some are able to cause human disease. They can cause a wide range of infections, with pulmonary infections being the most frequent (65-90%). In contrast to pulmonary tuberculosis (TB), direct human-to-human transmission of NTM has infrequently been reported. However, recent findings investigating outbreaks in patients with cystic fibrosis using thorough conventional epidemiological and state-of-the-art molecular typing investigations, such as whole-genome sequencing, have challenged the dogma of person-to-person transmission indicating potential transmission of Mycobacterium abscessus subspecies massiliense and M. abscessus between these patients.\(^3,4\) Mycobacterium abscessus, M. avium complex, M. kansasii, M. malmoense and M. xenopi are the clinically most important species. MAC is by far the most frequently encountered group of pathogens of NTM PD in European countries with M. avium subsp. hominisuis being the predominant subspecies recovered from human biospecimens; however, there are marked regional differences in the isolation of mycobacterial species.\(^5\)

There is growing evidence that the incidence of NTM lung diseases and associated hospitalizations are on the rise, mainly in regions with a low prevalence of tuberculosis. During the last three decades, an increasing incidence of pulmonary NTM isolation has been observed in Europe and several other regions worldwide. The increase seems to be associated with the declining incidence of TB in countries with a higher socioeconomic standard. Several factors may contribute to the emergence of NTM-PD, including an aging population, pre-existing chronic lung diseases, especially COPD, asthma and bronchiectasis, are the main risk factors for NTM-PD in Europe. Population-based studies focusing on the demographic change in NTM-PD remain scarce.\(^6\)

Depending on the causative NTM species, the clinical course and treatment response of NTM pulmonary disease (NTM-PD) can be very variable. NTM have often clinical and radiographic similarities to those of tuberculosis or to the pre-existing disease in patients with bronchiectasis. Patients typically present with fatigue, fever, weight loss, asthenia, and/or anorexia. Respiratory symptoms may consist of cough, sputum production, hemoptysis, or dyspnea and can be secondary to respiratory tract or parenchymal diseases.\(^6\) A plain chest radiograph may be inadequate for evaluating radiological features. High-resolution computed tomography scans more precisely demonstrate the extent of parenchymal lung damage, particularly by visualization of nodular bronchiectatic or small cavity lesions.\(^7,8\) The nodular bronchiectatic pattern is the predominant form of MAC-induced disease, accounting for approximately 50% of cases. The rates of fibrocavitary and other forms are less common.

Hypersensitivity pneumonitis due to mycobacteria, also called ‘hot tub lung’, is a hypersensitivity reaction occurring in patients who are exposed to MAC antigens.\(^9,10\) The diagnosis is established based upon clinical, radiological, and immunological criteria plus the optional presence of corresponding mycobacteria in the respiratory system. There is a continuing debate on optimal management of these patients. Many patients have been reported to be cured by avoidance of antigen and/or corticosteroid therapy suggesting that hot tub lung is more likely a form of hypersensitivity pneumonitis than a primary infectious disease.

The diagnosis of NTM lung infection is based on the American and British Thoracic Society criteria for NTM diagnosis (7) which include the following: (1) a radiograph or CT scan of the thorax, demonstrating bronchiectasis, infiltrates, multiple nodules, multifocal bronchial disease, and/or cavities, plus (2) typical clinical symptoms and exclusion of other diseases with similar symptoms and radiological signs, including TB, plus (3) at least 2 sputum samples which are positive on culture from 2 separate expectorated samplings or 1 positive culture from at least 1 bronchial wash or lavage (both of which are only relevant for patients with nodular bronchiectatic disease, who do not expectorate sputum) or isolation of mycobacteria from a sterile site, including lung tissue obtained by transbronchial or open lung biopsy. In addition to the current diagnostic guidelines, molecular tests for species identification and antibiotic susceptibility testing (AST) should be part of any diagnosis of NTM-PD where available. Smear microscopy of respiratory secretions yields positive results in approximately half of patients with probable or ascertained disease. Acid-fast bacilli are more likely to be visible in patients fulfilling the ATS criteria; they can be regularly detected in patients presenting with cavities and are only rarely seen in patients with nodular bronchiectatic NTM-PD.

Treatment recommendations are mostly based on expert opinions and traditions. The scientific evidence for most recommendations is narrow and is largely derived from retrospective cohort studies, drug susceptibility surveys, or animal experiments. The cornerstones of most anti-NTM drug regimens are macrolides, but there are exceptions such as M. kansasii -PD. Clarithromycin and amikacin are the only drugs with a shown correlation between in vitro drug susceptibility and in vivo efficacy in MAC-PD. Clarithromycin is usually combined with some rifamycins and with ethambutol. No data are available that suggest any superiority of either clarithromycin or azithromycin in the treatment of pulmonary MAC disease. In clinical practice, azithromycin is frequently used due to its preferable dosing schedules and better gastrointestinal tolerance. Azithromycin also is considered less prone to interaction with rifamycins than is clarithromycin.

A treatment duration of 12 months after sputum culture conversion is generally recommended for most NTM-PD, but it is very well possible that any standardized treatment recommendation is inadequate in the majority of cases. Evidence-based individualization of treatment duration is not available, mainly due to the lack of biomarkers which would indicate treatment success and could guide physicians to discontinue antibiotics at a more appropriate time. In multidrug and extensively drug-resistant TB, shortening the therapy durations to 3-12 months can, under certain circumstances, be as effective as the recommended 20-month treatment duration, and this could apply to diseases caused by other mycobacteria as well. Due to
the complexity of the therapy of patients with NTM infections, treatment should be coordinated by physicians with sufficient experience and in constant consultation with certified reference centers.

REFERENCES

14 | CHRONIC COUGH

1 Chronic Cough: The Diagnosis and Investigation

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Background: Cough frequently occurs in infants and children. The prevalence of allergic diseases, such as asthma and nasal allergies, is increasing globally, and the number of patients complaining of chronic respiratory symptoms has increased as well. However, the optimal method for assessing childhood cough, which differs from cough in adults, has not been established. A previous survey suggested that parents’ recognition of their children’s respiratory symptoms differs from that of physicians, and that actually evaluating the overnight cough frequency in children is too difficult for most parents. We believe that correct information obtained by objective cough monitoring is necessary to improve the patients’ outcomes and enhance their parents’ satisfaction with the treatment. In addition, such information is sought by researchers studying the physiology and etiology of childhood cough.

Methods: We recently developed an original objective method of measuring overnight cough in pediatric patients using a cough monitor, which is simple and safe to use and effort-independent.¹ Our original cough monitoring system consisted of a high-resolution microphone, a highly-sensitive accelerometer and a recorder. The software program used to calculate the number of cough sounds and the accelerometer were newly developed by our laboratory. A personal computer was used to perform the calculations. Our system showed a good correlation with the natural cough counts obtained using the current gold standard, the video-audio method.¹ Our recent studies attempted to classify the cough severity and to evaluate the characteristic pattern of cough frequency in children with chronic cough induced by asthma², psychological cough³ and pertussis⁴ using our objective overnight cough monitoring system.

Results: Asthma: the total overnight cough count of 34 asthmatic children was higher than that of 15 non-asthmatic children (P < 0.001). The total overnight cough count in children with severe asthma exacerbation was higher than that in children with moderate asthma exacerbation (P < 0.05).² In an examination of overnight coughing in children with asthmatic exacerbation using a cough monitor, the susceptible time of cough was clear and reported to be from 22:00 to 24:00 in the evening and from 4:00 to 6:00 in the early morning. This pattern was not observed in non-asthmatic children. The total cough counts and cough patterns in asthmatic children were not affected by gender, age, cause of asthma exacerbation or therapy.

Psychological cough: in two patients with psychological cough that showed a characteristic barking cough, the frequency of coughs during the waking period was extremely high (80 times in 30 minutes), while that during sleep was markedly reduced.³ Furthermore, the properties of the coughs during sleep differed from those that occurred while the patients were awake.

Pertussis: in two children with pertussis, a high frequency of coughing was found and characteristic short-time coughing attacks (cough bursts) were seen many times over the course of the night.⁴ These cough bursts were seen all night, and there was no time at which they were particularly concentrated.

Conclusion: In these recent studies, we showed huge cough counts and unique patterns of nocturnal cough frequency in children with asthma and other chronic cough diseases. In addition, we noted the characteristics of the time-dependent cough frequency pattern in each disease, which had not previously been reported in detail. The
use of a cough counter for an objective cough examination may improve the diagnostic approach and the therapeutic management of asthma and other chronic cough. Asthma is the most common basal disease of childhood chronic cough. The objective measurement of overnight coughing will facilitate the precise medication of asthmatic patients.

Furthermore, it has been suggested that psychogenic cough cannot be diagnosed based solely on an interview regarding the characteristics of the patient. According to our analysis using the cough counter, the characteristics of the psychological cough may be precisely measured and thus result in a more accurate diagnosis. Further studies will be needed to obtain conclusive evidence regarding the basal mechanism and to improve the quality of treatment for pediatric patients with chronic cough.

REFERENCES

2 | Novel Therapies for Chronic Unexplained Cough in Children

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In children, a chronic cough is defined as a persistent cough that lasts for 4 weeks or longer. In adults, a cough that lasts for four to 8 weeks is considered a subacute cough while a chronic cough lasts for greater than 8 weeks. When the etiology of the chronic cough is known, for example protracted bacterial bronchitis, asthma, tic cough, or bronchiectasis, then therapy is well defined and directed toward the specific known cause. Chronic unexplained cough is a chronic cough where there is no clear etiology either by testing or by lack of response to common therapies. For chronic unexplained cough, traditional therapies such as antibiotics, bronchodilators, mucolytics, inhaled corticosteroids, antihistamines and decongestants, or medications to treat gastroesophageal reflux are ineffective and have no role in therapy unless, for example, there is airway eosinophilia in patients with cough-dominant asthma.1,2 There is a paucity of pediatric data from well-controlled studies that evaluate therapy for chronic unexplained cough in children. There are, however, robust data for the treatment of chronic unexplained cough in adults and these data will be reviewed with comments on the applicability for children.

Speech therapy and physical therapy with breathing maneuvers has proven to be effective in older children and adults with tic or psychogenic/habit cough. These maneuvers can also help reduce the drive to cough when there is increased cough sensitivity; more commonly called laryngeal hypersensitivity.3,4 It is important to note that when a tic cough coexists with other forms of tic suggesting an underlying disorder like Tourette syndrome, the treatment should appropriately be directed toward the underlying neurologic disorder.

Adults with chronic cough, particularly those with lung cancer, have shown some benefit with the use of inhaled lidocaine or morphine but because of the significant side effects of these and opioid drugs such as codeine, use should be avoided in children.5 There is no indication for their use in treating childhood cough.

Chronic unexplained cough is thought to be due to an increase in sensitivity of the cough reflex which, in turn, is similar to chronic pain or chronic itch.6 For that reason, medications such as gabapentin that are used to treat chronic pain are often effective in the treatment of chronic unexplained cough in adults.7 Gabapentin is also been demonstrated to be effective in children, but it carries the cost of side effects limiting its use. Cough can be triggered through the transient receptor potential (TRP) channels in the airway and in animal models, TRP antagonists showed great promise. However, randomized clinical trials in adults were disappointing showing minimal benefit for these antagonists.8 More exciting are the data on the P2X3 receptor antagonists, particularly gefapixant (MK-7264 – Merck and Co.) that has shown remarkable benefit in treating chronic or unexplained cough in adults.9

At the time of this writing, there are no published pediatric data. Because there are relatively few side effects of this medication other than mild dysgeusia, pediatric studies are being considered. A potential study population for the use of this type of receptor antagonist in children might be the chronic cough of pertussis for which there are no effective therapies.

Very recently, Prof Surinder Birring from King’s College, London published a study looking at PA-101, a new formulation of an old drug, cromoglycate. There was no benefit observed in adults with chronic refractory cough, except in the subpopulation of adults with chronic cough and idiopathic pulmonary fibrosis where there was very significant benefit. The mechanism of action is unclear but almost certainly does not relate to the usual action ascribed to cromoglycate which is mast cell stabilization. This is an old drug with a strong safety profile making it a promising candidate for the treatment of some forms of chronic unexplained cough in children.

As we understand more about chronic cough and its relationship to other chronic sensory neurologic problems such as chronic pain or chronic itch, there is hope that we will have several chronic therapies for this vexing problem.
REFERENCES

Algorithm for Management of Chronic Cough

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The importance of chronic cough
Chronic cough is one of the most common presenting symptoms to pediatric respiratory specialty physicians. Chronic cough is often dismissed as “only a cough” in the general medical community. However, the burden of the symptom is significant to parents and the children; both in terms of personal cost with impaired quality of life (QoL) and at a societal level where physician visits, medication expenses as well as absenteeism and presenteeism are substantial.

Indeed, a multi-center (n = 346) study involving children presenting for the first time to respiratory specialists with chronic cough found that; (a) ~80% had seen > 5 doctors for their cough and (b) their QoL was as poor as those with cardiac disease.

Further, the presence of chronic cough reflects an underlying serious disorder. Delayed diagnosis (eg foreign body) may cause chronic respiratory morbidity. Further, early diagnosis of chronic respiratory diseases leading to appropriate management and subsequent resolution of cough and improved QoL is important. In the study involving 346 children mentioned above, ~12% had a serious underlying illness (eg bronchiectasis). Thus, in the evaluation of children with chronic cough, determining which children require further investigations and/or treatment is a key management strategy. Using a cough algorithm is one such strategy that has the potential to reduce the morbidity of chronic cough, lead to earlier diagnosis of chronic underlying illness and reduce the unnecessary costs and adverse events from medications used.

Is there evidence using a cough algorithm improves clinical outcomes?
Under the auspices of the American College of Chest Physicians (ACCP), systematic reviews addressing whether the above question was undertaken, in addition to whether the cough management or testing algorithm differs depending on the duration and/or severity? The systematic reviews found high quality evidence that using cough management protocols (or algorithms) improves clinical outcomes in children aged ≤ 14 years with chronic cough (> 4 weeks duration) but there were no studies that addressed whether the management or testing algorithm should depend on the duration and/or severity of chronic cough. The highest evidence for using a chronic cough pathway is that from the ACCP including a randomized controlled trial and several cohort studies whereas the evidence for other pathways was restricted to single cohort studies. However, the performance of cough algorithms is likely dependent on the setting (eg study population, expertise of the clinicians, study setting, etc).

What are the key components of a cough algorithm? As described in the ACCP systematic reviews, management of chronic pediatric cough should depend on the associated characteristics of the cough and clinical history. Pediatric cough management algorithms are largely based on the etiology of the cough i.e. not using an empirical approach aimed at treating upper airway cough syndrome due to a rhinosinus condition, gastroesophageal reflux disease and/or asthma unless other features consistent with these conditions are present. Effectively, differentiating ‘specific cough’ from ‘nonspecific cough’ requires a systematic careful elucidation of the cough characteristics and associations, in addition to general pediatric issues. A chest radiograph and spirometry (when age-appropriate) should also be undertaken. Other tests may be required in accordance to the clinical setting and the child’s clinical symptoms and signs and not routinely performed and undertaken.

REFERENCES

15 | INTERVENTIONAL BRONCHOSCOPY

1 | Interventional Flexible Bronchoscopy in Pediatrics

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Pediatric flexible bronchoscopy (FB) as a diagnostic instrument has become a standard tool in the armamentarium of the modern pediatric pulmonologist. With this more prevalent use over the past three decades, procedures in which interventions beyond visual inspection and bronchoalveolar lavage (BAL) have similarly become more common. The emphasis of this review is on the role of pediatric bronchoscopy for such interventional procedures. Pediatric Interventional Bronchoscopy is emerging slowly; as the demarcation lines of flexible bronchoscopy vis-à-vis rigid bronchoscopy are being established, and as the range of feasible procedures is being explored, which are predominantly dictated by the limitation imposed by the size of the pediatric bronchoscope and its working channel. This size limitation is one of the reasons that pediatric interventional bronchoscopic procedures are performed less frequently in the pediatric compared to the adult practice, the other cause being the relatively lesser need for tissue diagnosis in pediatrics, due to the rarity of respiratory malignancies in the former. This summary follows the paradigm utilized in a previously published review and is arranged by groups of intervention undertaken by bronchoscopy.

Use of flexible bronchoscopy for acquisition of diagnostic material: Predominant among invasive procedures used in pediatrics is endobronchial biopsy (EBB) and to a lesser degree transbronchial biopsy (TBB). EBB obtains material from the airway mucosa under direct visualization. The procedure is largely recognized to be safe and is vastly utilized in research. The main clinical focus has traditionally been for diagnostic sampling of tuberculosis and ciliary disease, but also for nonspecific breathing disorders. The conclusion proposed by this author is that a large body of literature supports the great value of EBB in characterizing airway disease, in particular childhood asthma, and to a lesser degree cystic fibrosis, but there is insufficient evidence to support wide clinical use of EBB for patient management. Additionally, ethical questions regarding the procedure have been raised in the literature as to the adequacy of the procedure beyond research. Transbronchial biopsy is limited to use of larger scopes, and aimed at obtaining parenchymal tissue samples that include alveoli for histologic inspection. TBB is done without direct vision and carries a higher risk of complications. It has an established role in clinical care, in pediatrics almost exclusively for assessment of rejection after lung transplantation; however in limited circumstances it can be utilized for diagnosis of diffuse lung disease and potentially spare transthoracic lung biopsy. An exciting novel technique that replaces forceps with a cryoprobe to obtain adequately-sized TBB samples has been established in adult procedures, but its role in the pediatric practice has yet to be defined. Limited experience in pediatrics is available for transbronchial needle biopsy. The main constraint is due to size limitation, since the procedure is guided by endobronchial ultrasonography (EBUS) that is sized to older patients. When performed, however, good diagnostic yield has been reported.

Bronchoscopy for removal of obstructive, noxious or damaging materials from the airway or the lung: Aspiration of foreign bodies represents a worldwide problem in pediatrics. The role of flexible bronchoscopy when foreign bodies of the airway are suspected or for removal of such foreign bodies remains inconclusive. The preference of use of flexible scope is often dictated by unavailability of the traditional rigid scope, but mastery in the procedure with the flexible scope can lead to its eventual preference. However, the risk of complications with dislodgement of foreign body or an obstructive complicated mucus plug requires caution. A paradigm for decision-making in such circumstances has been proposed by Martinot et al(6) A recent evolution that opens new horizons is offered by the recent introduction of the cryoprobe for grasping a foreign body by freezing it instead of using forceps for removal.(7) A unique use of the flexible scope is for treatment of alveolar filling disorders; predominantly pulmonary alveolar proteinosis and to a lesser degree lipid aspiration, in which the therapy includes whole lung lavage by large volume of saline.

Management of the Narrowed or Obstructed Airway; Debridement, Dilatation, and Stenting: Impingement on airway lumen by tissue projecting into the lumen can result from various types of mechanical irritants and inflammatory processes both often compounded by infection. These conditions can be approached by debridement using the forceps, compression by high-pressure balloon catheters and laser photo-resection all via FB. An interesting addition to the
treatment options has been recently described with the use of cryoprobe on 156 pediatric patients with airway stenosis and obstruction who responded well to bronchoscopic cryotherapy.(8) Over the past two decades, there has been a growing body of information on the use of tracheo-bronchial stenting in pediatrics that has slowly gained recognition as an acceptable technique for the treatment of central airway obstruction. New types of stents including biodegradable have expanded the range of options, yet the use of stents in pediatrics remains limited in most centers.

**Use of bronchoscopy for other procedures:** FB for direct instillation of therapeutic agents such as rhDNase, antibiotics and antifungal therapy, has been reported sporadically. A novel and attractive method to control persistent diffuse alveolar hemorrhage via instillation of activated factor VII with dramatic results has been reported in pediatrics.(9) FB for diagnosis and sealing of pneumothorax has been sporadically reported. Use of the FB for distal wedging and injection of contrast material for radiologic segmental bronchography is useful where other radiologic diagnostics prove insufficient.

**New horizons: Fetal Bronchoscopy:** A distinctly novel horizon in pediatric bronchoscopy is a report by Quintero, et al. (10) of a first fetal bronchoscopy. The bronchoscopy was undertaken for a large mass (eventually proven to be CPAM) and resulted in intraoperative expansion of normal lung parenchyma in both the affected and unaffected lungs, with subsequent dramatically normalized lung growth until birth. Limited additional experience had been accumulated since this original publication.

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2 | Bronchoscopy—Use of the Stents

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Tracheobronchial (TB) narrowing, either congenital or acquired, may produce significant respiratory distress and even fatal consequences. Traditionally, victims who fail medical management need more invasive surgeries such as tracheostomy, tracheoplasty, thoracotomy, bronchoplasty and/or extracorporeal life support (ECLS). TB stents can provide an immediate, adequate, durable and stable lumen and improve quality of life. Metallic stent placement has been introduced as an attractive option in children since 1990s. Selected patients gain benefit from this less-invasive therapy. However, they do have complications and associated technical problems, especially in pediatric patients. Our team mainly uses flexible endoscopy (FE) for both diagnostic and various therapeutic FE (TFE) interventions, which are all supported with noninvasive ventilation (NIV). Since 1997, we have gradually developed novel TFE techniques for TB stent implantation with uncovered balloon expandable metallic stent (BEMS) and subsequent management of associated problems and finally retrieve them once indicated.

In the last 20+ year period, TFE techniques with forceps, balloon and/or laser have been used to implant, undergo regular surveillance, maintain functions, and re-expand the diameters of these BEMS. Short-length (30-36 cm) endoscopes of OD 3.2 to 5.0 mm coupled with the NIV, without ventilation bag, mask or airway tube, have been used to support the entire procedures. A total of 165 BEMS were implanted in 101 consecutive children, including 90 tracheal, 16 carinal and 59 bronchial stents. At the time of placement, the mean age was 35.6 ± 54.6 months (range 0.3-18.2) and the mean body weight was 13.9 ± 10.6 kg (range 2.2-60). The surveillance period was 10.5 ± 6.3 years (range 0.3 ± 18.2). Satisfactory clinical improvements were noted immediately in all but two patients. Eighty-six (85.1%) patients were still alive with stable respiratory status, except for two patients necessitating TFE management every 2 months. In
surviving patients, 78 (59.1%) stents, including 49 tracheal, 25 bronchial and 4 carina stents were successfully retrieved mainly with rigid endoscopy. Implanted stents could be further expanded for growing TB lumens. The final stent diameters were positively correlated with implanted duration. Altogether, 33 stents expired (15 patients), 78 were retrieved (45 patients), and 54 remained and still functioning well (41 patients), with their mean stent duration of 7.2 ± 9.1, 37.3 ± 36.5 and 85.3 ± 63.1 months, respectively.

**Conclusion:** In pediatric patients, TFE with short-length scopes coupled with a NIV support can provide a safe, feasible and effective modality in placing and subsequent managing of TB BEMS with acceptable long-term outcomes.

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### Utility of Bronchoscopy Cryotherapy in Children

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Cryotherapy works on the basis of the Joule-Thomson effect by which a gas (several cooling agents can be used as cryogen) stored in a liquid state at high pressure (most commonly nitrous oxide or liquid nitrogen or CO2) is abruptly decompressed, passing to a gaseous state that produces a rapid fall in temperature, typically reaching −80 to -100°C. This extreme cold can be used through the working channel of the bronchoscope via a specialized cryoprobe or directly with the use of spray cryotherapy. Rapid tissue freezing produces intracellular ice crystals that cause cell death and ischemic necrosis, while respecting collagen structures. When applying cryotherapy to lesions, cell destruction is homogeneously induced around the 3-5 mm cryoprobe, while surrounding tissue up to a radius of 3-10 mm is less homogeneously affected, and blood vessels and perivascular cells are most affected. Several factors enhance the degree of cell death accomplished during cryotherapy: lower temperature, faster freeze rate, slower thaw rate, repeat freeze–thaw cycles, and the amount of tissue frozen. Lowering the temperature to ~40°C at a rate of ~100°C per minute is needed to achieve adequate cell death (90%) within an area being treated. James Arnott in 1850 invented a device using salt and crushed ice solution to treat breast and skin cancer by freezing. Endobronchial cryotherapy with rigid cryoprobe was successfully used in the 1960s. HETZEL, et al. first described the cryorecanalization technique using a flexible catheter cryoprobe. Following cryotherapy, reproducible mucosal ulceration starts to heal from 6 hours and becomes healed by 2 weeks. This method may have an advantage in promoting tissue regeneration as the extracellular matrix is preserved during the process. Cryonecrosis and subsequent repair of the frozen tracheal cartilage lagged the mucosal changes, but also normalized by 4 weeks. During the following decades, many centers adopted this method of endobronchial cryotherapy to manage many airway disorders. Tissue sensitivity to cryotherapy is dependent on its water content, thus tumor mass, granulation tissue, mucous membranes and endothelium due to their more water content are cryosensitive tissues whereas fat, collagen, connective tissue, nerve sheets and cartilage are considered cryoresistant tissues. There are two types of cryoprobe that can be used with both fiberoptic and rigid bronchoscopes. The introduction of a flexible cryoprobe with interchangeable tips allows cryotherapy to be extended to disorders in the upper airways and upper lobe bronchi. The main indications of cryotherapy in the pediatric age group are:

1. Nasal stenosis
2. Polypsis
3. Foreign body removal especially live objects (Leech)
4. Chronic rhinitis
5. Pharyngeal stenosis
6. Laryngeal stenosis
7. Laryngeal papillomatosis
8. Subglottic stenosis (secondary stenosis following endotracheal intubation, tumors, hemangioma,...)
9. Tracheo-bronchial
10. Foreign body removal
11. Stenosis and obstructions (Tuberculosis, Mycoplasma-induced stenosis)
12. Bronchial and transbronchial lung biopsy
13. Adjuvant therapy for tracheobronchial fistula

The flexible cryoprobe (Erbkryo, ERBE Cryosurgery, and Germany) can be used with a fiberoptic bronchoscope under light general anesthesia with propofol while maintaining the patient’s own respiration helped by local lidocaine with the spray and go method. In general, the following interventional technique is used:

1. The cryoprobe is introduced via a flexible bronchoscope.
2. The cryoprobe tip is placed on the foreign body or pushed into the tissue to be sampled. Freezing is maintained for 2 to 3 seconds for foreign body removal and 3 to 5 seconds for ablation (using a footpad).

3. By freezing the tissue on the probe's tip, removal is made easy. The cryoprobe, together with flexible bronchoscope withdrawal (while maintained pressure on footpad) and the foreign body or tissue sample (of up to 10 mm) is frozen to the tip of the cryoprobe and easily extracted.

4. Rapid thawing of the extracted material is induced in a water bath. In recent years, many centers have started to use this technique by using flexible probes in pediatrics and even a few in infants. Despite the limited studies, it seems that bronchoscopic cryotherapy may be an effective and safe method in pediatric airway diseases.

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16 | ENVIRONMENT AND LUNG HEALTH

1 | Indoor Air Pollution and Lung Health in Low and Middle-Income Countries (LMIC)

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Indoor Air Pollution - A Global Problem: Globally, more than 90% of children under the age of 15 years breathe polluted air, with the World Health Organization (WHO) recently reporting that around 3 billion people still rely on polluting open fires or simple stoves fuelled by kerosene, biomass (wood, animal dung and crop waste) and coal for household cooking and heating. This is especially inherent in low and middle income countries (LMIC) and strongly linked to poor socioeconomic circumstances.

Despite global attempts to improve lung health in children, lower respiratory tract infections (LRTI) remain the leading cause of under-5 mortality, particularly in LMIC. Further, increasing evidence points to lung growth trajectories being set in early-life with life-long consequences, highlighting this vulnerable period as critical to lung health.

Indoor air pollution (IAP) is a consequence of alternate fuel use often in combination with poor ventilation and overcrowding and is strongly linked to the energy ladder which ascribes cleaner and more efficient fuel with improved socioeconomic status. Although rapid urbanization and migration of communities occurs, many people still rely on cheaper and often more polluting energy sources. The Sustainable Development Goals (SDGs) recognize the importance of social and environmental factors as determinants of health and in particular SDG 7 focuses on universal access to affordable, reliable, sustainable and modern energy. However, it is also the combination of IAP, exposure to tobacco smoke, outdoor pollution and climate change that further compounds the risk of environmental exposures on lung health.

Indoor Air Pollutants and Assessing Exposure: Indoor air pollutants are a combination of chemical compounds released during household activities including cooking, heating, smoking, use of cleaning products and from building materials. While there may be numerous pollutants, the most common inorganic vapors include ozone (O₃), carbon monoxide (CO), nitrogen dioxide (NO₂) and sulphur dioxide (SO₂), and the vapor forms of organic pollutants, such as polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs) [benzene, toluene, xylene], and aliphatic chemicals. Particulate matter (PM) is a further major contributor to IAP ranging in size from ultrafine to up to 10 µm (PM₁₀) still being of respirable size.

Assessing IAP exposure is either through self-reports, pollutant measurements using personal or fixed samplers, modeling data or biomarkers, all of which carry limitations. There is an increasing need for simple and reliable methods to assess IAP.

Impact on Lung Health: The impact of IAP on lung health begins in the antenatal period where exposures have been linked to impaired lung development and disturbed development of the immune system with subsequent decreased lung function in infancy and childhood, increased respiratory symptoms and the development of childhood asthma. The postulated mechanisms by which antenatal IAP affects lungs is through an interplay of environmental and epigenetic factors. A large African birth cohort study found that antenatal, compared to postnatal IAP exposures, were the predominant risk factor for LRTI and wheezing in infancy.

In terms of postnatal exposure, two independent meta-analyses also found that IAP exposure was associated with an almost doubled to 3-fold increased odds of developing LRTI. Further, IAP impacts on lung defense mechanisms and the lung microbiome with increased risk of both acute and chronic respiratory symptoms.

While there is mounting evidence from high income settings linking air pollution to impaired lung function, this has not been well studied in LMIC settings where the burden of IAP exposures is significant. However, novel data from the Drakenstein Child Health Study, a South African birth cohort study, have shown that infants exposed to IAP during pregnancy had impaired lung function at 6 weeks and subsequently had smaller size-adjusted lung volumes, increased lung clearance index and reduced respiratory system compliance at both 1 and 2 years of age, suggesting increasing effects seen with time.
In terms of non-communicable diseases, asthma is the commonest chronic disease in children in both high income and LMIC settings and a number of studies including the International Study of Asthma and Allergies in Childhood, have shown an association between IAP exposure and the development of both asthma and chronic obstructive airway diseases.9

Children in LMIC often present with chronic respiratory symptoms. There are often limited diagnostic utilities available with a reliance on clinical findings.9 Further, research and health system capacity building is required to improve care of children with these conditions. While interventions such as improved cooking stoves and better household ventilation can decrease children’s exposure to IAP, universal access to clean fuel is what is ultimately required. The impact of these exposures on genetic, epigenetic and immunological changes requires further investigation. Studies from high income countries have reported the impact of early-life smoke exposure on the genetic programming that control life-long lung development, aging and susceptibility to obstructive lung diseases.2 A better understanding of this can lead to targeted intervention to improve child lung health.

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2 Strategies to Minimize the Effects of Air Pollution on Respiratory Health

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Air pollution is a global health threat that causes millions of human deaths annually. Unfortunately, pollution is a virtually inevitable consequence of human interaction with nature. For example, outdoor air pollutants such as industrial emissions, road traffic, residential heating, air traffic, construction, agricultural activities, war and fire accidents are derived from human activities. Indoor air pollutants are generally released from smoking, building materials, air conditioning, house cleaning or air refreshing products, and wood, fuel, or coal usage in cooking, heating or lighting.

The World Health Organization (WHO) estimates that half of the world’s population relies on inefficient and highly polluting solid fuels such as charcoal, straw, dung, crop residues, wood and kerosene to meet their basic energy needs.1 These fuels are usually burned inside or next to the home environment in inefficient ways (eg open fires), which leads to high levels of indoor and outdoor pollution. Worldwide, the global burden of lung disease is substantial, accounting for an estimated 7.5 million deaths per year, approximately 14% of annual deaths worldwide.1 Unfortunately, in the absence of major interventions, the air pollution death toll is projected to double by 2050. As expected, the poorest regions of the world carry by far the greatest burden.1

Long-term exposure to high levels of pollution increases the risk of COPD, lung cancer, tuberculosis, acute respiratory infections, asthma, sleep disorder breathing and cardiovascular disease.2 Key risk factors that have been the drivers to the development or deterioration of these diseases include smoking, indoor and outdoor pollution, and occupational exposures. The distribution of these diseases and the risk factors varies greatly by age, geography, and setting.

Thinking global, acting locally: Public Health Interventions to Reduce.

Air Pollution: It is well understood that pollution has a profound effect on health; therefore, reduction of pollution should have a positive effect on health, particularly in susceptible individuals. Pope and colleagues showed that a reduction in exposure to PM2.5
Different interventions are available to reduce exposure to air pollution. Interventions range from national or regional regulations to very specific local actions that may involve either single or multiple governmental sectors. While most interventions attempt to comply with air quality standards, the final aim may vary in some cases. For example, some interventions seek to reduce emissions and others to improve health directly. In some other cases, a reduction in air pollution occurs as a side effect of an intervention with different goals such as an intervention to reduce congestion and improve traffic flow. Another example occurred during the 2008 Olympic Games where the Chinese government was able to control air pollution. This resulted in a reduction of outpatient visits for asthma from 12.5 visits per day to 7.3 visits per day, a 41.6% reduction during the Olympic Games as compared with before the games started.

In general, there are three types of interventions: those acting on the source of pollution (eg, cooking devices, alternative fuels, reducing vehicle emissions, changing diesel engine technology, and other regulations to clean up emissions), those improving the living environment (eg, improved ventilation), and those causing changes in user behaviors (eg, change in operation of source, smoke avoidance). Efforts to reduce exposure to tobacco, indoor air pollutants, outdoor air pollutants, and occupational toxins will have a greater impact in reducing illness and death from different disease than will individual therapies provided to patients.

Air quality interventions are complex and involve multiple actors. Both public policy and individual action are required to reduce the effects of pollutants on respiratory health. Governments in developing countries need to implement better and new technologies (eg, cleaner cookstoves, cleaner cars, and cleaner factories) that will reduce health risks while allowing populations to enjoy the benefits of economic growth and development. Policy instruments typically used include: information, education, and communication; taxes and subsidies; regulation and legislation; direct expenditures; and research and development. Monitoring and surveillance of the burden of disease and of actions to reduce or eliminate the various drivers of lung disease must be constant and usually are carried out over an extended period of time.

But on the other hand, interventions at the individual level are also important and may include the avoidance of exercise or cycling near busy roadways to reduce exposure, conserve energy both at home and at work, carpool or use public transport, improvements in ventilation of home, keep all engines tuned (eg, car) and promoting recycling and reusing when possible.

**Indoor pollution:** Intervention studies to reduce biomass exposure have been a priority for the last 20-years, sadly showing conflicting results. In rural Mexico, a randomized trial of properly vented wood-burning cooking stoves versus open fires showed reductions in the decline in lung function and improvements in respiratory symptoms, when proper cooking stoves were used. However, many studies in Guatemala, Malawi, India and elsewhere have shown that these more efficient stoves could not decrease levels of household air pollution sufficiently to improve health. Using a randomized controlled trial, Smith, et al. found that an improved cooking stove halved the average exposure to carbon monoxide, but did not significantly reduce physician-diagnosed pneumonia among infants in Guatemala. Some explanations include lack of infrastructure, financial constraints, other disease risk factors (eg, malnutrition) and poor living condition of households.

In recent years, studies continue to show no impact of improved cookstoves on perinatal or child health. Mortimer, et al. report the findings of a cluster-RCT conducted in two rural districts of Malawi. This study aimed to test an alternative biomass stove comparing the latter with existing cooking methods (eg, open fires) to prevent pneumonia in children < 5 years of age in rural Malawi (Cooking and Pneumonia Study, CAPS). The major finding of this trial was that there was no difference between the intervention and control groups among children in pneumonia incidence (IRR of 1.01 [0.91–1.13; P = 0.80]) and severe pneumonia 1.30 [95% CI, 0.99–1.71; P = 0.06]. A recent meta-analysis assessing the health impact of improved cookstoves showed decreased respiratory symptoms among women, but no effect on child health. Nevertheless, considering that billions of people use biomass combustion for energy needs, improvement in cookstoves may help improve the long-term effects of this type of exposure.

Despite their potential benefits, the use of clean cookstoves and alternative fuel is not straightforward, and there have been persistent challenges in implementing these mitigation interventions such as: challenges in exposure measurements particularly personal exposure, challenges in identifying and managing cultural needs, impact in home concentrations, multiple sources of energy in the same household for different purposes (eg, cooking, heating, boiling water, lighting), and other sources of pollution (eg other people’s fuel use, burning of solid waste, traffic, and industrial emissions).

Another important source of indoor pollution is cigarette smoking. Cigarette smoking imposes a large and growing global public health burden, and it is the single most preventable cause of death in the world. More than 1.1 billion people worldwide smoke, with 82% of smokers residing in LMICs. Although many high-income countries have witnessed decreases in the prevalence of smoking, the prevalence continues to rise in many LMICs. Quitting tobacco consumption reduces illness by immediately providing short-term benefits and lowering the risk of all diseases caused by smoking. Tobacco taxation is widely used, and a significant number of studies demonstrate its effect in the reduction of cigarette smoking. Other initiatives for smoke control are: smoke-free areas (eg smoking bans in public places), education through social media and mass media campaigns, health warnings on product packaging, bans or restriction on tobacco marketing, and smoking cessation treatments.

**Outdoor air pollution:** Industries, households, cars, and trucks emit complex mixtures of air pollutants, many of which are harmful to health. Most fine particulate matter comes from fuel combustion from mobile sources (eg, vehicles) and from stationary sources (eg, power plants, industry, households, or biomass burning). Indoor
sources also contribute to outdoor pollution, and in heavily populated areas, the contribution from indoor sources can create extremely high levels of outdoor air pollution.

Technologies to reduce pollution at its source are plentiful, as are technologies that reduce pollution by filtering it away from the emission source. These include vehicle-specific interventions such as the use of lead-free gasoline, encouraging the use of more fuel-efficient vehicles, and/or policies that manage traffic demand or reduce “unnecessary” driving. Other key mitigation actions include implementation of urban tram or bus rapid transport in cities, exclusive bike lanes, charging private vehicles for entry into certain urban areas, making city parking more expensive and promoting the change to low-emission modes of travel (e.g., walking or cycling).

Power plants and industrial plants that burn fossil fuels may use a variety of filtering methods to reduce particles and scrubbing methods to reduce gases. For example, China has made strong plans to reduce air pollution that include shutting down high-polluting industries, promoting clean energy including renewable energy and natural gas, expanding coal-free zones, reducing rural indoor coal burning, improving coal quality, upgrading vehicle emission and fuel standards, as well as other sustainable energy measures. Several studies elsewhere suggest that if some of these measures are strictly implemented and the anthropogenic emissions are reduced accordingly, mean concentrations of pollutants might be reduced, thus improving health parameters.

The Southern California Children’s Health Study, a prospective study that followed the lung function of school-aged children showed that children exposed to ambient particles, NO2 or inorganic acid vapor had reduced lung function growth. Children who spent more time outside experienced larger deficits in lung function, suggesting a dose-response relationship. However, following aggressive pollution-reduction policies, air pollution decreased over the past several decades in southern California. The improvement in air quality was associated with a significant lung growth in children with declining levels of nitrogen dioxide, PM2.5 and PM10.

**Conclusion:** In summary, air pollution is a global public health problem and responsible for millions of deaths worldwide. It comes from a variety of sources and therefore a range of mitigation opportunities exist. Although there have been major efforts in implementing local interventions to control indoor and outdoor pollution, to achieve significant reductions these interventions need to be implemented in a national policy with international guidelines. Understanding the detrimental health effects of air pollution is critical for reinforcing support for new or better mitigation strategies. Given the large number of people affected, investments in identifying ways to reduce current levels of indoor and outdoor air pollution, even if large, are likely to have a tremendous impact on health. We need to make clean air available everywhere!

**REFERENCES**


3 | **Environmental Impact on Childhood Asthma**

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Genetics and environmental exposures in early life both influence the risk of developing allergic diseases and childhood asthma. Previous studies suggested that these two factors could have roughly equal contributions to the risk for developing asthma. However, a recent study of childhood allergic diseases and asthma in two Anabaptist groups, the Hutterites and the Amish, suggest that environmental factors are of prime importance. The founder populations of both of these communities originate from central Europe, and genetic factors are therefore quite similar. While both communities have rural lifestyles, there are substantial differences in environmental exposures. For example, the Hutterites have mechanized farms, and children have low exposure to barnyards and animals. In contrast,
Amish families practice traditional farming methods and mothers and children are exposed to a variety of animals and associated microbes. Notably, rates of asthma are vanishingly low for Amish families while Hutterite children have rates of asthma similar to that of the general US population. These findings suggest that traditional farming exposures can greatly lower the risk for developing allergic diseases and asthma, and this association may be related to the quality and quantity of microbial exposures.

A variety of early life environmental factors could influence the risk for developing allergic diseases and childhood asthma, including diet, infections and exposure to allergens, microbes, stress and pollution. Notably, early sensitization to multiple respiratory allergens is closely related to the subsequent development of recurrent wheezing and childhood asthma. Therefore, it is of great interest to identify factors that are influence early-onset allergic sensitization, and also atopic dermatitis which is also closely related to early sensitization.

Birth cohort studies have been conducted in a variety of different settings to determine relationships between early life environmental exposures and subsequent development of allergic diseases and asthma. For example, the Childhood Origins of ASThma (COAST) study was initiated in 1998 and enrolled children with an increased risk for developing allergies and asthma based on parental history. The Urban Environment and Childhood Asthma (URECA) study enrolled a population with similar parental risk factors, however the study population was selected from neighborhoods with high rates of poverty in four large urban areas (Baltimore, Boston, New York City and St. Louis). More recently, the Wisconsin Infant Study Cohort (WISC) study was initiated in 2013-study two groups of children: children raised on Central Wisconsin family dairy farms, and a comparison group of children from rural households in central Wisconsin without farm contacts.

In the COAST study, children were enrolled during the prenatal period and environmental assessments included diagnostic virology, and assessment of home exposures, and measures of immune development. Of the factors that were analyzed, pet exposure in the home had the greatest influence on the subsequent risk for allergic sensitization, and these associations were age-dependent. Of the 285 children followed through 3 years of age, 68 had a dog in the home from the time of birth and 33 had a dog and a cat in the home. At 1 year of age, having a dog in the home was associated with a significant reduction in the prevalence of active topic dermatitis, and this effect persisted through age 3 years. Dog exposure was inversely associated with a reduction in allergic sensitization at 1 year of age, however this effect faded with time. In contrast, having a dog in the home was associated with a reduction of wheezing beginning at age 3 years. In parallel, dog exposure was also associated with significant enhancement of PHA-induced cytokine responses from peripheral blood mononuclear cells. Subsequent studies have demonstrated that having a dog in the home has significant effects on the richness and diversity of exposure to beneficial microbes within the home. This suggests the possibility that some of the beneficial effects of dog ownership are related to associated microbes.

In the URECA study, the home and neighborhood environments had a number of adverse conditions, including high rates of tobacco smoke exposure and air pollutants, and increased psychosocial stress and exposure to indoor allergens such as cockroach and mouse. Notably due to a lack of green space and contact with animals, microbial exposure was generally low. House dust samples were obtained during the first 3 years of life for URECA participants for major allergens. Surprisingly, indoor exposure to three allergens (cockroach, cat, and mouse) was strongly and inversely related to recurrent wheezing at 3 years of age, and asthma at age 7 years. To determine whether the apparent protective effect of allergen exposure was related to associated microbes, house dust was also analyzed using a microarray and 16S ribosomal sequencing for environmental bacteria. Notably, reduced bacterial richness was a risk factor for developing sensitization to Aeroallergens, and the combination of allergic sensitization and recurrent wheeze. Notably, effects of exposure to allergens and microbes in early life were additive. Children who had neither recurrent wheeze nor allergic sensitization were most likely to grow up in homes that had high rates of exposure to both allergens and microbes. Conversely, children who had both atopy and recurrent wheezing were most likely to grow up in homes that had low levels of exposure to microbes and to allergens. These findings suggest the possibility that both allergen exposure and microbial exposures influence immune development to reduce rates of allergic sensitization and wheezing illnesses.

In Western Europe, the traditional farming environment has a number of factors that are inversely related to allergic diseases and asthma. These include contact with animals such as dairy cows and pigs, exposure to hay and silage, and consumption of raw farm milk. In addition, farm exposures may also reduce the risk of respiratory illnesses in early life. In the PASTURE birth cohort, farm exposures were inversely related to transient wheezing in infancy. Wisconsin children growing up on farms are less likely to develop early allergic skin disease, allergic rhinitis, and medically attended respiratory illnesses. Studies are now in progress to assess the role of microbial exposure and other farm-related exposures on microbial colonization of the infant and subsequent effects on the new development.

While suburban Wisconsin (COAST), poor urban neighborhoods (URECA) and farming environments (PASTURE and WISC) are clearly distinct, a common theme has emerged from these studies. In each of these three environments, early exposure to microbes and potential allergenic proteins were associated with a lower risk for allergic diseases and childhood asthma. These findings may lead to new strategies for disease prevention, particularly in children who grow up in urban environments with low levels of biological exposures. While there is convincing evidence that adverse environmental exposures such as diesel exhaust and ozone are detrimental to respiratory health and possibly mucosal immune development, it is also notable that other types of exposures in early life may be
necessary for immune and perhaps lung development to progress normally. This raises the hope that a better understanding of natural exposures to microbial and protein and possibly metabolic exposures could lead to treatments that would bring the benefits of growing up on the farm to children who are raised in urban environments.

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| 1 | Chinese Pediatric Action Plan for the Rational Use of Antibiotics |

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Antibiotics are the most frequently prescribed drugs, particularly to children for treatment of infectious diseases. This action plan was developed to strengthen antibiotic management, control antimicrobial resistance, safeguard children’s health, and promote children’s development. The main goal of the action plan is “to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way”.

Background: Antimicrobial resistance has become a serious global public health problem, and the World Health Organization (WHO) in 2011 proposed an appeal “Combat antimicrobial resistance: No action today, no cure tomorrow”. Subsequently, in 2015, the Draft Global Action Plan on Antimicrobial Resistance was launched, which addresses the issue of antimicrobial drug resistance. The goal of this initiative is to ensure long-term sustainable use of safe and effective drugs for the treatment and prophylaxis of infectious diseases. To actively respond to the challenges relating to antimicrobial resistance, the National Health Commission and 14 other departments jointly developed the National Action Plan to Stop Antimicrobial resistance (2016–2020) in 2016.

In the early 1990s, Chinese scholars started to pay attention to the abuse of antibiotics in pediatric cases and organized two expert seminars on the same topic in China: In 2000, the respiratory group of the Chinese Pediatric Society took the lead in the nationwide development of the Acute Respiratory Tract Infection Antibiotics Rational Use Guide for pediatric cases. In 2004, the Ministry of Health organized experts to develop the Guiding Principles for the Clinical Application of Antibiotics (hereinafter referred to as the Guiding Principles), which was later updated in 2015.

In China, 2 years after the implementation of the 2004 guidelines, the overall defined daily doses (DDDs) decreased by 22.6%, and the
difference in DDDs among hospitals was decreasing. In terms of antibiotic use indications, empirical treatment continuously decreased each year, from 82.2% in 2002 to 70.2% in 2006, and targeted treatment increased over time, from 11.2% in 2002 to 24.2% in 2006. Empirical treatment decreased, indicating that the intervention has promoted the rational use and management of antibiotics. Although overall, these hospitals can meet the requirements, however, in some areas, the use rate remained high, with empirical treatment as the predominant protocol. The use of antibiotics in children not only leads to the occurrence of antimicrobial resistance, but also affects the body’s microecology, especially when used in early life, leading to a disruption of the body’s immune homeostasis, which is associated with atopic diseases.6,7

(1) Lack of a monitoring network for antibiotic use and relevant research data in Chinese children.
(2) There are fewer varieties of available safe and effective antibiotics.
(3) Self-medication and self-purchase medication are common practices of parents of pediatric patients. Parents often purchase antibiotics before medical treatment when their children have fever or administer remaining drugs from a previous illness. Approximately 1/3 of patients with a common cold have used antibiotics before consulting a physician.3 78.9% of children with fever received medication before seeing a doctor, of which 69.7% were antibiotics.8
(4) The range of vaccination is not wide and has led to an increase in the use of antibiotics.
(5) The non-indicated medication phenomenon is prevalent. In the clinic, establishing the etiology and diagnosing early disease onset is generally difficult, especially in cases involving atypical clinical manifestations and test results, thus often resulting in the simultaneous use of antibiotics and antiviral drugs.
(6) The development of pediatric infectious diseases in China is subject to certain restrictions.

Overall goal: To improve the use of antibiotics, to prevent the development of antimicrobial resistance, and to reduce the drug resistance rate of certain bacteria within 3-10 years.
(1) To implement comprehensive management strategies at the national level and to promote the rational use of antibiotics in children in the medical institutions and the entire society.
(2) To establish a national pediatric antibiotic use and antimicrobial resistance surveillance network, to identify antibiotic management evaluation indicators, and design an antimicrobial resistance control evaluation system.
(3) To establish an antibiotic clinical application management mechanism in children’s hospitals that is governed by the president of the medical institution, led by the head of the infectious disease department, and combined with microbiologists and clinical pharmacy experts, to jointly establish a hospital antibiotic use regulatory group to control the irrational use of antibiotics.
(4) To strengthen the infrastructural construction of an infectious disease department, as well as require all pediatric medical staff to complete professional training of rational antibiotic use.
(5) To improve the social awareness of the rational use of medicines and control self-medication.
(6) To conduct research on antimicrobial resistance and establish at least 3-2 pediatric reference laboratories.
(7) For activities during “WHO Antimicrobial Resistance Week” each year. The theme for this year in China is “Carefully to Treat Antibiotics”.
(8) To establish, improve, and expand a pediatric antibiotic use and antimicrobial resistance monitoring system. Join the global monitoring projects, learn from the experience of other countries, and gradually establish China’s independently researched and developed monitoring network, and expand its use in the Asia-Pacific region.
(9) To develop pediatric antibiotic clinical application guidelines and a common antibiotics evaluation report system on the basis of relevant guidelines.
(10) To edit and publish a manual on the rational use of antibiotics in the treatment of pediatric infectious diseases.
(11) To improve the hospital management system: A) to establish commonly used antibiotics in the treatment of pediatric infectious cases in every hospital; B) to establish hospital recommendations on drug use; C) to establish a hospital ward and outpatient antibiotic use monitoring system; D) to implement regular training on antibiotic use among clinicians, educate parents of pediatric patients. E) to establish a real-time expert monitoring and evaluation system.
(12) To establish expert committees, control the use of special grade antibiotics.
(13) To encourage relevant scientific research, including antibiotic use, antimicrobial resistance, and so on.
(14) To improve information dissemination and education on the use of antibiotics via different forms of media to decrease the prevalence of self-medication and to improve public awareness.
(15) To conduct extensive international exchanges and cooperation, including that with other departments such as agriculture. More than half of the antibiotics produced in China are utilized in agriculture including animal husbandry and thus clinical data on the use of antibiotics and the preventive measure against drug resistance may also be applicable to these sectors.
(16) Other interventions: Develop new airway humidification and anti-inflammatory drugs to reduce unnecessary antibiotic use.
(17) To increase efforts to assist the State Health Commission to further implement the rational use of pediatric antibiotics, promote the rational use of antibiotics at the national level, release public service advertisements, and utilize spokespersons, cartoons, and corresponding media to disseminate information on the rational use of antibiotics.
(18) To establish expert groups at all levels, organize learning, and implement measures in this action plan.
(19) To establish the role of regional pediatric tertiary treatment centers in primary hospitals using advanced pathogen detection technologies and to determine the incidence and etiology of infectious diseases and to regulate the use of antibiotics.
(20) To strengthen supervision and inspection.

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5. 18222941


2 | CF Treatment: State of the Art

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The survival of patients with cystic fibrosis (CF) continues to improve. The better clinical status and improved survival of patients with CF is a result of the development of therapeutic strategies that are based on insights into the natural course of the disease. Current CF treatments that target respiratory infections, inflammation, mucociliary clearance and nutritional status are associated with improved pulmonary function and reduced exacerbations. Patients benefit from treatment at specialized CF centers by a multidisciplinary dedicated team with emphasis being placed on frequent visits, periodic testing, and monitoring adherence to therapy.

Early and aggressive therapy already at the stage when no apparent signs of significant lung disease are detectable, may delay the development and progression of CF. Identification of markers for early pulmonary disease in CF is crucial to monitor adherence to preventive therapy and determine its success. Currently, several surrogate markers are available that are used in both the decision making and evaluation of the timing and success of early intervention namely, pulmonary function tests (PFT), microbial cultures, imaging techniques, inflammatory markers, serological markers and several general signs such as exacerbation rate and nutritional status.

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 and further understanding of the molecular mechanisms of CF. New therapies based on the understanding of the function of CFTR are currently under development.

The current cystic fibrosis (CF) drug development landscape has expanded to include therapies that enhance CFTR protein function by either restoring wild-type CFTR expression or increasing (modulating) the function of mutant CFTR proteins in cells. Grouping CFTR mutations into classes according to the molecular mechanism by which the mutation disrupts normal protein synthesis or function is useful, especially in view of developing CFTR repair therapies. CFTR mutations are generally divided into seven classes: Class I mutations are mutations resulting in no CFTR protein production. This class includes nonsense mutations leading to premature translation termination resulting in truncated protein that undergoes degradation. For this class of mutations, molecules causing ‘read-through’ agents allow ribosomes to continue translation through the premature stop codon to produce a full-length CFTR protein, resulting in increased normal CFTR copies. Class II mutations cause defective CFTR processing, leading to production of a protein that undergoes proteosomal degradation and fails to reach the cell surface. For this class of mutations, ‘correctors’ facilitate CFTR processing and increase the quantity of mutated CFTR at the cell membrane. Class III are gating mutations in which altered protein at the membrane surface has reduced ability to support anion transit. In Class IV, CFTR reaches the cell surface, but with reduced function, Class V is characterized by a reduced amount of normally functioning CFTR, Class VI by its increased turnover and class VII by being pharmacologically "unrescuable". Thus, CFTR repair therapies that are mutation class-specific can be positioned as an advanced type of personalized treatment, geared towards correcting the basic molecular defect in a specific individual with CF. However, in each class, there is wide variability in the molecular mechanism by which the mutation disrupts CFTR function, suggesting association with several classes, leading to the term theratyping. The implication of this is that several modifiers and potentiators will be required to treat each patient, paving the way for a highly patient-specific, precision therapy approach.

Ivacaftor was the first drug showing CFTR potentiator activity that increases chloride transport by potentiating the channel open probability of the CFTR protein. This drug is associated with significant improvement in pulmonary function, weight and quality of life of patients carrying class III mutations. Furthermore, treatment at early age, 2 to 5 years old, was shown to increase in some of the patients the levels of fecal elastase to normal levels, suggesting correction of pancreatic insufficiency. In older patients with CF related diabetes, it was shown to improve glucose tolerance indicating improved pancreatic endocrine function.

The Phe508del mutation, a loss of a phenylalanine at position 508 in the CFTR protein, is the most common CFTR mutation worldwide. It belongs to class II mutations associated with decreased CFTR glycosylation, folding leading to significant reduced transport to the cell membrane. Orkambi and Symdeco were shown to improve slightly pulmonary function and more significantly the reduction in pulmonary exacerbations. Recently it has been shown that Symdeco is associated with improved pulmonary function and reduced exacerbation rate in patients carrying residual function mutations (classes IV, V and VI).
The current CFTR modifiers, although showing benefit to patients with CF, are far from curing CF. The patients continue to suffer from chronic infections and excessive neutrophilic inflammation, which by themselves cause progression of lung damage. The cost of the CFTR modifier therapies, and the possible need to take several of them in combination to achieve full CFTR correction of function, emphasizes the need for various, complementary cellular systems and clinical data that may together enlarge the basis for predicting CFTR drug response in a patient-specific manner.  

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3 | Treatment of Bronchiolitis: The Endotype Approach

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The use of bronchodilators and systemic or inhaled corticosteroids (ICS) to treat acute bronchiolitis is not endorsed in current expert guidelines, because a number of randomized-controlled trials (RCT) in infants and young children have failed to demonstrate reproducible benefits of these drugs over placebo. Yet, some infants with acute bronchiolitis will benefit from treatments such as inhaled bronchodilators and ICS; thus one explanation for the lack of benefit in RCTs is that the same treatment(s) may have harmful effects in another subgroup so that an overall beneficial effect is not observed. This model of research will necessarily have to move from the current symptom-based, “trial-and-error” approach, to a stratified, mechanism-based therapy. These findings lead to the conclusion that we are ignoring the evidence that the diagnosis of bronchiolitis encompasses several diseases with distinct underlying mechanisms, considerable heterogeneity in treatment responses, and ultimately different therapeutic targets.

Bronchiolitis is now according to the American Academy of Pediatrics (AAP) “a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing... characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm.” and this definition has not changed significantly since the past century. AAP guidelines exclude recurrent wheeze from the definition. There is no clear scientific evidence today for treating recurrent symptoms, that may occur weeks or months after a first episode, differently than a first wheezing event. “Acute bronchiolitis” and its many associated terms remains a fuzzy syndrome, with many flavors under the same umbrella.

Bronchiolitis may co-exist with viral pneumonia, present with more or less air entrapment, wheezing, cough or hyperreactivity, and a range from scarce to abundant production of secretions. These different observable characteristics (phenotypes) spurred a number of diverse mechanistic hypotheses, all supported and disputed by well-conducted studies over the years. This rationale includes innate inflammation, Th2-mediated bronchoconstriction, direct viral injury of the small airways, and airways plugging due to debris and mucus production. The fact that different mechanistic studies report contradictory findings does not necessarily make any of them incorrect but may be a consequence of the heterogeneity of the primary outcome.

The most frequent cause of acute bronchiolitis is respiratory syncytial virus (RSV), associated with >50% of hospitalizations in young infants. RSV dominates the winter season, but its burden may soon change should maternal immunization strategies or RSV-
specific monoclonal antibodies (mAb) of prolonged half-life prevent severe disease. Still, illnesses caused by different viruses prevail in slightly different age-and risk-groups, exhibiting different genetic susceptibilities, and varying cytokine profiles, but clinical presentations overlap sufficiently to cloud the diagnosis, making distinctions at bedside difficult if not impossible. Importantly, acute episodes can have markedly different long-term consequences. For instance, preventing severe acute RSV disease with a specific mAb lowers the incidence of recurrent wheezing until age 5 years, despite simultaneously increasing the absolute rate of infections with other viruses, like hRV.3-4

Furthermore, even RSV bronchiolitis is pleomorphic in its clinical presentation and can manifest with significant differences in short- and long-term consequences for specific subgroups. In middle-class urban and suburban populations, infants with loss-of-function single nucleotide polymorphisms in Asp299Gly and/or Thr399Ile (TLR4+/−) experience exaggerated Th2 responses in the respiratory tract during RSV infection and are not protected by the administration of RSV-specific mAb when premature.5 In addition, infants with a TLR4+/− genotype born at term experience an exorbitant ~90% hospitalization rate when visiting an emergency department with respiratory symptoms.5 Preterm infants, presumptively due to reduced levels of forced expiratory flows, are also at greater risk for severe bronchiolitis and recurrent wheeze during the first year of life,6 and should be treated as an independent phenotype.

Bronchiolitis evidently is not a single disease, but a collective noun used to describe a set of clinical symptoms and features which arise through different pathophysiological mechanisms. Subtypes of bronchiolitis sharing similar observable characteristics are often labeled as phenotypes; we should be moving to study bronchiolitis' "endotypes", that are defined on the basis of pathophysiological (underlying) mechanisms.5 In addition to the information derived from traditional hypothesis-driven studies, delineation of endotypes should benefit from advances in novel approaches to identify susceptibility genes for these ailments, next-generation sequencing technologies that enable single-cell RNA sequencing, and emerging fields of large-scale data-rich biology. Noninvasive methods for measuring lung function may also be of value in defining bronchiolitis endotypes. In these times of minimalistic approaches to pediatric practice, large collaborative prospective studies gathering detailed clinical information and laboratory samples should be fostered by governments and foundations, if we are to discriminate these disorders from each other.

One approach to "endotype" discovery, extensively used in asthma,6 uses data mining with various data-driven statistical and machine learning techniques to uncover patterns of clinical symptoms, different biomarkers, or "omics" data. This approach assumes that discovered patterns reflect pathophysiological mechanisms.6 In the field of bronchiolitis, one such technique (latent class analysis) identified three severe bronchiolitis profiles.7 Approximately half of infants clustered in a subgroup resembling typical RSV bronchiolitis, a third experienced very severe disease, and the rest—at increased risk for subsequent recurrent wheezing—were most often infected with rhinoviruses and had higher eosinophil counts and cathelicidin levels.7 Two other cohorts identified an additional profile of non-wheezing patients with milder illness. Recently, untargeted metabolomic analyses of urine in children with bronchiolitis discriminated those prone to recurrent wheezing as having a greater involvement of the citric acid cycle.8 However, to be genuinely useful, any pattern recognition has to be coupled with both biological and clinical interpretation.6

We can and should use responses to treatment for endotype discovery. Emergence of mAb targeting specific cytokines or cytokine receptors potentially involved in pathogenesis of certain endotypes of bronchiolitis may revolutionize the approach to disease diagnosis and alter disease severity, duration and/or long-term consequences, but can also facilitate endotype discovery. For example, severe RSV disease in middle-class TLR4+/− infants associates with high levels of IL-4 in respiratory secretions,9 severe RSV bronchiolitis in the U.K. has been linked to IL-9 levels,9 and hRV life-threatening illness in low income populations correlated with high levels of IL-13.10 Candidate interventions against these and other cytokines, today still costly, have been tested for other diseases.

Identification of "responders" to treatment with biologics may point out at the pathways critically important for disease expression in different subgroups, thus enabling the discovery of endotypes. Other drugs not recommended for general administration today, like β2 agonists, may find their niche once properly targeted. To be successful, we will have to find a way of bringing together information from population-based birth cohorts, studies in infants with manifest disease, the results of RCTs, and mechanistic studies, because neither of these in isolation will provide sufficient information for disaggregation.6

Much like asthma or fever, bronchiolitis is an umbrella-term that harbors several diseases with similar clinical manifestations, and likely both overlapping and unique mechanisms. Understanding these endotypes will permit the move from the current symptom-based approach towards mechanism-based treatments, enabling targeted interventions to decrease the burden of illness on infants, their families and the society.

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Young Investigator’s Oral Communications

A-27 | Immune Mediator Levels in the Upper Airways Predict Response to Azithromycin for Episodes with Asthma-like Symptoms in Young Children

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Background: The immune response in the airways during episodes with asthma-like symptoms in young children is presumed to determine the clinical outcome, although current knowledge largely relies on in vitro airway models. Azithromycin has been shown to reduce the duration of episodes with asthma-like symptoms, though efficacy may depend on the individual child’s immune response.

Objective: To investigate in vivo upper airway immune mediator levels during episodes with asthma-like symptoms in young children and their ability to predict the clinical response to azithromycin treatment.

Methods: Five hundred thirty-five children from the Copenhagen Prospective Studies of Asthma in Childhood-2010 mother-child cohort were examined for immune mediator levels in samples of upper airway epithelial lining fluid during episodes with asthma-like symptoms through ages 0 to 3 years as well as in the asymptomatic state at age 2 years. A subset of samples was also examined for CRP levels. In a sub-study, children aged 1 to 3 years with recurrent asthma-like symptoms were randomized to either a 3-day course of oral azithromycin (10 mg/kg) or placebo. In the current study, we compared the immune mediator levels before treatment and the clinical response to treatment with azithromycin.

Results: Four hundred ninety samples obtained during episodes with asthma-like symptoms and 434 samples obtained during asymptomatic periods were analyzed. The mediator concentrations during vs.
outside episodes were significantly upregulated for IFN-γ (ratio 1.73), TNF-α (2.05), IL-1β (1.45), IL-10 (1.97), and CRP (1.74), while CCL2 (0.65) was downregulated. Low levels of TNF-α and IL-10 and high levels of CCL2 predicted better treatment response to azithromycin (p-values ≤ 0.05).

Conclusion: The immune mediator profile of the upper airways was altered during episodes with asthma-like symptoms in young children. TNF-α, CCL2 and IL-10 levels predicted the response to azithromycin treatment and may potentially be used in future point-of-care testing.

A-85 | The Relation of Matrix Metalloproteinases 2 and 9 with Reticular Basement Membrane Thickening in Chronic Neutrophilic Airway Inflammation

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Introduction: Cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are characterized by persistent or repeated neutrophilic airway inflammation. Reticular basement membrane (RBM) thickening of varying extent has been described in these conditions. Although not fully understood, matrix metalloproteinases 2 and 9 (MMP2 and MMP9) and their imbalance relative to tissue inhibitors of metalloproteinases are suspected to play an important role in airway remodeling. To date, MMP levels have only been studied in bronchoalveolar lavage fluid (BALF), sputum or blood, but not directly in the airway wall. Sparse data on their relationship to airway remodeling and lung function are available.

Methods: We performed a cross-sectional study to evaluate the expression of MMP2 and MMP9 in bronchial wall in patients with chronic neutrophilic airway inflammation. After excluding patients with incomplete data, 49 children aged 0.5 to 17 years (median 9.80 years) were included. The study group consisted of 16 patients with CF, 7 with PCD and 10 with other forms of chronic neutrophilic airway inflammation (6 with non-CF and non-PCD bronchiectasis (BE) and 4 with chronic suppurative lung disease (CSLD), as defined by Chang AB, 2016). The control group included 16 patients undergoing bronchoscopy for a large airway pathology with no signs of chronic respiratory disease or atopy. Anthropometric characteristics of both groups did not differ significantly. Bronchoscopy was performed in clinically stable patients. Endobronchial biopsies were stained with hematoxylin-eosin to assess RBM thickness (as validated by Sullivan P, 1998). The number of MMP2- and MMP9-positive cells in lamina propria mucosae was assessed using indirect immunohistochemical methods (rabbit polyclonal antibodies Abcam ab73734 and ab37150) in relation to the total number of cells in the lamina propria (MMP2%, resp. MMP9%). Percentage of neutrophils and lymphocytes in BALF was assessed. Lung clearance index (LCI2.5) was measured using nitrogen multiple breath washout test in all patients before bronchoscopy. RBM thickness, MMP2%, MMP9%, BALF neutrophils and lymphocytes and LCI2.5 were compared between study and control groups and in three subgroups within the study group (CF, PCD and CSLD together with BE) using t-test. Spearman rank correlation (r) of MMPs% to RBM thickness, BALF cytology, LCI2.5 and anthropometry was tested in the study group (n = 33).

Results: RBM thickness, MMPs%, percentage of neutrophils in BALF and LCI2.5 were significantly higher in the study group than in controls (ΔRBM = 1.66 μm, P < 0.001; ΔMMP2% = 5.6%, P < 0.001; ΔMMP9% = 3.0%, P < 0.001; ΔLCI2.5 = 3.6, P < 0.001; Δneutro = 36.1%, P < 0.001). All of the differences remained significant when the three subgroups were compared separately to controls. Both MMP2% and MMP9% correlated with RBM thickness (Diagram 1 and 2). Only MMP2% correlated with LCI2.5 (r = 0.383, P = 0.041). No relationship was found between MMPs% and BAL cytology or anthropology.

Conclusion: MMP2 and MMP9 are upregulated in bronchial lamina propria mucosae in patients with CF, PCD, CSLD and BE. Their positivity is related to RBM thickness indicating their important role in airway remodeling. MMP2% is related to ventilation inhomogeneity but not to BALF neutrophilia.

Diagram 1. Correlation of MMP2% to RBM thickness: r = 0.427, P = 0.021.
Diagram 2: Correlation of MMP9% to RBM thickness: r = 0.364, P = 0.044.

D-38 | Correlation between Body Mass Index and Optimal Continuous Positive Airway Pressure Level in Children with Obstructive Sleep Apnea

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Background: A subgroup of children with obstructive sleep apnea (OSA) requires treatment with Continuous Positive Airway Pressure (CPAP). When initiating CPAP, determining a priori the required optimal CPAP level remains a challenge in children. While the correlation between Body Mass Index (BMI) and optimal CPAP is well recognized in adults, it is uncertain if such a correlation exists in children. The clinical guideline 1 for manual titration of CPAP in patients with OSA acknowledges the...
insufficient evidence for selecting a higher starting CPAP for patients with higher BMI.

**Aim:** The aim of this study was to determine if the optimal CPAP level for treatment of OSA in children correlates with their BMI.

**Methods:** A retrospective analysis of demographic, clinical and polysomnographic variables of children aged 2 to 18 years with OSA, who underwent CPAP titration studies between January 2009 - June 2018, at the KK Women’s and Children’s Hospital (Singapore) was conducted. Patients with known syndromes (except Down syndrome [DS]), craniofacial abnormalities, neuromuscular diseases or skeletal deformities were excluded. Polysomnograms were performed using the Sandman Elite™ sleep diagnostic system as per the 2007 American Academy of Sleep Medicine (AASM) guidelines and its subsequent updates. The sleep studies were scored and reported by qualified pediatric sleep physicians. Demographic, clinical and polysomnographic variables were collected from electronic records. BMI z-scores were calculated using the World Health Organization AnthroPlus software version 1.0.4 for non-DS children, and the Canadian Pediatric Endocrine Group (CPEG) calculator for DS children. Correlations between optimal CPAP level, BMI z-scores and polysomnographic variables were analyzed.

**Results:** 198 children (mean ± SD age = 13.1 ± 3.6 years, 142 [71.7%] males) underwent CPAP titration studies during the study period. BMI z-score had a weak, but significant positive correlation with optimal CPAP in the non-DS subgroup (n = 175, rs = 0.263, P < 0.001) but not in the DS subgroup (n = 23, rs = 0.251, P = 0.249). The univariable linear regression derived in the non-DS subgroup was: optimal CPAP (cm H2O) = 8.41 + 0.301 × BMI z-score (adjusted R² = 0.065, P < 0.001). Additionally, in non-DS children, optimal CPAP correlated positively with age, Obstructive Apnea Hypopnea Index (OAHII), Rapid Eye Movement (REM) Respiratory Disturbance Index (RDI) and Oxygen Desaturation Index (ODI), and negatively with minimum oxygen saturation (SpO2 nadir). In DS children, optimal CPAP correlated positively with age and ODI.

**Conclusions:** Optimal CPAP level for treatment of OSA in children has a significant positive correlation with BMI z-score in non-DS children, but not in those with DS. The developed univariable linear regression for optimal CPAP needs further refinement by including other relevant clinical and polysomnographic variables, as well as validation in large prospective studies.

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investigations are required before clinical application of intravenous PDE4i as an anti-inflammation agent to treat severe MAS.

I-162 Clinical Characteristics and Etiologies of Bronchiectasis in Korean Children: A Multicenter Retrospective Study


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Results: A total of 387 cases were enrolled. The mean age at diagnosis was 9.2 ± 5.1 years and 53.5% of the patients were boys. The most common underlying cause of bronchiectasis was pre-existing respiratory infection (55.3%), post-infectious bronchiolitis obliterans (14.3%), pulmonary tuberculosis (12.3%) and heart diseases (5.6%). Common initial presenting symptoms included chronic cough (68.0%), recurrent pneumonia (36.4%), fever (31.1%) and dyspnea (19.7%). The most predominantly involved lesions were left lower lobe (53.9%), right lower lobe (47.1%) and right middle lobe (40.2%). No significant difference was observed in the distribution of these involved lesions by etiology. The forced expiratory volume in 1 second (FEV1) levels were lowest in cases with interstitial lung disease-associated bronchiectasis, followed by those with recurrent aspiration and primary immunodeficiency.

Conclusions: Bronchiectasis should be strongly considered in children with chronic cough and recurrent pneumonia. Long-term follow-up studies on pediatric bronchiectasis are needed to further clarify the prognosis and reduce the disease burden in these patients.

F-111 Impact of Monitoring Lung Clearance Index as a Trigger for Bronchoalveolar Lavage and Treatment on Clinical Outcomes in Children with Cystic Fibrosis

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Introduction: Cystic Fibrosis (CF) lung disease is conventionally monitored by spirometry (FEV1). Many preschool/school age children with CF with normal FEV1 reveal abnormal lung clearance index (LCI) as assessed by multiple breath inert gas washout (MBW). LCI is correlated with early structural airway changes in CF patients as assessed by computed tomography (CT) and is associated with overall pathogen infection load. Hence, potential benefits from using LCI to monitor CF lung disease are recognizable. We tested whether LCI-triggered intervention with bronchoalveolar lavage (BAL) and associated, cause-directed treatment, might benefit robust clinical outcomes in children with CF.

Methods: A 2-year, longitudinal randomized clinical trial. MBW and spirometry were performed every 3 months in children with CF between 5 to 18 years. Additionally, the CF Questionnaire Revised (CFQ-R) score was obtained yearly and BAL and CT performed at enrollment and after 2 years. Patients were clinically stable at first and last visit. All patients maintained monthly outpatient visits including treatment according to local guidelines. In the control group, physicians were blinded to MBW results. If LCI increased more than one LCI unit from the baseline value in the intervention group, BAL was performed and treatment was initiated/revised
according to microbiological growth in BAL fluid. Primary outcome was change in FEV1 z-score. Secondary outcomes were treatment burden and change in BMI z-score, overall CFQ-R score and CF CT score (Brody). The trend in slope for each outcome between the groups was assessed by a baseline corrected linear mixed model with a random regression correlation structure.

**Results:** In total, 29 children were enrolled and randomized to the control (14 patients) and intervention (15 patients) groups. In the control and intervention groups, baseline median (interquartile range) age was 9.9 (7.1-11.9) and 11.8 (9.2-13.0) years and FEV1 z-score was 0.2 (-0.4 to 0.6) and 0.0 (-0.4 to 0.5), respectively. BAL was performed 44 times in total in the intervention group excluding BAL at first and last visit. Overall, the mean (95% confidence interval) percent of days on any antimicrobial treatment during the study was 53% (33-73%) in the control group and 73% (59-87%) in the intervention group. In the baseline corrected analysis, FEV1 z-score decreased non-significantly over time in both groups with no significant difference between groups in slope (intervention vs. control group: -0.07 vs. -0.05 z-scores per year, P = 0.84). BMI z-score, overall CFQ-R score and overall CF CT score increased non-significantly in both groups during the study period, with no significant differences between the groups in slope for each outcome (P = 0.65, 0.85 and 0.96, respectively).

**Conclusion:** This study did not demonstrate a beneficial effect on clinical outcome measures of quarterly MBW-driven intervention with treatment based on LCI-triggered BAL. One explanation could be an overall high treatment level and good clinical status of participants in both the control and the intervention group. Additionally, we speculate that intervention based on LCI increases >15%-25% as suggested in recent publications compared to an average of recent clinically stable LCI-measurements, may be more suitable in future studies.

J-124 | **The Yield of AFB Smear and TB Culture in the Diagnosis of Childhood TB Using Sputum Induction with N-Acetylcysteine: A Randomized Controlled Trial**

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**Background:** Microbiological diagnosis of childhood tuberculosis is of paramount importance with the emergence of multi-resistance TB. It has continuously challenged physicians due to the paucibacillary nature of TB in children and their difficulty in expectoration and producing an appropriate specimen. **Objectives:** This study aims to compare the diagnostic yield and safety of sputum induction using N-acetylcysteine with spontaneous expectoration for the microbiological confirmation of pulmonary tuberculosis among children at the Philippine General Hospital. **Design:** This is a randomized trial with cross-over design for both the control group and experimental group. **Methods:** Inpatient and outpatient pediatric patients (4-18 years old) suspected to have TB (pulmonary, extrapulmonary or drug-resistant TB) based on clinical and/or radiological features were enrolled in this study. Patients were randomized into two groups, consisting of 56 patients for each group: Group A (sputum induction with N-acetylcysteine followed by spontaneous expectoration/gastric aspiration after 3 days) and Group B (spontaneous expectoration/gastric aspiration followed by sputum induction with N-acetylcysteine after 3 days). Collected specimens were examined for acid fast bacilli smear and culture and sensitivity testing. The percentage yield was compared between groups and within each group. All patients were pretreated with a bronchodilator before the procedure and observed for any adverse events during the procedure.

**Results:** The sequence effects of group A and group B were analyzed using t-test, which showed no significant difference (P = 0.7290) on microbiological yield whether sputum induction or spontaneous expectoration was performed before the other. Nineteen patients (33.9%) had positive sputum AFB and/or culture results for the sputum induction (IS) group, while only 3 (5.3%) were positive for the spontaneous expectoration (SE) group. Of the 19 patients from the IS group, 8 (42.1%) patients were positive for AFB but negative for culture results, 5 (8.9%) patients were positive for culture but negative for AFB results, and 6 (10.7%) patients were positive for both AFB and culture results. For the SE group, 1 patient (1.8%) had positive AFB only, while the other 2 (3.6%) patients were positive for both AFB and culture results. Sputum induction with N-acetylcysteine produced a greater microbiological yield of AFB and TB culture compared to spontaneous expectoration. In the IS group, 6 had a positive TB culture while 14 had positive AFB. In the AFB smear, there was 1 additional patient on the second specimen and 2 additional patients on the third specimen. In the SE group, 5 had a positive TB culture while 3 had positive AFB. Participants who had positive AFB results on spontaneous expectoration also yielded positive AFB smear results on sputum induction. Patients from the sputum induction group who had positive TST results and radiological findings of pulmonary involvement or normal chest X-ray results were correlated with an increased likelihood of bacteriologically-confirmed TB disease. There were no observed serious adverse effects.

**Conclusion:** Sputum induction with N-acetylcysteine is a safe and effective method for microbiological confirmation of TB in children. The microbiological yield of sputum AFB obtained after sputum induction is statistically significantly better compared to spontaneous expectoration.

N-45 | **Artificial Intelligence-Enabled Acoustic Analysis Technology for Accurate Detection and Interpretation of Breath Sounds in Children**

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Aims: The study aimed to develop and validate an automated breath and adventitious sound monitoring system using Artificial Intelligence-enabled acoustic analysis technology.

Background: There is high interobserver variability in the detection of breath sounds on auscultation with the stethoscope. There is also considerable overlap of adventitious sounds in common illnesses such as viral wheeze, bronchiolitis, asthma, and pneumonia. Accurate detection of adventitious sounds (e.g., wheeze and crepitations) is important in the diagnosis of these common respiratory conditions.

Methods: A support vector machine (SVM) classifier for identifying the type of breath and adventitious sounds present on auscultation was developed using recorded breath sounds from children. The acoustics of various adventitious sounds have different time and frequency domain behaviors or distributions. Based on this theory, a set of patent-pending features were devised to distinguish the different breath sounds detected in children (aged 0–16 years). Two independent physicians performed auscultation on children, blinded to their clinical diagnosis. The breath sounds were assigned into single label or Multilabel categories. Single label sounds were identified as normal breath sounds, crepitations, or wheeze. Multilabel sounds consisted of both crepitations and wheeze together. Concordance in the assessment of breath sounds between clinician and the automated system was assessed. Cross validations (CV) were performed and model parameters were selected based on the lowest CV error, which was subsequently used to finalize the SVM classifier with the complete data set. Recordings obtained from the commercial R.A.L.E. Repository were also used in the training and validation of the classifier.

Results: Ninety-three breath sound samples were prospectively collected, out of which 81 were concordant and 12 were discordant between the two independent physicians. The 81 concordant breath sounds consisted of 73 single label sounds and 8 multilabel sounds. Within the 73 single label sounds, 45 were that of normal breath sounds, 18 of wheeze, and 10 of crepitations. Performance of the classifier on the 73 single label sound samples showed an average predictive accuracy of 94%.

Discussion: A further gathering of adventitious sounds in the multilabel category (consisting of both crepitations with rhonchi and additional respiratory sounds, e.g., bronchial breath sounds, stridor, stertor, and transmitted sounds) will help achieve a more detailed multilabel classifier with greater capability in detecting and interpreting adventitious sounds in a pediatric clinical context.

Conclusion: The algorithm developed was found to be capable of classifying normal breath and adventitious sounds with high accuracy compared to the human observers. Integration of the automated breath sounds detection algorithm into a portable mobile device with a stethoscope head can provide accurate auscultation findings to aid in the diagnosis and management of respiratory diseases in patients.
A randomized double-blind clinical trial, including preterm infants born at ≥ 32 + 6 to 36 + 6 weeks' gestation, between May 2015 and January 2017. The control group received 400 IU of cholecalciferol daily compared to 800 IU daily in the intervention group. We measured the levels of 25(OH) vitamin D at birth (cord blood), 6 months and 12 months, and followed the respiratory morbidity in both groups.

Results: Fifty subjects were recruited during the study period: 25 subjects in each group. The median 25(OH) vitamin D levels in the control group vs. the intervention group were: 26.5 vs. 34 nmol/L (p = 0.271) at birth, 99 vs. 75.5 nmol/L (p = 0.008) at 6 months and 72.5 vs. 75 nmol/L (p = 0.95) at 12 months of age. Regarding respiratory morbidity, the intervention group, which had significantly lower vitamin D levels, had 3.5 vs. 1.9 (p = 0.014, n = 11) at 6 months and 72.5 vs. 75 nmol/L (p = 0.014, n = 9) at 12 months of age. A significant negative correlation was found between the mMRC dyspnea scale and FEV1 (% predicted) (Spearman r = -0.78, P = 0.014, n = 9). Furthermore, duration of the follow-up period was found to be significantly negatively associated with RV (% predicted) (Spearman r = -0.67, P = 0.013, n = 13).

Conclusion: Doubling the daily intake of vitamin D in the first year of life does not increase its serum levels when compared to the control group. We found a reversed association between serum vitamin D levels and the number of respiratory diseases in premature infants during the first year of life.

A-33 | Pulmonary Function Evaluation in Pediatric Patients with Primary Immunodeficiency Complicated by Bronchiectasis

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Background: Primary immunodeficiency (PID) accompanied with recurrent respiratory infection is thought to have a devastating effect on pulmonary function. The major aim of this study was to investigate the relationships between chest computed tomography (CT) scan morphology of bronchiectasis, clinical severity of dyspnea, and deterioration of pulmonary function parameters.

Methods: Children diagnosed with PID in a tertiary pediatric referred center in northern Taiwan were enrolled and retrospectively reviewed. Demographic and clinical data including age, sex, age at diagnosis of PID, follow-up period, chest CT images (modified Reiff scores), pulmonary function test (PFT) parameters, quality of life questionnaires (mMRC dyspnea scale) were collected and analyzed. Spearman's correlation was used for correlation between continuous variables. All statistical analyses were performed using SPSS software (version 20.0; NY, USA).

Results: A total of 19 children with PID were enrolled. Among the latter, 13 patients were diagnosed as having bronchiectasis based on chest CT scans. Modified Reiff scores of chest CT scans were negatively correlated with FEV1 (% predicted) (Spearman r = -0.74, P = 0.009, n = 11) and FEV1/FVC ratio (Spearman r = -0.71, P = 0.014, n = 11). A significant negative correlation was found between the mMRC dyspnea scale and FEV1 (% predicted) (Spearman r = -0.69, P = 0.041, n = 9) and FVC (% predicted) (Spearman r = -0.78, P = 0.014, n = 9). In contrast, the mMRC dyspnea scale was positively correlated with RV (% predicted) (Spearman r = 0.85, P = 0.016, n = 7) and RV/TLC (Spearman r = 0.86, P = 0.014, n = 7). Furthermore, duration of the follow-up period was found to be significantly negatively associated with FVC (% predicted) (Spearman r = -0.67, P = 0.013, n = 13).

Conclusions: In pediatric patients with primary immunodeficiency, chest CT scan appears to be a good tool for not only the diagnosis of bronchiectasis, but also the degree of pulmonary function impairment. A further analysis reveals that the quality of life impairments of these patients could be particularly due to the airflow obstruction and air trapping related to bronchiectasis.

A-39 | Characteristics of Breath Sound in Infants with Risk Factors for Asthma Development

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**Methods:** A total of 443 infants (mean age, 9.9 months; range, 3-24 months) were included in the present study. The breath sound parameters of the frequency limiting 99% of the power spectrum (F99), the roll-off from 600-1200 Hz (Slope) and spectrum curve indices, the total area under the curve of the dBm data (A3/AT) and the ratio of power and frequency at 50% and 75% of the highest frequency of the power spectrum (RPF75 and RPF50), were evaluated. Using an ATS-DLD based original Japanese questionnaire, we examined the characteristics of airway conditions of infants.

**Results:** Altogether, 283 infants who had no history of acute respiratory infection were analyzed. The RPF75, RPF50, Slope and F99 in infants with positive results of allergy and atopic dermatitis were significantly more increased than those in the infants with a negative result.

**Conclusions:** Our results show that the breath sounds of infants with risk factors of asthma development reveal residual airway changes, even in a healthy state. Breath sound analysis may be useful for assessing the airways of infants for asthma development.

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**Correlation of BMI with Clinical Presentation and Duration of Hospitalization among Filipino Children Admitted with the Diagnosis of Asthma**

**Introduction:** Obesity and asthma are common disorders, and the prevalence of both has increased in recent decades. This study aims to recognize the correlation between body mass index (BMI) with clinical presentation and duration of hospitalization in children and adolescents diagnosed with asthma and admitted in a tertiary government hospital.

**General Objective:** To determine the correlation of BMI with the number of symptoms (clinical presentation) and duration of hospitalization among children aged 5 to 18 years old admitted with a diagnosis of asthma.

**Design:** Cross-sectional analysis.

**Subjects:** Patients 5 to 18 years old admitted with a diagnosis of asthma from June 2015 to March 2016. Those with comorbidities of pneumonia, cardiac disease, tuberculosis and demise were excluded.

**Methodology:** Weight and height were measured upon admission and plotted on the appropriate Center for Disease and Control (CDC) BMI-for-age growth chart for all included patients. Subjects were classified according to their Body Mass Index as Obese, Overweight, Normal/Healthy weight and Underweight. Symptoms and signs related to asthma were recorded upon admission. Date of discharge was determined from medical records and duration of hospitalization (days) was computed.

**Statistical analysis:** SPSS version 10 for Windows was used. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean ± SD was generated. Point and interval estimates of the odds ratio were also computed. Analysis of the different variables was performed using ANOVA, the Chi-square test and Pearson correlation analysis.

**Results:** A total of 148 patients were included, with a mean age of 9.25 years and equal sex distribution. The majority had a healthy weight (56.5%). Among the symptoms studied, there was a significantly higher proportion (P value < 0.001) of subjects with shortness of breath among the obese and underweight groups. A higher proportion of subjects (P value < 0.001) with higher number of asthma symptoms were noted among the obese and underweight groups. Significantly positive correlation coefficients of 0.415 (P value < 0.0001) between BMI and number of symptoms and 0.654 (P value < 0.0001) between BMI and duration of hospitalization were also noted.

**Conclusion:** The results of this study showed that there was a significant correlation between BMI and days of hospitalization and the number of symptoms. A positive correlation was noted in which with increasing BMI, the hospitalization days and the number of symptoms also increased and vice versa. A significantly higher proportion of obese, overweight and underweight children with asthma presented with shortness of breath.

**Keywords:** Body Mass Index, Obesity, Underweight, and Asthma.
treatment and present a PBB-extended or a recurrent PBB, potentially associated with the development of bronchiectasis, remains controversial.

**Aim:** The purpose of our study was to evaluate the efficiency and tolerance of a long duration treatment with low doses of azithromycin in the PBB-extended.

**Methods:** A register was established that included all patients aged between 0 and 16 years who underwent a bronchoscopy at the Queen Fabiola Children’s University Hospital between January 2012 and December 2017 for chronic cough and who were treated by low dose azithromycin for a minimum of 3 months for a PBB-extended.

**Results:** The response rate in our cohort was higher than 80% after a median treatment duration of 6 months. Less than 30% of the patients experienced a recurrence of PBB within 6 months after stopping the treatment and no side effects were recorded. Multiple hospitalizations for respiratory infections appeared to be the only factor associated with treatment failure.

**Conclusions:** Our study suggests that azithromycin may be an effective and better tolerated alternative to prolonged classic antibiotic therapy in the treatment of the PBB-extended, along with the necessity to confirm our results with a randomized protocol.

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**A-57 | Prevalence of Childhood Asthma in Ulaanbaatar, Mongolia in 2009**

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**Background:** Bronchial asthma is a common but important chronic disease in children throughout the world. To take measures against the prevalence of childhood asthma, many researchers have surveyed the actual statuses of childhood asthma in developed countries; however, in most Asia-Pacific developing countries including Mongolia, such surveys have never been sufficiently conducted To date. We have thought that this survey, though performed in 2009, will provide important and meaningful information even now in taking measures to prevent prevailing bronchial asthma in children in Mongolia or the countries under similar statuses.

**Methods:** The asthma prevalence and patient background information in Mongolian children aged 6 to 7 living in Ulaanbaatar were examined using a written questionnaire modified for their parents from that prepared by the International Study of Asthma and Allergies in Childhood (ISAAC).

**Results:** The estimated prevalence of asthma in Mongolian children was 20.9%. The following 3 risk factors were found to be related to asthma: (1) having allergic rhinitis symptoms, (2) mothers’ smoking, and (3) history of severe respiratory infection before 1-year-old.

**Conclusions:** The asthma prevalence in Mongolian children was higher than that in the world and Asia Pacific countries reported by ISAAC. The higher prevalence was probably attributable to household smoking (especially mothers) in draft-free houses designed for the cold area as well as severe air-pollution due to rapid industrialization and urbanization in Mongolia. Smoking prohibition in the mother (including family members) and a reduction of exposure to air pollutants are urgently needed to prevent developing childhood asthma.

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**A-69 | Clinical Characteristics and Risk Factors of the Wheezing and Asthma Phenotype in Children Under 5 Years Old**

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**Background:** Asthma in children under 5 years old is difficult to diagnose. The clinical presentation of asthma varies with age, and there are no tests that can diagnose asthma with certainty in young children. Thus, the clinician is left to try to define different asthma phenotypes based on clinical characteristics.

**Patient and methods:** Diagnosis of asthma and definition of clinical phenotypes based on patient history, diagnostic work-up, and treatment responses following the PRACTAL 2008 and GINA 2014 guidelines.

**Results:** There were 309 children under 5 years old to be diagnosed and classified according to asthma clinical phenotype. Of these, there were 218 males and 91 females, with a male/female ratio of 2.39/1. There were 184 children under 2 years of age (59.5%) and 125 children over 2 years of age (40.5%). There were 197 children classified as virus-induced asthma (63.8%), 1 child as exercise-induced asthma (0.3%) and 111 children as allergic asthma (35.9%). A specific allergic trigger could be identified in 5 children with allergic asthma. Virus-induced asthma was more common in children under 2 years of age (67.5%) while allergic asthma was more common in children from two to 5 years of age (49.0%) (OR= 2.44 (1.47-4.06; P = 0.000). Allergic asthma was more common in males (79.3%) and virus-induced asthma more common in females (34.5%) (OR= 2.02 (1.13-3.61); P = 0.010). There were no statistically significant differences for family history with regard to allergies and an increase of eosinophils in virus-induced and allergic phenotype. Fever and crepitation were more common in virus-induced asthma than allergic asthma. Other clinical signs and symptoms did not differ between the 2 groups of virus asthma and allergic asthma. The percentage of hospitalized children from 5 or more times/year was 42.3% in the allergic asthma group, higher than the 24.4% in virus asthma with a statistically significant difference (OR = 2.28 (1.35 to 3.87; P = 0.001). The percentage of children who missed school because of asthma from 19 days or more/year was 45.9% in the allergic asthma group and higher than 22.8% in the virus-induced asthma group with a statistically significant difference (OR = 2.87 (1.69 to 4.89); P = 0.001). The percentage of children with parental leave from work...
to care for asthma from 22 days or more / year was 69.4% and higher than 52.8% in the virus-induced asthma with a statistically significant difference (OR = 2.03 (1.20 to 3.41); P = 0.004).

**Conclusions:** Viral asthma is common in children under 2 years old while allergic asthma is common in children from two to 5 years old with a history of allergic diseases. Fever and crepitation are common in viral asthma. Allergic asthma affects the quality of life of children more than viral asthma.

**Keywords:** asthma phenotype; viral asthma; allergic asthma.

**A-70 | Multicenter Compliance Study of Asthma Medication for Children in Korea**


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The KAPARD Work Group on Asthma Medication Compliance.

**Background:** Compliance is a major component of successful medical treatment. However, noncompliance remains a barrier to effective delivery of healthcare worldwide.

**Methods:** Twenty healthcare facilities (secondary or tertiary hospitals) belonging to the Korean Academy of Pediatric Allergy and Respiratory Diseases (KAPARD) participated. Questionnaires were given to patients currently receiving treatment in the form of inhaled or oral or transdermal patch for mild to moderate asthma.

**Results:** A total of 1838 patients responded to the questionnaire. Mean age was 5.98 ± 3.79 years (range, 0-18 years). With help from their caregivers, the percentage of patients that answered “taking as prescribed” was 38.04% for inhalant users, 50.09% for oral medication users, and 67.42% for transdermal users. Transdermal patch users had significantly greater compliance when compared to the other two groups (P < 0.001). 34.15% of inhalant users, 70.33% of oral medication users, and 93.00% of transdermal patch users felt that their medication delivery system was “Easy” or “Very easy” to use (P < 0.001). "Method of administration" was deemed to be the most difficult part of the treatment regimen to follow, and 76.7% of patients preferred once-daily administration (ie, "Frequency of administration").

**Conclusions:** Asthma medication compliance in young children was found to be better in the transdermal patch group. This may be due to requiring fewer doses and easy to follow instructions. From a compliance point of view, the transdermal patch seems more useful for long-term asthma control in children compared to oral or inhaled medicine.

**Keywords:** Multicenter; KAPARD; Asthma Medication; Compliance.

**A-83 | Efficacy of Evaluation of Lactobacillus rhamnosus GG in a Der p-Sensitized Animal Asthma Model**

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Asthma is one of the most common chronic inflammatory diseases. People with asthma have sensitive Airways which react to triggers causing mucosa swelling and airway narrowing. The incidence of asthma is increasing every year. There is increasingly more research for asthma therapy of which probiotics is one of them. Probiotics are microorganism which can provide health benefits to the host, regulate microbial balance in the intestine, control the immune microenvironment and alleviate the condition of allergy and inflammation.

In this study, we used Dermatophagoides pteronyssinus (Der p) to induce female BALB/c mice allergic reaction. The mice received intraperitoneal Der p sensitization on day 1 to day 3 and intranasal Der p sensitization on day 14, 17, 21, 24, and 27. This animal asthma model had been established. In addition, the Der p-sensitized mice were randomly assigned to two groups. One was fed LGG (Lactobacillus rhamnosus GG) on days 1 to 14 to test the prophylactic effect on asthma; the other group was fed on days 14 to 27 to test the treatment effect on asthma. The normal control group consisted of non-sensitized mice who received normal saline rather than Der p.

According to the results, LGG treatment group, whether before or after Der p-sensitization, can suppress airway inflammation and
airway hyperresponsiveness, decrease IgE and Th2 cytokines (such as IL-4, IL-5 and IL-13) and raise IFN-γ and TGF-β.

In conclusion, oral LGG can prevent and treat Der p-sensitized airway inflammatory reaction. Therefore, oral LGG may have a role in allergic airway disease prevention and treatment.

Keywords: asthma, Lactobacillus rhamnosus GG (LGG), probiotics, airway hyperresponsiveness, IFN.

A-102 | Perception of Dyspnea during Acetylcholine-Induced Bronchoconstriction Correlates with Eosinophilic Airway Inflammation in Asthmatic Children

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Background: Few studies have examined the relationship between dyspnea perception and eosinophilic airway inflammation in asthmatic children.

Objective: We tested the hypothesis that eosinophilic airway inflammation is associated with poor perception of airway obstruction.

Methods: Two hundred seventeen asthmatic children (median age, 10.7 years) were evaluated using the acetylcholine chloride (Ach) challenge test. FENO was examined before the Ach challenge test. The BHR was assessed as the provocative concentration of Ach causing a 20% decrease in forced expiratory volume in 1 second (FEV1) (PC20). Perception of dyspnea was scored using a modified Borg scale after each dose of Ach. The dyspnea threshold was defined as the point at which the Borg scale score became higher than 0. We evaluated the dyspnea perception score at a 20% decrease in FEV1 relative to baseline (PS20) and % drop in FEV1 at the dyspnea threshold (% drop FEV1-Th).

Results: PS20 was negatively correlated with FENO (r = -0.198, P = 0.004) and positively with PC20 (r = 0.37, P = 0.001). The % drop in FEV1-Th was negatively correlated with PC20 (r = -0.39, P = 0.001), but not with FENO.

Conclusions: Eosinophilic airway inflammation is able to induce relative insensitivity to dyspnea in asthmatic children with moderate airway constriction. This may consequently lead to the undertreatment of asthma.

A-107 | Characteristics of Acute Severe Exacerbations of Asthma in Children in the Intensive Care Unit, Children Hospital 1

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Objective: To determine the characteristics of the epidemiology, clinical, paraclinical and treatment of acute severe exacerbations of asthma in the intensive care unit, Children Hospital N01 from 01/03/2008 to 30/4/2015.

Methods: Case series

Results: There were 69 cases of acute severe exacerbations of asthma in this study. The near-fatal group accounted for 19%. The 12 months to 5 years age group accounted for 58%. Female/male = 1.2/1. Sixty-one percent of children were from Hô Chi Minh City. Admission to ICU increased recently. Dyspnea was the chief complaint, accounting for 88%. Cough, wheezing, dyspnea were essential symptoms. Fifty-one percent had a history of asthma. Preventer medication ownership was recorded in 34% of cases. The rate of impaired consciousness was 59.4%. 26% had a pH < 7.3% and 33% had a PaCO2 > 40 mm Hg. Chest X-rays showed hyperinflation, infiltrates and atelectasis. Time of treatment was 7 days (6,11), days in ICU was 2 days (2, 4). Ten children were intubated, 43.5% received NCPAP; 72.6% of children older than 1 year were given MgSO4, 65% children were given diaphyllin, 20% children were given salbutamol and 6% children were given adrenaline subcutaneously. All intubated patients received pressure control ventilation. Inspiratory pressure was 14 to 16 cmH2O to achieve tidal volume of approximately 6ml/kg, mean PEEP was 7 cmH2O, FiO2 was approximately 80% and I/E was 1/2 - 1/3. Intubated patients spent longer days in hospital and days in ICU.

Conclusions: Appropriate treatment at first is crucial to lower the number of children to be intubated. Mechanical ventilation still remains the last recourse in the treatment of near fatal exacerbations of asthma after MgSO4, diaphyllin and salbutamol.

A-132 | Peanut and Brazil Nut Sensitization Profile among Asthmatic Patients in Southern Taiwan

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Aim: To know the relationship between serum-specific immunoglobulin E (IgE) to peanut and Brazil nut among atopic diseases in southern Taiwan.

Method: Sera of individuals with suspected atopic diseases were collected for the measurement of serum-specific IgE (FEIA ImmunoCAP, Thermo Fisher Scientific) to peanuts, cashew nuts, Brazil nuts, almonds and coconuts. Cases with possible sensitization to these nuts (serum-specific IgE ≥ 0.35 kU/L) were selected and their clinical relationships with physician-diagnosed atopic dermatitis and asthma were analyzed.

Results: Compared with the non-sensitization group, people with peanut/tree nut sensitization had a higher prevalence of atopic dermatitis, but no such difference was noted in the prevalence of allergic rhinitis. In the situation of asthma, people with sensitization to peanuts and Brazil nuts, but not other nuts, had a higher prevalence of asthma than those without sensitization to any nut (P < 0.001 and P < 0.05, respectively). Binary logistic regression analysis also showed positive associations between peanut (OR: 1.164, P value = 0.017) and Brazil nut (OR: 1.304, P value = 0.055)
sensitization and asthma. The associations between peanut and Brazil nut sensitization and asthma were independent of the prevalence of other atopic diseases.

Conclusion: Those with allergic reactions to nuts have higher rates of asthma although sensitization to specific food allergens such as peanuts and Brazil nuts may predispose individuals to asthma in Southern Taiwan.

A-142 | Asthma and the Risk of Pneumococcal Invasive Disease: A Systematic Review and Meta-Analysis

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Background: Asthma is the most common chronic disease in childhood, and invasive pneumococcal disease (IPD) is a leading cause of global morbidity and mortality. Current guidelines recommend supplementary vaccination with pneumococcal polysaccharide vaccine (PPSV23) in asthma only for patients treated with prolonged high-dose oral corticosteroids. Here we evaluated the risk of IPD among children with asthma after the introduction of pneumococcal conjugate vaccines (PCV).

Methods: We searched four electronic databases and included all observational studies of IPD or pneumonia in populations receiving PCV that reported data for children with asthma and healthy controls. Primary outcomes were occurrence of IPD and pneumonia. Secondary outcomes included mortality, hospital admissions, hospital length of stay, intensive care unit admission, respiratory support, costs, and additional medication use.

Results: Four studies met the inclusion criteria; three retrospective cohorts (~26 million person-years) and one case-control study (n =3,294 children) qualified for the meta-analysis. Children with asthma had ~90% higher risk of IPD than healthy controls (OR = 1.90, 95% CI: 1.63-2.11, I² = 17%). Pneumonia was also more frequent among children with asthma than among controls, and one study reported that pneumonia-associated costs increased with asthma severity.

Conclusions: After introduction of PCV, children with asthma continue to have a higher risk of IPD than children without asthma. Further research is needed to assess the need for supplemental PPSV23 vaccination in asthmatic children, regardless of their use of oral steroids.

A-165 | Polymorphic Markers of CDHR3 are Associated with Preschool Wheeze and Forced Expiratory Indices

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Background: A recent genome-wide association study reported rs6967330 of CDHR3 encoding for human rhinovirus-C (HRV-C) receptor to be a novel risk factor for recurrent severe asthma exacerbations in Caucasian preschoolers. However, there is limited data on its importance in Asian populations. The relevance of CDHR3 to childhood lung functions is also unknown. This cross-sectional study investigated the associations between CDHR3 and wheezing illnesses and lung function of preschool children in Hong Kong.

Methods: Chinese children younger than 6 years of age were recruited from randomly selected nurseries and kindergartens throughout Hong Kong. The demographic, early-life exposures and allergy phenotypes of these preschool children were recorded by validated and modified ISAAC questionnaire. These children underwent incentive spirometry to measure their forced expiratory indices. Their buccal swabs were collected for DNA extraction and tagging single-nucleotide polymorphisms (SNPs) of CDHR3 were determined by TaqMan genotyping assays. Genotypic and haplotypic associations between these SNPs and wheezing and lung function traits were analyzed by multivariable regression and R-package haplo.stats 1.7.7, respectively.

Results: The mean (SD) age of a total of 1341 children was 4.7 (1.0) years. Forty-one percent of them had domestic exposure to cigarette smoking, whereas 17% and 11% had wheeze ever and current wheeze respectively. Current wheeze was associated with rs6967330 and rs140154310 of CDHR3, with the respective odds ratios (ORs) being 1.63 and 2.20. Two of these SNPs were also associated with frequency of wheezing illnesses over the past 12 months, with ORs being 1.57 (P = 0.034) for rs6967330 and 2.14 (P = 0.024) for rs140154310. Current wheeze was also associated with the 3-locus GAC haplotype of CDHR3 (OR, 1.54 and P = 0.048). Two CDHR3 SNPs rs408223 and rs140154310 were associated with FEV0.5, FVC and FEV0.5/FVC, and the GGG haplotype was associated with FEV0.5.

Conclusions: CDHR3 is a candidate gene for wheezing illnesses and forced expiratory indices in Chinese preschool children, which supports the importance of HRV-C infection in altering the susceptibility for early-life wheezing. Our findings need to be replicated in prospective studies.

Funding: Direct Grant for Research (4054367) of CUHK and Health and Medical Research Fund (17161332).

A-174 | Development and Validation of an Adherence Questionnaire for Adolescents with Asthma on Controller Inhaled Corticosteroids

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Background: Poor adherence leads to poor asthma control. Objective monitoring of adherence, however, is often difficult. A simple questionnaire to identify poor adherence and factors that hinder adherence may be useful in clinical practice.

Methods: A 53-item working questionnaire was developed based on concepts obtained through semi-structured interviews of adolescents with asthma who were treated with inhaled corticosteroids (ICS). The questionnaire was then administered to adolescents (9-15 years old)
with asthma on ICS at multiple hospitals and clinics in Japan. Adherence to ICS medication was separately evaluated by "confidential" questions to ask frequency of "forgetting to take medicine" by nonmedical study staff. The best model to predict adherence was formed by multivariate logistic analysis. Validation of the model was performed using answers to the questions from a separate group of ICS-treated asthma patients of the same age.

**Results:** Responses from 445 adolescents were used as development data set and those from separate 275 adolescents were used as validation data set. A 6-item logistic model was selected from the development data set. It showed good statistical fit and well discriminated poor adherence with AUC at 0.814 and 0.759 in development and validation datasets, respectively. Probability of adherence was calculated as propensity score in the logistic regression model and named as the Pediatric Asthma Adherence Questionnaire (PAAQ) score. The PAAQ scores for the physicians' ratings of adherence differed significantly in the hypothetical direction.

**Conclusion:** The PAAQ may be a useful tool to evaluate adherence in adolescents with ICS-treated asthma.

**A-208 | Effect of Long-term Inhaled Corticosteroid Therapy on Adrenal Suppression Growth and Bone Health in Children with Asthma**

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**Introduction and Objectives:** Possible adrenal suppression and effects on bone metabolism and growth are concerns of long-term use of inhaled corticosteroids (ICS) in children. Describing the effect of ICS on the above and Vitamin D levels in children with asthma compared to a control group of asthmatic children who were not on ICS was the primary objective. Effect of the dose and duration of ICS on the above parameters were assessed in the cases as a secondary objective.

**Method:** This was a comparative descriptive cross-sectional study conducted at the University pediatric unit, Lady Ridgeway Hospital from September 2017 to June 2018. Seventy children aged three to 9 years diagnosed as having asthma on inhaled corticosteroid therapy for more than 6 months were included as cases. Children who were on oral steroids for exacerbations a week before the study, asthma with other chronic illnesses and children over 9 years old to avoid the confounding effects of pubertal growth acceleration seen at this age, were excluded. Comparison group consisted of 70 age-matched children with asthma who were not on ICS.

Heights were assessed according to their Mid Parental Heights (MPH). Serum calcium, alkaline phosphatase and vitamin D levels were assayed in both groups. Low dose short Synacthen test was performed on cases and serum cortisol at 0, 30, 60 minutes of the test was performed to assess HPA axis function. Peak cortisol level > 500nmol/l at 30 minutes was considered to have passed the test and exclude adrenal suppression. The average daily dose of ICS was categorized as low, medium and high according to published literature.

**Results:** Both the associations between long-term ICS and growth (chi square value = 0.785, P < 0.376) and calcium levels (P = 0.88) were not statistically significant. A significant association was found between long-term inhaled corticosteroid therapy and ALP level (P < 0.01) although the interquartile ranges of serum ALP in both groups were within the normal range for the age.

There was no statistically significant difference in vitamin D levels in both groups (P = 0.886), although Vitamin D levels were deficient in 34% of cases and 41% of controls (< 50 nmol/l). Interestingly suppressed cortisol levels were seen in 24% of cases. Cumulative doses of ICS in 70 cases were low, medium and high in 41%, 41% and 17% of children respectively.

A significant association was found between the dose of inhaled corticosteroid therapy and adrenal suppression (chi square value= 29.80, P < 0.001) and the duration of corticosteroid therapy and adrenal suppression (chi square value= 12.291, P < 0.01).

**Conclusion:** ICS had no impact on the growth and bone profiles in children. However, 25% of children who were on long-term ICS showed adrenal suppression which was significantly associated with the dose and duration of therapy.

**A-219 | Vitamin D Deficiency in Jordanian Children with Bronchial Asthma**

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**Objective:** Asthma is caused by complex interactions of genetic and environmental factors. Vitamin D deficiency is being linked to an array of immunologically based diseases, one of which is asthma. The aim of this study is to assess the level of serum vitamin D in children with bronchial asthma and to correlate it with the severity of the condition. Additionally, we aim to determine whether vitamin D deficiency is associated with atopy and allergen sensitization in children with bronchial asthma.

**Methods:** This study included 98 children with bronchial asthma, aged between 4 and 14 years. Serum 25-hydroxy vitamin-D levels were determined. Severity of asthma was determined according to the Global Initiative for Asthma (GINA) assessment and the Asthma Control Test (ACT). Skin prick testing for inhaled allergen sensitization was also performed.

**Results:** Our results showed a high prevalence of vitamin D deficiency among asthmatic children. Vitamin D levels were deficient in 41.8% of asthmatic children and insufficient in 34.7%. Only 23.5% had sufficient vitamin D levels. The severity of asthma symptoms showed a
significant correlation with vitamin D deficiency. Additionally, children with vitamin D deficiency tended to use more systemic steroids than those with normal vitamin D levels. However, there was no association between vitamin D deficiency and atopy in asthmatic children.

**Conclusion:** Our study clearly demonstrates the importance of verifying vitamin D levels in children with bronchial asthma. This could be a target for modifying treatment modalities and determining new risk factors for asthma development and severity in pediatrics.

**A-221 | Drug Use and Quality of Life in Asthmatic Children 1 Year before and after Admittance in an Outpatient Pediatric Asthma Clinic**

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**Purpose of the study:** To compare quality of life and drug use in asthmatic children before and after their attendance in a specialized asthma clinic.

**Background:** Asthma is the most common chronic condition during childhood. Despite this, asthma is often both overdiagnosed and underdiagnosed resulting in fragmented therapy, deterioration in quality of life as well as increased direct and indirect costs. Since 2014, and due to the financial crisis, the Greek state has introduced e-prescription as a tool for better control of pharmaceutical prescription and pharmaceutical expenditure. This platform, in which almost all Greek citizens are registered, provides the possibility of a documented assessment of the patient’s medication use and allows estimations of direct pharmaceutical costs.

**Materials and Methods:** Forty-six asthmatic children 7 to 14 years old, classified as step 3 or 4 according to GINA guidelines 2018.

Antibiotic, antihistamine and nasal steroid use as well as quality of life (QoL) were measured in asthmatic children admitted to an outpatient pediatric asthma clinic of a tertiary care pediatric hospital, 1 year before and 1 year after.

Quality of life (QoL) was measured with the DISABKIDS Questionnaire, which is a validated questionnaire, completed both by children and their parents. The measures used for the study were the DISABKIDS chronic generic measure (DCGM-37) and the DISABKIDS Condition-specific module for asthma. The DISABKIDS chronic generic module (DCGM-37) consists of 37 rating-scaled items assigned to six dimensions: Independence, Emotion, Social inclusion, Social exclusion, Limitation, and Treatment. These six dimensions can be combined to produce a general score for HRQoL. The condition-specific asthma questionnaire (DISABKIDS Asthma Module – 17 questions) consists of two domains: the impact domain, concerning limitations and symptoms, and the worry domain, concerning worries related to asthma. In the study, both DISABKIDS self-report versions (child version) and proxy versions (completed by one of their parents) were used.

**Results:** Total antibiotic use appeared to have decreased 1 year after follow-up in a specialized asthma clinic. Both the overall use (p 0.08) and the use of amoxycillin / clavulanate (p 0.01) were statistically significant. The use of amoxycillin, cephalosporins and macrolides was also found to be reduced. A statistically significant reduction was also found in the use of antihistamines (p 0.048). In terms of quality of life, a statistically significant improvement was found in the worry domain of asthma both in children (p 0.012) and their parents (p 0.013) as well as in the impact domain for parents (p 0.05).

**Conclusions:** Antibiotic, antihistamine and nasal steroid use in asthmatic children in need of step 3 or 4 treatment according to GINA guidelines is significantly reduced after attending an asthma clinic. Quality of life is improving.

**2 | ALLERGIC BRONCHOPULMONARY DISORDERS (EXCLUDING BRONCHIAL ASThma)**

**B-133 | Cut-off Values of Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis in Asthmatic Children**


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**Introduction:** Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease occurring primarily in patients with asthma and cystic fibrosis. The diagnostic criteria for ABPA have been evolving, although the latter are for adults. There are no separate diagnostic criteria for children. The objective of our study was to evaluate cut-off values of total IgE, Aspergillus-specific IgE, Aspergillus-specific IgG, and eosinophil count in differentiating ABPA in asthmatic children.

**Methods:** In this prospective cross sectional study, we enrolled consecutive children between 5 to 15 years of age with poorly controlled asthma (partly controlled and uncontrolled as per GINA guidelines) between July 2016 to March 2018. We excluded children with cystic fibrosis. The enrolled children were investigated for ABPA that included total IgE, Aspergillus-specific IgE, Aspergillus-specific IgG, skin prick test for Aspergillus, serum precipitins, absolute eosinophil count (AEC), chest X-ray, and chest CT (in selected patients). ABPA was diagnosed as per recent criteria: if both of the following criteria were fulfilled: (1) total IgE > 1000 IU/ml and positive skin prick test (SPT) to Aspergillus or Aspergillus-specific IgE > 0.35 kUA/L; (2) at least of two of following three: presence of precipitating antibody or Aspergillus-specific IgG > 27 mg/L; chest radiology suggestive of ABPA; and total eosinophil count > 500 cells/mm3. Data were analyzed using STATA 12.0. We used the receiver operating characteristic (ROC) curve along with area under the curve (AUC) to determine the utility of various parameters to differentiate children with ABPA from those without. To determine best cut-offs, Youden’s index was used (sensitivity + specificity -1).

**Results:** We included 106 asthmatic children (male: female 72:34) with mean (SD) age of 10.2±2.6 years. The prevalence of ABPA was 12/106 (11.3%; 95% CI, 5.2%, 17.5%). Among baseline characteristics including spirometry of included children, only the presence of brownish sputum
was greater in ABPA children. Among diagnostic criteria, all were significantly different between children with ABPA and without ABPA except Aspergillus-specific IgG and positive SPT. The AUC (95% CI) of ROCs are shown in Figure 1. The difference between AUC of total IgE and Aspergillus-specific IgE vs. Aspergillus-specific IgG was significant. The sensitivity and specificity of total IgE (>1000 IU/ml), Aspergillus-specific IgE (> 0.35 kU/A/L), AEC (> 500/mm3) and Aspergillus-specific IgG (> 27 mg/L) cut-offs as defined by diagnostic criteria was 100% and 65.9%, 75.0% and 79.8%, 91.7% and 57.0%, and 27.3% and 87.5% respectively.

The best cut-off values as per Youde's index of total IgE, Aspergillus-specific IgE, AEC, and Aspergillus-specific IgG were 1806 IU/ml, 0.63 kU/L, 786/mm3, and 16.8 mg/L, respectively with corresponding sensitivities and specificities of 75% and 76.6%; 75.0% and 88.3%; 83.3% and 74.2%; and 63.4% and 71.5%, respectively.

Conclusions: Aspergillus-specific IgE levels had the best discriminative value followed by total IgE, AEC, and Aspergillus-specific IgG for ABPA in asthmatic children. The currently proposed cut-off values may not be appropriate for children.

Reflections and concrete proposals for action: There is need to develop childhood-specific diagnostic criteria for ABPA.

C-76 | Comparing High Flow Nasal Cannula with Noninvasive Ventilation Modes in the Management of Bronchiolitis in the Pediatric Intensive Care Unit

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Background: Various modalities of Noninvasive respiratory support are used for infants and young children who are hospitalized to the intensive care unit with acute bronchiolitis. High Flow Nasal Cannula (HFNC) is one of the new modalities of delivering high concentration oxygen therapy and has been widely used in the last decade.

Methods: This is a one-year retrospective study that was conducted in our pediatric intensive care unit (PICU) comparing the intervention failure rate of three different Noninvasive respiratory support modalities (bi-level positive airway pressure (BIPAP), continuous positive airway pressure (CPAP) and HFNC) for infants and young children between the ages of 1 month and 2 years admitted with the diagnosis of bronchiolitis. A sample size of 137 patients was collected with a median age of 2 months. Children who required HFNC were older (mean 4.5 months) than children who required BIPAP (2.7 months) while the mean age for children who required CPAP was (2.8 months).

Results: HFNC carried a higher failure rate in comparison with the other two respiratory support modalities (50.6% for HFNC n39/77 vs. Zero % for CPAP n0/10% and 8% for BIPAP n4/50, P < 0.01). Among the 39 patients who failed HFNC, (90%) were successfully shifted to BIPAP and weaned off later, while the other 4 were intubated and needed mechanical ventilation. On the other hand, all 4 patients who failed BIPAP were intubated and mechanically ventilated. No difference was found between the three groups in terms of gender or the causative virus. No respiratory complications or mortality was reported in the three groups. In the BIPAP group, oxygen requirement was significantly reduced at 24 hours from the start of the intervention and afterward in comparison with the HFNC group (P < 0.01 - 0.02), although not statistically significant with the CPAP group. No difference was observed in length of PICU stay or hospital stay between the three groups.

Conclusions: This study highlights the superiority of BIPAP and CPAP over HFNC for acute bronchiolitis patients in PICU. Further prospective randomized trials are recommended to confirm this finding.

C-100 | A Study of Human Coronavirus Infections in Children with Community—Acquired Pneumonia from 2015 to 2016 in Zhejiang, China

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Objective: To study human coronavirus (HCOVS) infections in children with community-acquired pneumonia (CAP) in Zhejiang.

Methods: From November 2014 to November 2016, the nasopharyngeal aspirations (NPAS) or throat swabs from children diagnosed with CAP were collected from the Children’s Hospital, Zhejiang University School of Medicine. Respiratory specimens were screened for 18 respiratory viruses, including HCOVS (OC43, 229E, NL63 and HKU1) by Luminex Liquid Chip Technology. In addition, the epidemiological characteristics, severe pneumonia and complications of children infected with HCOVS were analyzed.

Results: A total of 404 cases of CAP children with NPAS or pharyngeal swabs were collected. The total virus detection rate was 52.23% (211/404), while the HCOVS detection rate was 0.5% (2/404). One case was HCOV-Oc43, and the other was Hcov-Hku1. Neither of the two children was infected with HCOVS alone, and enteroviruses and rhinoviruses were detected in both cases. The age
of onset of HCOV-positive children in both cases was less than 1 year old, and both cases were severe pneumonia.

**Conclusion:** HCOVS infections are rare in children with CAP in Zhejiang. HCOV S infections can cause severe pneumonia.

**C-130 | ARDS in Children with Ventilator-Associated Pneumonia at Children’s Hospital Number 1**

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**Background:** Ventilator-associated pneumonia has the highest mortality rate among nosocomial infections. The Pediatric Acute Lung Injury Consensus Conference Group issued new recommendations regarding PARDS (Pediatric Acute Respiratory Distress Syndrome) in 2015. This study describes the characteristics of PARDS in children with ventilator-associated pneumonia (VAP) in our hospital.

**Aim:** To investigate the features of ARDS in ventilator-associated pneumonia in pediatric patients from the Intensive Care Unit – Children’s Hospital Number 1 from August 2015 to May 2016.

**Study design:** Descriptive, prospective study. (Prospective cross-sectional study)

**Results:** Sputum specimens from 33 pediatric subjects were collected to determine microorganism agents. The positive rate with culture of onset VAP, the pathogens consisted of Gram-positive bacteria (predominantly *Streptococcus pneumoniae*) and atypical bacteria with proportions of 60% and 40%, respectively, while in late-onset VAP, the bacterial etiology profiling was Gram-negative bacteria 39.1%, Gram-positive bacteria 30.4% and atypical 30.5%. All of the children were on pressure control invasive ventilation. Children with mild ARDS accounted for 63%, moderate ARDS 24% and severe ARDS 13%. The mortality rate from this study was 15%.

**Conclusion:** In our study, all of the children were on pressure control ventilation; most had mild or moderate ARDS; there were 13% children with severe ARDS. The mortality rate from this study was 15%.

**Keywords:** ventilator associated pneumonia (VAP), Acute Respiratory Distress Syndrome (ARDS), bacterial pathogen, pediatric.

**C-134 | Bacteria and Viruses that Trigger Cough in Children outside Epidemic Seasons**

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We performed real life observations on the etiology of the different viral or bacterial nasopharyngeal infections in children with acute (acute bronchitis and bronchiolitis) and chronic cough (asthma or chronic wet cough) outside of winter epidemic conditions.

**Material and methods:** For a period of 6 months (April-October 2018), we collected nasopharyngeal and deep throat swabs from 74 children (36 females and 38 males, aged 1.5 – 11.9 years) divided in 4 groups as follows: 24 children with bronchial asthma (BA), 20 with chronic wet cough (CWC), 24 with bronchiolitis and bronchitis (AB), and 10 healthy children (HC) as a control. All children with BA and CWC were tested during acute exacerbation. The children taking antibiotics Before obtaining the samples, as well as those with X-ray changes corresponding to pneumonia were excluded. The children with CWC, AB and HC were without any personal or family history for asthma. From the obtained samples, specific microbiological agent detection was performed by culture examination. Additionally, PCR and/or serology for adenovirus, Bordetella pertussis and B. parapertussis, human metapneumovirus (hMPV), influenza virus A and B, adenovirus, rhinovirus (RV), parainfluenza virus, Mycoplasma pneumonia, bocavirus and respiratory syncytial virus (RSV) were performed.

**Results:** None of the children had positive result for Bordetella, Mycoplasma and influenza or parainfluenza virus, perhaps due to excluded cases with pneumonia and the season in which the samples were obtained. In the HC, we did not identify viral pathogens or any bacterial colonization in the throat samples. In 20% of the nasal swabs, *Staphylococcus aureus* was cultured. In 33% of the patients from the AB group, we found only viruses – RSV, RV and hMPV, while in 25%, we found combined infection with virus and bacteria. Isolated bacteria consisted mainly of *Moraxella catarrhalis* while *Streptococcus pneumoniae* had an equal prevalence of 33% of the children in this group. Only one child had *Staphylococcus aureus*, found in the nose but not in the throat swab. In the BA group, we found virus infection only in 25%, predominantly adenovirus, followed by RV and RSV. In 56% of the cases, *Streptococcus pneumoniae* was confirmed in the throat swabs vs. only 33% for isolated *Moraxella catarrhalis*. There were no other bacteria isolated in the BA group. In the CWC group, we found only in 10% of viral infections mainly hMPV, followed by adenovirus and RV. Fifty percent had isolated *Streptococcus pneumoniae* while the remaining 40% had polymicrobial etiology including *S. aureus*, *H. influenzae*, *S. pyogenes*, *E. aerogenes*.

**Conclusion:** The “wait and see” strategy is not advisable for children with CWC since only 10% have isolated viruses and 40% have polymicrobial flora found; thus antibiotics should be given for these children as soon as possible. Outside winter epidemic seasons, *M. catarrhalis* and *S. pneumoniae* (non vaccine serotypes) are still the most prevalent bacteria while RV, RSV and adenoviruses are the predominant viral cough triggers.

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C-146 | Etiological Profile of Pneumonia in Hospitalized Children – Effect of the Pneumococcal Vaccine

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We analyzed the current etiological profile of pneumonia in children after introduction of the pneumococcal vaccine in Bulgaria.

Material and methods: For a period of 3 years (December 2015 - November 2018), we collected the clinical and laboratory data of 285 children (150 females and 135 males, aged 1 - 17.9 years) which had been hospitalized for pneumonia (confirmed by X-ray and clinical presentation). We specifically looked for immunization status and comorbidities. The laboratory data included – CRP, full blood count, sputum culture examination, PCR and/or serology for respiratory viruses, Chlamydia and Mycoplasma.

Results: 105 children had been taking antibiotics Before hospitalization while the remaining 180 patients were antibiotic naïve. In 44.9% of the cases, we could not prove etiological agent, while bacteria were confirmed in 41.6% and viruses in 16.2% (in 4.6%, we found combined virus and bacteria), and fungi were found in 2.5%. When dividing the cases according to prior antibiotic use, the distribution was: 38.8%, 48.3%, 15% and 2.2% for antibiotic naïve vs. 55.23%, 28.5%, 18.9% and 2.8% for the others respectively (P = 0.002). When looking at the bacterial isolates and prior antibiotic use, we did not find any significant difference regarding Mycoplasma pneumoniae isolation (P = 0.36) although there was one for Streptococcus pneumoniae (P = 0.015), mainly due to the standard guidelines to GPs to start with penicillin antibiotic for pneumonia. As expected Mycoplasma was isolated in older children, while Streptococcus was mainly isolated in younger patients. Mean age for children with bacterial pneumonia was 6.54 years, for those with viral pneumonia 4.34 years., for combined (viral+bacterial) 3.08 years. and for fungal pneumonia 10.42 years (P = 0.000). The values for CRP were lower in cases with Mycoplasma and in cases with non-compact infiltrate changes on X-rays (P = 0.002 and P = 0.000). Almost 2/3 of the children have been immunized with pneumococcal vaccine (66%). The immunized patients had higher numbers of viral and lower numbers of bacterial isolates – 25.7% and 37.23% vs. non-immunized patients – 4.12% and 48.45%, respectively (P = 0.002). There was no difference in Streptococcus pneumoniae isolation and vaccination status, but there was a major drop in Mycoplasma isolates in vaccinated patients (6.9% vs. 32.98%, P = 0.000). For the patients with asthma only, we could not identify the microorganism in 14%, while in 48.5% and 51.2%, we found viruses and bacteria, respectively (co-infection was found in 23.26%). In 50% of children without asthma, we did not isolate the etiological agent and there was co-infection only in one case, while viral pneumonia and bacterial pneumonia was confirmed in 10.6% and 39.3% respectively (P = 0.008). All children but 3 were discharged healthy for mean 6.54 days in hospital stay. The mentioned 3 patients had severe complications and required surgical intervention.

Conclusion: In the future, we could expect more viral pneumonia with increasing vaccination coverage and maybe we should reevaluate our treatment guidelines.

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C-154 | Factors Associated with the Need for Pediatric Critical Care in Community-Acquired Pneumonia versus Hospital-Acquired Pneumonia

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Objective: To compare the need for pediatric critical care in a tertiary children’s hospital with a diagnosis of community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP). Furthermore, we conducted a pilot study to evaluate the possible medical biomarkers which are associated with longer pediatric intensive care unit stay.

Methods: An observational, retrospective cohort analysis was conducted in children who were admitted to our tertiary children’s hospital with a diagnosis of CAP or HAP. Patient demographics, clinical characteristics, and comorbidity were collected between January 2012 and December 2013. The following prospective pilot study was conducted in children who were admitted to our pediatric intensive care unit (PICU) due to pneumonia progression. We evaluated the clinical profiles and medical biomarkers. The primary endpoint was the duration of PICU stay with associated predicting factors.

Results: A total of 548 patients with 598 episodes of pneumonia (310 males; 288 females) requiring admission to our children’s hospital were included. The mean age at admission was 59.6 ± 1.95 months and the average length of stay was 11.4 ± 0.70 days. 530 episodes were identified as CAP and the other 68 episodes were HAP. Patients with CAP had significantly shorter lengths of hospital stay and duration of ICU stay than those with HAP (8.2±10.5 vs. 36.5±31.5 days, P < 0.001; 2±6.9 vs. 10±18 days, P < 0.001). The most common co-morbidities in CAP were neurological diseases and atopy history. Among the CAP patients, 90 episodes (17%) led to ICU admission during treatment course with the most common comorbidities being neurological diseases. However, in HAP patients, cardiovascular diseases were the most common co-morbidities as well as those (38.2 %) who required PICU care. The overall mortality rate was 3.8%, with the mortality rate being significantly higher in the HAP group (P < 0.001).
The pilot study included 8 children with the diagnosis of pneumonia in PICU from Jan 2015 to Dec 2015. Neither progressive ARDS mobility nor mortality occurred. The mean age at diagnosis was 37.5 ± 30.4 months. The average number of days of PICU stay was 6.9 ± 4.7 days. The median duration of hospital stay was 14 days. Patients were divided into two groups: PICU stay more than 7 days and less than 7 days. The values of pro-BNP, AaDO2, platelets, CRP and CI in patients with PICU stay more than 7 days showed a significant difference with those less than 7 days in the initial PICU admission (P < 0.05). However, the values of thoracic fluid content (TFC) or even TFC corrected by cardiac output were not significantly different between the two groups. The levels of sputum 8-isoprostane and urinary 8OHdG revealed a trend of decreasing level after disease relief.

Conclusions: In this study, we found that (1) HAP resulted in significantly longer lengths of hospital stay and PICU stay than CAP. The possible risk factors for the need of critical care are associated neurological disease in CAP and heart disease in HAP; (2) the possible biomarkers of pro-BNP, platelet, CRP, CI, 8-isoprostane and 8OHdG may predict the duration of PICU stay in our pilot study. These results not only help further our understanding of the risk of pneumonia in children who require critical care but also provide chances for better intensive respiratory care.

C-176 | Biomarkers as Outcome Predictor of Children Hospitalized with Severe Community-Acquired Pneumonia in West Nusa Tenggara Province General Hospital

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Background: Pneumonia is a leading cause of respiratory morbidity and mortality in children younger than 5 years of age.1 The incidence of severe cases of Community-Acquired Pneumonia (CAP) in low-and middle-income countries is still high.2 Although severe CAP can be diagnosed by clinical features and chest X-ray, it could be useful to measure biomarkers to predict the outcome.

The aim of the study was to determine the association between C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Leukocyte Count (LC), and Neutrophil-to-Lymphocyte Ratios (NLR) with outcome of children hospitalized with severe CAP.

Methods: Ninety children aged between > 28 days to < 5 years hospitalized with diagnosis of severe CAP in the Pediatric Department of West Nusa Tenggara Province General Hospital from January to October 2018 were enrolled. Data on demographic and clinical characteristics, and laboratory examination were recorded. All subjects were treated in accordance with the hospital CAP protocol and prospectively monitored until discharged.

Results: Out of 90 subjects, 68% were ages < 1 year, 59% male, 87% passive smoke exposure, 56% lived in crowded environment, 62% came from low family income, 97% showed infiltrate on chest X-ray 81% with comorbidity and Fe deficiency anemia was the most common (64%). C-reactive Protein, ESR, LC, and NLR were not significantly associated with hospital length of stay and duration of oxygen consumption (P > 0.05). After adjustment for CRP, LC, NLR, and age, ESR was found associated with mortality, with every increase in one log of ESR decreasing the log odds of death about 3.3 (P = 0.043).

Conclusion: Higher ESR was associated with lower risk of death. However, none of the biomarkers were associated with hospital length of stay or duration of oxygen consumption.

Keywords: Community-Acquired Pneumonia, outcome, children, biomarker.

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C-203 | Interferon-gamma Level in Nasopharyngeal Secretions of Infants with Bronchiolitis

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Background: Viral bronchiolitis is one of the leading causes for hospitalization of infants and respiratory syncytial virus (RSV) is associated with the majority of these cases. IFN-γ is an essential cytokine in the viral cell-mediated immune response and suppresses the production of Th2-type cytokines. The present study assessed IFN-γ expression in RSV infection and whether this profile was influenced by the infants’ atopic status, family history of asthma and recurrent wheezing.

Methods: Twenty-seven infants (21 boys and 6 girls), aged 4 to 23 months (average 13 months), hospitalized at the Pediatric Department of the Alexandrovska University Hospital with first or
recurrent episode of bronchial obstruction were enrolled in this study.

Detailed history, physical examination, blood sample and nasopharyngeal aspirate (NPA) collection were performed. The viral etiology of the respiratory tract infections was determined using polymerase chain reaction (PCR) and the concentration of IFN-γ in NPA by ELISA kits.

**Results:** The mean NPA levels of IFN-γ in RSV (+) infants – 4.3 (0-30.1) pg/ml was lower than RSV (-) infants – 14.43(0-49) pg/ml, (P = 0.12). A gender difference in IFN-γ was detected with significant higher values in girls (OR, 1.95; [CI] 0.85–4.26; P = 0.05). The cytokine ratio did not differ between infants with or without atopic status and family history of asthma. Moderate-to-severe bronchiolitis in 7 cases (20%) was associated with lower IFN-γ level (OR, 0.8; [CI] 0.64–1.13; P = 0.06), none of them required mechanical ventilation. Decreased IFN-γ production correlated with the recurrent episodes of wheezing (P = 0.05).

**Conclusions:** Our study proves that RSV infection is associated with decreased IFN-γ responses and their correlation with severity and recurrence of wheezing were the main outcome measures.

**C-226 | Clinical Features and Outcomes in Pediatric Empyema: A Retrospective Cohort Study**

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**Abbreviations:** CHW: The Children’s Hospital Westmead; CDF: Chest drain and fibrinolytics; VATS: Video-assisted thoracoscopic surgery; PCV: Pneumococcal conjugate vaccine; PCR: polymerase chain reaction; IQR: interquartile range; PICU: Pediatric Intensive Care Unit; MSSA: Methicillin-sensitive Staphylococcus aureus; MRSA: Methicillin-resistant Staphylococcus aureus; MDR: multidrug resistant.

**Background:** Hospitalization rates for pediatric empyema have increased in the US, UK and Australia despite declining rates of Methicillin resistant Staphylococcus aureus (MRSA) and Methicillin-sensitive Staphylococcus aureus (MSSA) chest infections. Several RCTs comparing primary interventions (CDF vs. VATS) have shown no difference in clinical outcomes.

**Objectives:** This retrospective cohort study included admitted patients requiring intervention for empyema. Across 2011–2018, admission rates to hospital and intensive care were analyzed for trends in incidence and disease severity. Outcomes were compared between primary CDF and VATS. We compared associations with treatment failure and reintervention following primary CDF.

**Results:** One hundred and ninety-five patients were included, 176 with primary CDF and 18 with VATS. Rates of hospital and ICU admission increased during the study. We report a difference in chest drain duration (-68h) 95%CI 14.6h–121.4h, (p = 0.01), postoperative length of stay (-3.9d) 95% CI 0.14–7.66, (p = 0.05) and reintervention rate (6% vs. 28%, p = 0.04) in favor of VATS. Reintervention following primary CDF was associated with ICU admission (41% vs. 22%, OR 2.795% CI 1.1–6.9, p = 0.04) and persistent fever post-intervention (10d vs. 5d, p <0.0001).

**Conclusion:** Rates of empyema needing intervention increased with increasing rates of ICU admission. There were significant differences in clinical outcomes between CDF and VATS, favoring VATS. Reintervention following primary CDF was associated with persisting fever, bronchopleural fistula and ICU admission. Future research to determine how to best select patients for primary VATS is needed to reduce the need for reintervention following primary CDF.

**FIGURE 1 | Trends in Empyema by year**

**FIGURE 2 | Odds Ratio for Reintervention by Days Febrile following CDF intervention**
**Purpose:** Classification and management of congenital cystic lung disease (CCLD) remain unestablished. This study aims to establish the novel classification and management guideline for CCLD.

**Materials and Methods:** In the nationwide survey conducted by the Japan Study Group of Chest Surgery, 874 CCLD patients were identified and involved in the primary study. Of the latter, 428 patients born between 1992 through 2012 and treated at the 10 high-volume centers (194 prenatally and 234 postnatally diagnosed) were furthermore reviewed with pathological and statistical analysis. Based on these results and the systematic literature review, a revised classification and a treatment guideline for CCLD were drafted.

**Results:** The present classification divides CCLDs into 5 major subtypes according to the embryological background: 1) pulmonary airway malformations including congenital pulmonary airway malformation (CPAM), 2) lung bud malformations including intra- and extra-lobar bronchopulmonary sequestration, 3) foregut malformations including bronchiocentric cyst, 4) bronchial atresia (BA), and 5) the others. Pathological analysis indicated that 37.5% of the BA cases showed CPAM type 2-like lesions such as microcystic maldifferentiation and parenchymal maldevelopment of the pulmonary hyperplasia that should be distinguished from CPAM. Among the patients who were previously diagnosed to have intralobar bronchopulmonary sequestration, a cohort of patients who showed bronchi facing in the opposite direction of the accessory lung bud in the resected lung were excluded from the lung bud malformations. Thus, the eligibility of each subtype was clarified, and the hybrid or combined lesions of the different subtypes were actively excluded in the present classification. In the survey, casually 10%-15% of the prenatally diagnosed patients seemed to carry a high risk for critical perinatal features such as fatal hydrops and neonatal respiratory distress. The fetal lung lesion volume ratio was significantly higher among these symptomatic patients compared to the asymptomatic patients (2.04±1.71 vs. 0.98±0.50, P < 0.00071). CPAM appeared to be more strongly associated with these critical features compared to other subtypes, when the eligibility of CPAM was properly assessed. Among the asymptomatic neonatal patients, 56.3% developed infectious symptoms before the age of 2 years. The prenatally diagnosed patients acquired significantly higher %VC when operated earlier than those diagnosed postnatally (98.3±11.9 vs. 81.7±9.7, P < 0.0222). Persistent cystic lesion in the lung required further surgical intervention in 4 patients, whereas carcinogenesis was not observed in the series.

**Conclusions:** Based on these observations and the systematic literature review, fetal MRI assessment, an early surgery during the infantile period and avoidance of pneumonectomy were recommended especially in the patients with CPAM in the present guideline.
noninvasive support for respiratory distress among infants ≥ 28 weeks' gestational age in a randomized, controlled trial. However, the comparison of gas exchange efficiency and lung protective effect among high amplitude bubble continuous positive airway pressure (BCPAP) and high flow CPAP (mimicking HFNC) treated rats with acute lung injury (ALI) had not been investigated.

**Objectives:** To test the hypothesis that high amplitude BCPAP support after acute lung injury may have different effects on gas exchange efficiency and lung injury protection compared to high flow CPAP (mimicking HFNC) support in rats with ALI.

**Methods:** After normal saline lavage lung injury, all rats initially received high tidal volume mechanical ventilation (9 ml/kg) for 30 minutes, then were randomly divided into three groups: high amplitude BCPAP group using the bubble technique with 135 degrees of expiratory limb (n = 4); standard BCPAP group using the bubble technique with 0 degree of expiratory limb (n = 4); and high flow CPAP (mimicking HFNC) group using the high flow technique (2 L/min, n = 8). All groups were killed 2.5 hours after BCPAP or high flow CPAP (mimicking HFNC) support. Arterial blood gases, respiratory rate, peak inspiratory pressure (PIP) and mean airway pressure (MAP) of rat lung during respiratory support, wet-to-dry lung weight ratio, lung homogenate and/or bronchoalveolar lavage fluid tumor necrosis factor-α, macrophage inflammatory protein-2, interleukin-6 and total protein levels were measured and compared among groups after study completion.

**Results:** The high amplitude BCPAP group exhibited a significantly higher PaO2, lower PaCO2 and significantly lower alveolar protein, PIP, MAP, wet-to-dry lung weight ratio and cytokine level compared to high flow CPAP (mimicking HFNC) group. High amplitude BCPAP group also exhibited a lower cytokine level compared to the standard BCPAP group. No difference in gas exchange efficiency was observed between the two BCPAP groups.

**Conclusion:** High amplitude BCPAP support decreases lung inflammation, increases gas exchange efficiency and lung compliance compared to high flow CPAP (mimicking HFNC) support in rats with ALI, and may have a better lung protective effect than standard BCPAP.

**Keywords:** bubble continuous positive airway pressure, high-flow nasal cannula, respiratory support, acute lung injury.

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**D-110 | Clinical Characteristics of Nontraumatic Chylothorax in Pediatric Patients**

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**Background:** Chylothorax is a condition in which chylous fluid accumulates into the pleural space. The etiologies of chylothorax are various and traumatic or postoperative chylothorax is common. Nontraumatic chylothorax in children is rare and more difficult to treat than traumatic chylothorax. In some cases, they are refractory to conventional treatment, leading to severe morbidity and mortality. Thus, the purpose of this study is to analyze the clinical features of chylothorax in pediatric patients in our hospital and seek appropriate therapeutic management.

**Methods:** A retrospective review was performed in 63 patients with chylothorax from January 2000 to December 2018 in the Children's Hospital of Seoul National University. Traumatic or postoperative chylothorax was excluded. A total of 20 patients with nontraumatic chylothorax were included in our study. Etiology, treatment, and outcome of chylothorax were analyzed.

**Results:** Nontraumatic chylothorax was diagnosed in 20 patients. Male patients (14/20 = 70%) were more frequently affected than female (6/20 = 30%) patients. Eighteen patients were diagnosed before 1 year of age (90%), only two patients were diagnosed after 1 year of age (6 years old, 12 years old respectively). The most common cause of spontaneous chylothorax was idiopathic factors, constituting 45.5% (13), three cases were related to high central venous pressure due to venous thrombosis and recurrent sepsis, 2 cases were related to Down syndrome, 1 case was Noonan syndrome, and the remaining case was Gorham stout syndrome. Seventeen patients needed a respiratory support device, 6 of the latter received low flow oxygen supplementation. 11 patients received ventilator support. Dietary modification (NPO or MCT base feeding), conventional medication (somatostatin or octreotide), sirolimus, surgical management were administrated to our patients. In the neonate and infant group, three patients who were related to venous thrombosis died because of recurrent septic shock before chylothorax management was administered. Fifteen patients received a dietary modification (NPO or MCT base feeding) and nine patients improved by conservative management. One patient died due to heart failure before medical treatment. Somatostatin or octreotide was used in 5 patients who failed dietary modification, but only one patient improved with octreotide. Among the somatostatin or octreotide failure group, 4 patients received surgical management (pleurodesis or thoracic duct ligation). Three of these patients improved, although one patient died after thoracic duct ligation operation because of post-op ARDS. Two patients who were diagnosed after 1-year of age were refractory to nutritional modification and conventional medication such as somatostatin or octreotide. However, lymphatic intervention and surgical treatment were not suitable for these two patients. Considering that their underlying disorder consisted of Noonan syndrome and Gorham stout syndrome, we used sirolimus to treat the refractory chylothorax. After administration of sirolimus, their chylothorax improved compared to before.

**Conclusions:** Most of the nontraumatic spontaneous chylothorax in pediatric patients occur in newborns and the most common cause of chylothorax in the neonatal and infantile period is idiopathic. On the other hand, nontraumatic chylothorax in childhood is rare and tends more to be accompanied by the underlying syndrome. Moreover, the treatment failure rate is higher in the childhood group. In such cases, sirolimus which is an mTOR inhibitor, can be beneficial to patients who tend to be refractory and cannot be treated with lymphatic intervention or operation.
**D-145 | What Kind of Abnormalities are the Characteristics of Lung Sounds of Congenital Tracheal Stenosis? - Our 10-Year Experience**

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**Introduction:** Abnormal lung sounds, especially such as stridor, rhonchi and wheeze, are caused by a narrowed airway. As a nature of children, their airways are narrow, and easily collapsed in various diseases. So we must pay attention when diagnosing children with abnormal lung sounds. Nevertheless, pediatricians often make mistakes in misdiagnosing congenital tracheal stenosis as laryngomalacia or asthma without considering the importance of these symptoms, because these are frequently encountered in daily practice, and most of the patients improve as they grow. It is a serious problem to have the diagnosis of tracheal stenosis delayed because of the pediatrician's confident way of thinking.

**Objective:** To determine the frequency of congenital tracheal stenosis among patients who presented with continuous abnormal sounds on auscultation such as stridor, rhonchi and wheeze in our outpatient department.

**Methods:** We carried out a retrospective study in which we analyzed clinical history, diagnosis and management of 226 patients who had presented with abnormal continuous lung sounds to our institute between October 2008 and October 2018. Abnormal lung sounds were defined as persisting for more than 3 weeks or having been repeated more than once. Diagnoses were made by clinical symptoms and chest X-ray. Paranasal sinuses and neck X-rays were taken when physicians judged them necessary. CT scans were performed when tracheal stenosis was suspected, as well as flexible laryngoscopy for almost all of the patients with stridor to confirm whether they had laryngomalacia or not.

**Results:** A total of 226 patients (male: female= 153: 73) were included. The most common symptom was stridor in 104 patients, followed by wheeze/rhonchi in 62 patients, and biphasic abnormal sounds in 58 patients. In 2 patients, classification was impossible from their medical charts. Seventy patients were diagnosed as laryngomalacia, 25 patients with asthma, 18 patients with protracted bacterial bronchitis, and 16 patients with sinobronchitis.

Eleven patients (4.8%) were diagnosed as congenital tracheal stenosis, all of whom were male. Two of them had vascular ring and one had pulmonary artery sling. Patients with Down syndrome, 22q11.2 deletion syndrome, and preterm low birth weight infants were included. All patients with congenital tracheal stenosis presented with biphasic abnormal sounds. The median age at diagnosis was 12 months (1 month to 5 years). The median delay between the onset of symptoms and diagnosis was 7 months (1 to 48 months). Seven of 11 cases were repeatedly treated as asthma before diagnosis. All patients were carefully managed especially to prevent respiratory tract infections after diagnosis, and only one patient needed mechanical ventilation for a short period when he suffered from bronchitis. Surgery for vascular rings was performed in 1 of 2 patients. None had undergone tracheoplasty.

**Discussion:** Congenital tracheal stenosis is not a rare disease among patients with abnormal lung sounds. Prolonged and recurrent respiratory complaints in infancy or childhood should alert the pediatricians to the possibility of tracheal stenosis.

**D-160 | Childhood Interstitial Lung Disease in Immunocompetent Children in Japan: 9 Years’ Experience**

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**Purpose:** Specific genetic causes for childhood interstitial lung disease (chILD) in immunocompetent patients have been identified within the past decade. However, little is known about the pathogenesis of many forms of chILD, and treatment approach has not been standardized. A national survey was carried out by the Japanese Society of Pediatric Pulmonology (JSPP) To identify the histopathology and response to current treatment, especially hydroxychloroquine, which is contraindicated for children younger than 6 years old in Japan.

**Methods:** A questionnaire was sent to pediatricians who registered a chILD patient to the JSPP. We conducted the survey over a period of 9 years, between 2010 and 2018. Children (0-15 years) were included in the survey with persistent hypoxemia (PaO2 less than 60 torr or SpO2 less than 90%) for more than 2 weeks, diffuse infiltrates on CT scanning, and elevated serum markers such as KL-6, Sp-A, or Sp-D. Immunodeficiency and other diseases which present with similar symptoms to chILD were excluded. The questionnaire included information on the patients’ clinical symptoms, family history, pathological histology, clinical genetic findings, treatments and clinical outcomes. Informed consent was obtained by all patients’ guardians before participating in the survey.

**Results:** Twenty-six cases were identified, including 15 males and 11 females. Age of onset was between 0 months and 8 years. Fourteen (53%) cases presented in the first year of life. Lung biopsy was performed in 11 (42%) cases. Five cases showed changes of nonspecific interstitial pneumonia (NSIP), 1 case with desquamative interstitial pneumonia (DIP), 1 case with cryptogenic organizing pneumonia (COP), 1 case with usual interstitial pneumonia (UIP), 1 case with acute lung injury (ALI), and 2 cases untagged. Genetic testing was performed in 21 (80%) cases. Mutation in Sp-C gene (SFTPC) was detected in 8 cases, ATP binding cassette subfamily A member 3 (ABCA3) in 1 case, NK2 homeobox 1 (NKX2-1) in 1 case, coatomer associated protein subunit alpha (COP2) in 1 case, and no
mutation was detected in 10 cases. In the first half of the study period, only 5 out of 16 (31%) cases were diagnosed with genetic testing without lung biopsy, which increased to 8 out of 10 (80%) cases in the latter half. Prednisolone was used in 24 (92%) cases and hydroxychloroquine in 20 (76%) cases with no onset of retinopathy. Conventional treatment with prednisolone or hydroxychloroquine, monotherapy or in combination, resulted in a good response in 17 (65%) cases. Three (11%) children died despite all therapies. In addition, it turned out that 1 case was diagnosed as juvenile idiopathic arthritis 4 years after registration.

**Conclusions:** This is the first nationwide prospective study regarding chILD in Japan. The histopathology in this study is similar to that reported previously. There is increasing emphasis on genetic studies in the diagnosis of chILD as it can help avoid unnecessary lung biopsy. Corticosteroid and hydroxychloroquine were the main therapeutic agents in our study. Hydroxychloroquine therapy was tolerated in many cases, with no significant side effects.

**D-180 | The Change in Lung Function in Bronchiolitis Obliterans Syndrome after Hematopoietic Stem Cell Transplant in Children**

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**Background:** Bronchiolitis obliterans syndrome (BOS) is a life-threatening respiratory complication of allogeneic hematopoietic cell transplantation. Even though the lung function test is crucial in the diagnosis and monitoring of BOS, there is little information on the association of the change in lung function with prognosis in children with BOS.

**Methods:** Twenty three children aged 11.8±4.9 years with BOS after allogeneic hematopoietic cell transplantation were enrolled, and their clinical data were reviewed retrospectively. All subjects repeated the pulmonary function test at an interval of 1 month after occurrence of BOS.

**Results:** Among 23 subjects with BOS, 6 (25.0%) subjects expired due to respiratory failure, 4 (17.4%) subjects underwent lung transplantation, and 16 (69.6%) subjects needed O2 therapy. The mean value of FEV1% predicted at the diagnosis of BOS was 37.0±13.0%, and it rose after 12 months (47.0±24.9%). FEV1% predicted at diagnosis of BOS tended to be lower in subjects with oxygen therapy (34.7±12.2) than in subjects without oxygen therapy (45.8±11.1), [YJ1] although there was no statistical significance. The changes in FEV1% predicted at 3 months after BOS diagnosis were significantly lower in the subjects with oxygen therapy (-19.4±24.3%) than in subjects without oxygen therapy (8.6±21.9%). However, there was no significant difference in the change over 3 months of FEV1% predicted values between the two groups at 6, 9, and 12 months.

In addition, the group with a negative slope of FEV1% predicted change during the first 3 months had a higher likelihood of O2 therapy, compared to the group with a positive slope of FEV1% change during the period (HR of 3.57, P = 0.059).

**Conclusion:** The change in FEV1 during the first 3 months after BOS was significantly different between the subjects with and without oxygen therapy. These results suggest active intervention strategy is needed during the first 3 months after BOS To improve the prognosis.

**D-181 | Clinical Outcomes of Lung Transplantation in Children: Single Center Study**


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**Background:** Lung transplantation is the final treatment modality for end-stage lung disease and the survival rate has recently improved. Korea is a latecomer in lung transplantation, but the number of cases is gradually increasing since the first lung transplantation in a child was performed in 2011.

**Methods:** We retrospectively evaluated the outcomes and survival rate of children between the ages of 0 and 18 years who received a lung transplant at the Asan Medical Center between August 2011 and December 2018. A total of 14 children underwent lung transplantation.

**Results:** The mean age of the lung transplant recipients was 11.1±5.2 years (1.7-18.6 years), and 7 were male and 7 were female among the 14 children. Nine children underwent bilateral whole lung transplantation, 4 underwent bilateral lobar lung transplantation, 1 underwent right lobar lung and left whole lung transplantation, and there was one patient who received heart-lung transplantation. The reasons for lung transplantation were bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation (HSCT) (5 of 14 patients, 35.7%), chemotherapy induced lung injury (2 of 14, 22.0%), cystic fibrosis (2 of 14, 14.3%), primary pulmonary hypertension (1 of 14, 7.1%), interstitial lung disease after HSCT (1 of 14, 7.1%), lung injury induced by humidifier disinfectant (1 of 14, 7.1%), bronchopulmonary dysplasia (1 of 14, 7.1%), and pulmonary alveolar proteinosis (1 of 14, 7.1%). Most patients received intensive care (9 of 14, 64.3%) including extracorporeal life support (6 of 14, 42.9%) before lung transplantation. Among the 14 children, only 2 patients died (14.3%), 1 patient died of fungal infection and 1 patient died of postoperative bleeding. The mean
observation period was 2.0±2.4 years. The one-year survival rate was 87.5% (7/8). Among the complications after lung transplantation, there were 3 cases of changing the immunosuppressants due to adverse drug reactions, and 2 cases of diaphragm palsy. In addition, polyneuropathy, fungal infection, postoperative bleeding, right pulmonary vein stenosis and sepsis each occurred in one case.

**Conclusion:** In Korea, pulmonary complication after HSCT was the main cause of lung transplantation, unlike other countries. Although the follow-up period is not sufficient to evaluate late outcome of lung transplantation, early outcome of lung transplantation in Korea was comparable to the results from the International Society for Heart and Lung Transplantation. Lung transplantation can be an accepted treatment option for end stage lung disease in Korean children.

**D-198 | Effectiveness of Hypertonic Saline Nebulization Before Chest Physiotherapy in Non-Cystic Fibrosis Bronchiectasis - A RCT**

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**Introduction:** Non-cystic fibrosis bronchiectasis is a major contributor to the chronic respiratory morbidity in both developed and developing countries. Failure to expectorate mucus resulting in progressive airway damage is the hallmark of bronchiectasis which stresses the importance of airway clearance as the key step in its management. Multiple airway clearance techniques have been introduced although research in children is limited. Pre-medication with Hypertonic Saline (HS) nebulizations before airway clearance is an established method in managing bronchiectasis in cystic fibrosis (CF) and non-CF bronchiectasis in adults. This study is aimed to assess the effectiveness of HS nebulizations Before physiotherapy over conventional physiotherapy in children with non-CF bronchiectasis.

**Objectives:** Primarily to compare the change in FEV1 from pretreatment phase to posttreatment phase between the two groups. Secondarily to compare improvements in FVC, FEV1/FVC ratio, PEFR, MEF25-75 and the frequency of exacerbations between the two groups.

**Design and Methods:** Ethical clearance, clinical trial registration (SLCTR/ 2018/010) and parental and assent consents were obtained. Before the study. This was an RCT conducted at the Lady Ridgeway Hospital for children, Colombo from February to December 2018. All children aged 5 to 15 years diagnosed to have non-cystic fibrosis bronchiectasis were included. CF was excluded with two negative sweat tests. Chronic colonization of *Pseudomonas*, children who do not comply with physiotherapy, follow-up plan or spirometry, and presence of typical extra pulmonary features of CF were excluded. Computer-generated variable blocked randomization was performed for the two groups after a baseline spirometry. The test arm received 200 µg of inhaled salbutamol followed by hypertonic saline nebulizations Before chest physiotherapy twice daily for 8 weeks. Control arm received all except HS nebulization. Parents were adequately trained on the usage of inhaled medication, home nebulizations and technique of chest physiotherapy. Spirometric parameters and number of exacerbations after 8 weeks of therapy were documented. Data was processed with Microsoft Excel, independent t test and the Mann-Whitney U test where statistical significance was taken as p value less than 0.05.

**Results:** Sixty-five children were primarily enrolled. (34 in HS group, 31 in conventional group). Mean ages of HS and conventional arms were 9.6 years. (SD 3.4) and 8.8 years. (SD 3.5) respectively. Percentage of predicted FEV1 of the HS and conventional arms were 61 (23) and 63(25) respectively. The mean improvement in predicted FEV1 was significantly higher (P = 0.002) in the HS arm 15.5(3.7) than conventional arm 4.5(8.9). The HS group showed a higher mean improvement in predicted FVC 18(5.9) compared to (P < 0.012) the conventional group 7.1 (5.7) and significant growth (P = 0.001) of PEFR was demonstrated in HS 15.3(7.4) compared to the conventional group 5.2(6.2). Mean improvement in predicted MEF 25 to 75 was significantly higher (P < 0.001) in test arm compared to the control arm, however FEV1/FVC ratio was comparable. Number of exacerbations were comparatively lower (P = 0.005) in the test arm 0.3(0.51) than the control arm 1.5(0.76).

**Conclusions:** Hypertonic saline nebulization is an effective strategy to improve airway clearance as it improves dynamic lung volume including FEV1 and FVC and improves PEFR and MEF75-25 significantly.

5 | FETAL AND NEONATAL RESPIRATORY DISORDERS

**E-63 | Short-Term Outcome in Extremely Preterm Infants Who Underwent the Automated Control of Inspired Oxygen Concentration**

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**Objective:** To investigate the short-term outcome in extremely preterm infants who underwent the automated control of inspired oxygen concentration with CPAP.

**Method:** We performed a retrospective cohort study of extremely preterm infants born before 28 weeks of gestational age in our NICU. Study subjects were divided into two groups: AUTO group who underwent the automated control of inspired oxygen concentration (AUTO) with CPAP, and MANUAL group who underwent manual control of inspired oxygen concentration (MANUAL) with CPAP before introduction of AUTO in our NICU. We retrospectively investigated the patient characteristics and short-term outcome related to the respiratory system (reintubation rate, duration of CPAP, introduction rate of home oxygen therapy) and retinopathy of prematurity (incidence, stage, and therapy rate), the Mann-Whitney U test and Chi-squared test were used for statistical analysis, and logistic regression was used for multivariable analysis.
Result: A total of 47 infants were eligible for this study. There were 25 and 22 infants in the AUTO group and MANUAL groups, respectively. In the AUTO and MANUAL groups, the median (range) of their gestational age in weeks was 25.1 (23.3-27.9) and 25.5 (23.7-27.9), P = 0.25, birth weight in grams was 690 (461-990) and 789 (442-1178), P = 0.02, the rate of maternal steroid administration was 73% and 36% (P = 0.01), age at study entry in days was 2 (54-48) and 31 (2-67), P = 0.31. Reintubation rate was 56% and 50% (P = 0.68), duration of CPAP (day) was 28 (6-62) and 26 (3-38, P = 0.29), and introduction rate of home oxygen therapy was 20% and 27% (P = 0.56). The incidence of total retinopathy of prematurity (ROP) was 64% and 77% (P = 0.32), the incidence of ROP over stage II was 24% and 59% (P = 0.02), and therapy rate for ROP was 8% and 14% (P=0.53) in each group. There was a statistically significant association between the decreasing risk of ROP over stage II and use of AUTO by multivariable analysis adjusted for confounding factors (odds ratio: 0.22 [95% CI: 0.06-0.76], P = 0.02).

Discussion: In this study, the incidence of ROP over stage II was significantly decreased in extremely preterm infants who underwent AUTO with CPAP. It is suggested that exposure to the excessive oxygen levels and the fluctuation of oxygenation are related to the incidence of ROP. Large studies indicate the strict SpO2 target range. But in fact, the manual control of inspired oxygen concentration during respiratory support is not sufficient for the maintenance of SpO2 within the latter. AUTO can maintain SpO2 within the target range compared to the manual control of inspired oxygen concentration. AUTO has the potential to prevent ROP by decreasing the exposure to excessive oxygen levels and the fluctuation of oxygenation. Several limitations should be considered in our study. This was a retrospective, single-centered, non-randomized study; a further multi-centered prospective study is needed.

Conclusion: The automated control of inspired oxygen concentration might help to reduce the severity of ROP in extremely preterm infants.

E-71 | Examination of Lung Function after very Low Birth Weight Prematurity, with Regard to Cognitive Function

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Introduction: The lung function of children born as very low birthweight (VLBW) premature was examined in several studies. Since their pulmonary function is decreased, lower respiratory tract infections in this population may have a more severe clinical course. In our study, in addition to lung function measurement, we also wanted to see whether there is a connection between mental abilities and pulmonary function.

Methods: Before the examination, a license was obtained from the ethical committee of the University of Szeged. The parents of each participant signed a written consent. We examined 52 children (age: 7.3 ± 1.2 years, mean ± standard deviation) who were treated during their neonatal age in our NICU as VLBW prematures. For the lung function tests, a Piston PDD-301s spirometer was applied. The results of the patients were compared to the ERS/ATS statement conformed database of the spirometer, in accordance with their weight, height and age and were expressed as a percent of the expected value. On the same day, the patients performed a Raven progressive matrix test. Four patients could not produce an evaluable pulmonary function test. We compared the lung function tests of the 21 patients with the best cognitive function test performers (Group 1, Raven 1-2 = 75 -> 95 percentile) with the 16 worst performers (Group 2, Raven 4-5, in one case 7 = 10-50 percentile and < 5 percentile in one case). Patients who fulfilled the criteria of bronchopulmonary dysplasia (BPD: need of supplemental oxygen for ≥ 28 days; 18 cases) were compared to patients without BPD (28 cases). Groups were compared with Student unpaired t-test.

Results: In the examined population, we found the following percentage values: FEV1 90.8 ± 17.3%, FVC 86.5 ± 23.2%, FEF25-75% 79.7 ± 25.4%, MEF50% 85.7 ± 27.3%. There was no significant difference whether between the lung function test parameters or between the age and body size values or of the two groups. When we compared patients with and without BPD, there were lower, albeit not significantly different values regarding the expired volumes in favor of the non-BPD cases (FEV1, FVC), while there were significantly lower expiratory flows in the case of the patients with BPD. There was no significant difference between the Raven test results of the BPD and non-BPD patients.

Conclusions: We could also detect in our smaller population that VLBW patients at the age of 6 to 8 years have lung function test values in the lower normal region of the reference range. This may raise the presumption of the higher susceptibility of these children to respiratory tract diseases also in the later decades of life. BPD patients have lower pulmonary function test results than non-BPD patients. On the other hand, we could not find any connection between low Raven test performance and lung function results.

E-77 | Prognosis Predictive Factors in Infants with Esophageal Atresia and Tracheoesophageal Fistula

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Background: Esophageal atresia (EA) and/or tracheoesophageal fistula (TEF) is one of the rare congenital anomalies occurring in 1 out of 3,000-5,000 births. There has been improvement in the survival of these infants during recent decades. The diagnosis of TEF with EA is commonly made during the first 24 hours after birth. Preoperative flexible endoscopy (FE) is not yet routinely included in the diagnostic and postoperative assessment. This study aimed to evaluate the predictive factors that affected patients’ prognosis and the role of flexible endoscopy application in managing infants with EA and/or TEF in a tertiary medical center.

Methods: We enrolled patients who were admitted into our hospital due to suspected EA and/or TEF and accepted an FE examination for one or more times between Jan. 2000 and Dec. 2017. All associated medical and surgical records were retrospectively reviewed. The analyzed data included basic characteristics, diagnosis, age of surgical repair, associated anomaly, timing of FE before and after surgical repair, and mortality. Factors related to patient's mortality were analyzed.

Results: A total of 33 patients were enrolled, including 28 (84.8 %) cases referred from other hospitals. Their mean birth weight was 2448 ± 603 gm, including 19 (57.6%) low-birth-weight infants, 17 (51.5%) cases with cardiac anomalies, 12 (36.4%) cases aged > 90 days, and 12 (36.4%) cases underwent FE before reconstruction. The most common classification of enrolled cases was type C (84.8%). Additional other airway anomalies were found in 23 (69.7%) cases, including tracheomalacia, bronchostenosis, lung hypoplasia, and laryngeal cleft. One case underwent naso-tracheo-fistula-gastric catheter insertion before surgery. The mean age of receiving surgical reconstruction was 5 ± 7 days. The most common postsurgical complication was anastomotic stenosis (25, 75.8%) that required laser therapy (9, 27.3%), balloon dilatation (17, 51.5%), or stent implantation (2, 6.1%). Gastroesophageal reflux was also commonly found in 21 (63.6%) cases. The overall 2-year survival rate was 72.7% (27/33). Significant factors related to 1-year mortality were post-reconstruction referral (P = 0.004), age of reconstruction > 7 days (P < 0.001), and cardiovascular surgery requirement (P = 0.032).

Conclusions: In infants with EA and/or TEF, FE is feasible for the early identification of associated airway and esophageal anomaly, as well as postoperative diagnosis and therapeutic interventions. Post-reconstruction referral, age of reconstruction > 7 days, and cardiovascular surgery requirement were significantly related to 1-year mortality of infants with EA and/or TEF.

E-103  |  Oxygenation and Mechanical Ventilation after Patent Ductus Arteriosus Closure in Preterms Less Than 1800gm: Comparison of Transcatheter and Surgery

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Background: Patent ductus arteriosus (PDA) is a common cardiovascular complication among premature infants and may be responsible for prematurity-related complications. Surgical ligation is considered when medical treatment has either failed or was contraindicated. Transcatheter occlusion, which was established in term infants, has recently been applied to premature population. Previous reports stated that the complication and success rates were not statistically different between the transcatheter technique and surgical ligation. In this study, our aim was to compare the oxygenation status and oxygen dependence between these two techniques.

Method: We performed a retrospective study of infants born with birth body weight less than 1800gm and admitted to the National Cheng Kung University Hospital from September 2014 to June 2018. Infants with hemodynamically significant PDA and were either contraindicated to or had failed medical therapy were included. We identified 30 patients and divided the latter into the transcatheter group (Group A, N = 13) and surgical ligation group (Group B, N = 17). The basic demographic data, FiO2 change, pulmonary score, intubation days, ventilator-dependent days, oxygen-dependent days and mortality within 1 year were evaluated.

Results: The birth body weight, gestational age, post-menstrual age on procedure day, body weight on procedure day, pulmonary score and FiO2 before procedure were not different between these two groups. The range of body weight on procedure day was from 478 to 1602gm in group A and from 551 to 1646gm in group B. The overall mortality within 1 year was similar (P = 0.360). The overall incidence of chronic lung disease was not significantly different (2/10 vs. 8/16, P = 0.218).

When comparing the FiO2 change before and 5 days after the procedure, the transcatheter closure group had a significant improvement in FiO2 compared with the surgical ligation group on post-procedural day1 (-9.23±23.12 vs. 5.82±14.80, P = 0.039), day3 (-10.58±23.25 vs. 5.88±12.47, P = 0.020) and day5 (-15.08±27.208 vs. 3.41±10.869, P = 0.043). The oxygen-dependent days (P = 0.053) were not significantly different. In subgroup analysis, very low birth weight (VLBW) infants also had more FiO2 reduction in the first 5 days after procedure (P = 0.044). Compared with the surgical ligation group, the decline in pulmonary score was significantly greater in the transcatheter group (-0.50±0.7 vs. 0.08±0.29, P = 0.018).

Conclusion: Compared with surgical ligation, transcatheter occlusion of PDA can reduce FiO2 during post procedure day 1 to day 5 for infants with BBW< 1800gm. The decline in pulmonary score is greater in the transcatheter group. There is a trend of less oxygen-dependent days in the transcatheter treatment group. Further study is necessary to confirm the effect on lung functions.

E-126  |  Current Pre- and Post-natal Management of Congenital Pulmonary Airway Malformations (CPAM) in Nordic Countries

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Introduction: Congenital pulmonary airway malformations (CPAM) are rare disorders of which the incidence is not precisely known. This malformation might threaten the fetus, but it can also disappear spontaneously, or neonates can be asymptomatic with the malformation. According to previous studies, CPAM may increase the risk for lung infections and lung malignancies, which is also the argument used when treating asymptomatic CPAM-patients with surgery.

Purpose of the study: The purpose of the present study was to investigate whether there are differences between the treatment protocols between Nordic countries.

Material and methods: A questionnaire was sent to 16 Nordic centers dealing with pre- and postnatal management of patients with congenital lung malformation. This questionnaire was aimed to collect information on pre- and postnatal treatment protocols in the centers involved.

Results: The treatment protocols of this malformation vary largely in Nordic centers. Prenatal ultrasound was the primary examination in all centers. Magnetic Resonance Imaging (MRI) was used routinely as next prenatal examination in four centers for every CPAM-patient with persistent finding in ultrasound during whole pregnancy (4 of 11). Five centers (5 of 11) used MRI if needed for differential diagnosis. Various prenatal interventions were used in cases of fetal hydrops caused by CPAM. Shunting macrocystic lesion was used in 4 out of 11 centers, maternal cortisone in 9 out of 11. Over half of the centers (7/11) consulted and co-operated with centers that performed fetal surgery and 3 out of 11 did consider ex utero intrapartum (EXIT) surgery.

Postnatally surgery was performed in every center (100%) for symptomatic CPAM-patients. One center (14%) did not remove CPAM but instead performed follow-up on asymptomatic patients. Two centers (29%) performed mini-invasive surgery. The number of postoperative controls varied from one to three visits. As immediate postoperative complication, two centers (29%) reported prolonged air leak, which sometimes required reoperation. In our survey, we also asked if there was morbidity among the patients who were chosen for follow-up only. Two centers (29%) reported sequelae, one center reported infections and one center had removed pulmonary neoplasm, which had originated from CPAM.

Conclusion: According to the present study, treatment protocols vary both for prenatal and postnatal management between the centers. To be able to optimize the management of CPAM, evidence-based treatment protocols are needed.

E-147  |  Evaluation of Pharyngeal Pressure Provided by Two High-Flow Nasal Cannula Devices in Preterm Infants

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Background: High-flow nasal cannulas (HFNCs) are shown to transmit a continuous positive distending pressure to the infant’s upper airway. A strong association reportedly exists between the pharyngeal pressure, measured as a substitute for the continuous positive airway pressure, and flow rate of HFNC. However, the influence of the differences in the devices and the cannulas used for HFNC on pharyngeal pressure has not been well verified. This study aimed to assess the pharyngeal pressure exerted by two commonly used HFNC devices: Optiflow junior and Precision flow in preterm infants.

Method: Pharyngeal pressure was measured in 12 preterm infants receiving respiratory support with HFNC using the Optiflow junior or Precision flow at the neonatal intensive care unit of the Kurashiki Central Hospital and the Kakogawa Central City Hospital from 2016 to 2017. The flow rate gradually increased from 1 L/kg/min to 4 L/kg/min (maximal flow rate of 8 L/min), and the pharyngeal pressure was measured over 1 minute at each flow rate in a resting state with active mouth closure. The mean pharyngeal pressure value for 1 minute was defined as the pharyngeal pressure at that flow rate.

Result: The median gestational age of the subjects was 28 weeks (range 24–29 weeks), and the median birth weight was 959 g (range 438–1602 g). At the time of measurement, the median corrected gestational age was 34.8 weeks (range 31.0–36.9), and the median weight was 1290 g (range 953–1932 g). Eight infants used the Optiflow junior: four used premature size cannula (tip OD 2.4 mm), and the remaining four used neonatal size cannula (tip OD 2.8 mm). Four infants used Precision flow: three used single prong cannula (tip OD 1.9 mm), and the remaining infant used double prong, infant cannula (tip OD 1.9 mm). Pharyngeal pressure tended to rise to flow rate dependence with any type of cannula. In patients managed with the Optiflow junior, the mean pharyngeal pressure at the flow rates of 1, 2, 3, and 4 L/kg/min for premature size cannula were 2.3, 3.0, 3.1, and 3.6 cmH2O, respectively, and for neonatal size cannula were 0.5, 1.9, 3.0, and 3.7 cmH2O, respectively. In patients managed with Precision flow, the mean pharyngeal pressure for each cannula at flow rates of 1, 2, 3, and 4 L/kg/min for single prong cannula were 1.8, 3.9, 4.7, and 5.0 cmH2O, respectively, and for double prong, infant size cannula were 2.6, 5.7, 6.0, and 7.0 cmH2O, respectively.

Conclusion: When using the same flow rate, the pharyngeal pressure provided by each device and cannula was different in the preterm infants. With Optiflow junior, the maximum pharyngeal pressure provided by any cannula was < 4 cmH2O; however, with Precision flow, it was ≥ 7 cmH2O. The structure of the dedicated circuit of each device and the outer diameter of the tip of the cannula may have affected the pharyngeal pressure.

6  |  CYSTIC FIBROSIS

F-34  |  Clinical Characteristics of Cystic Fibrosis in Japan

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Background: Cystic fibrosis (CF) is an inherited multisystem disorder which causes exocrine pancreatic insufficiency in early life and...
severe chronic lung disease in children. While being the most common life-limiting recessive genetic trait among Caucasian populations, frequency of CF is reported to be approximately 1 in 350,000 live births in Japan, making the clinical features unclear and causing delays in diagnosis. The purpose of this study was to describe the clinical features of CF cases in Japan.

Methods: We conducted a complete literature review of CF case reports in Japan between 1994 and 2015. Patients who did not meet the domestic diagnostic criteria or the report which did not contain sufficient data were excluded from the study. We investigated clinical features of 53 patients described in 44 case reports, including one patient of our own.

Results: Among the 53 patients, 27 were male and 26 were female. 45 were Japanese and 7 had a foreign nationality. Four cases had consanguineous-marriage parents. The mean birth week was 37.6 weeks (±3.6 weeks) and the average birth weight was 2.843g (±701g). The median age of diagnosis was 2.1 years (0 to 43 years). At the time of diagnosis, the mean weight and height were -3.0 ± 2.0 SD and -2.0 ± 0.9 SD, respectively. The most common symptom seen at the time of diagnosis was meconium ileus during the neonatal period (100%), failure to thrive during infancy (63%), and chronic respiratory symptoms among older generations (97%). Other features frequently seen were airway system activation, fecal ileus, insulin-dependent diabetes mellitus. Six cases required continuous home oxygen therapy, 2 of which eventually underwent lung transplantation. Liver transplantation was performed in one of 6 cases with liver cirrhosis. Responsible gene mutation, cystic fibrosis transmembrane conductance regulator (CFTR) mutation, was identified in 32 cases. Among 50 abnormal alleles, 36 alleles were identified in previous reports, but 14 alleles had never been described. Conclusion: Classic symptoms of CF are often seen in Japan because of the delay in diagnosis. The delay contributes to the poor weight gain of the patients at the moment of presentation. While clinical characteristics were similar to those of Caucasian populations, genotypes were somewhat different from other populations. Some patients had a completely new mutation whose pathogenesis is not proven. This might suggest difficulty of genetic diagnosis which is commonly done in other countries as a screening test in the early stage of one’s life. CF should be kept in mind as a differential diagnosis for children with meconium ileus, poor weight gain, or chronic respiratory problems To diagnose early in Japan.

F-56 | Decreased Pseudomonas aeruginosa Prevalence in Children after Separation of Pediatric from Adult Cystic Fibrosis Clinics

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F-158 | Agreement between Two Concomitant Sweat Conductivity Tests

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**Background:** Even though it is considered as a screening test, sweat conductivity (SC) analysis seems to be an alternative diagnostic method to the coulometric quantitative test (CQT) for the diagnosis of Cystic Fibrosis (CF). It is widely accepted that coulometry requires specialized technicians, in addition to being performed only in referral centers. On the other hand, SC sweat analysis is a semi-automated procedure, simpler and faster than the conventional CQT. Specially in poor-resource settings, it allows the decentralization of the diagnostic network and, consequently, a wider accessibility to CF diagnosis. To date, there are no studies comparing two concomitant conductivity tests performed in the same patient.

**Objective:** to assess the agreement between two sweat conductivity results performed concomitantly in young infants.

**Methods:** This was a prospective, cross-sectional study in which two sweat samples were obtained from the two arms among 100 consecutive patients, using the Wescor Macroduct collection system (Wescor, USA). Conductivity analysis was performed through the Sweat Conductivity Analyzer (Wescor, USA). To test the intra-individual variability, the Cohen’s kappa coefficient was applied. Statistical analyses were performed through SPSS version 18.0 (SPSS Inc., USA). Conductivity tests were classified according to the reference values recommended by the manufacturer, i.e., positive (above 80 mmol/L), borderline (60-80 mmol/L), and negative (less than 60 mmol/L).

**Results:** The age of the participants ranged from 23 to 89 days, with a mean age of 48.5 days of life; 55% of them were boys. Nine out of the 100 recruited infants had a positive SC test, i.e., values greater than 80 mmol/L in both tests. There was no disagreement between the two conductivity tests in the same patient. Cohen’s Kappa index value was equal to 1.0 (Standard Error of Kappa = 0.000), showing a perfect agreement between values obtained in both tests. The number of agreements expected by chance was 83.6, i.e., 83.6% of the observations.

**Conclusion:** Since the strength of agreement was perfect, it reveals a high reliability of SC. Apart from its role as a screening test, it seems that it has a place as a diagnostic tool in CF.

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**F-204 | Feasibility of Multiple Breath Washout in a Clinical Setting in Infants with Cystic Fibrosis**


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**Background:** Multiple Breath inert gas Washout (MBW) is a sensitive method to identify ventilation inhomogeneity in the peripheral airways of the lungs. Newborn screening (NBS) for cystic fibrosis (CF) is increasingly used and a tool for monitoring pulmonary disease at an early age is needed. We aimed to assess the feasibility and value of MBW as a clinical monitoring tool after decision to implement MBW in early infancy as a routine method.

**Method:** All CF children diagnosed since NBS implementation in May 2016 were selected for MBW measurements at their routine outpatient visits. Infant MBW training sessions were conducted by experts. Within possibilities, MBW measurements (at least 2 acceptable runs) were obtained within 3 months of age and every 3 (±1) months for 1 year. All children were sedated with dexmedetomidine and standardized MBW measurements were performed using the Exhalyzer D 3.2.1 system with sulfur hexafluoride (SF6) as tracer gas.

**Results:** Thirteen infants with mean age (range) 10.5 months (1 – 19 months) were included. At initial MBW measurement, the mean LCI (range) was 7.33 (6.19 - 9.98). The CF infants were mainly below the upper limit of normal (ULN) LCI 7.72 (based on unpublished data on healthy infants). Three CF infants presented with an LCI above the ULN. We scheduled 43 MBW measurements, 39 of which were successfully obtained in sufficiently sedated children during routine outpatient visits. Three tests were cancelled due to clinical signs of lung infections and one due to insufficient sedation. All cancelled tests were rescheduled and performed within 2 to 4 weeks. MBW measurements were technically safe as no adverse events were observed. Criteria for technical acceptability was met in 39/39 (100%) tests. The time required for an acceptable test differed with a mean time (range) 15 minutes (7 – 58). Two test occasions were not performed within the timeframe of 3 ±1 months, while all other tests were conducted within the scheduled timeframe during the 1-year implementation period.

**Conclusion:** Our results indicate that longitudinal SF6 MBW is feasible for lung function testing in infants with CF from 3 months of age. Our experience showed that successful measurement required expert training of operators. Furthermore, our study demonstrated that intranasal Dexdor® is an effective and safe sedative for infant lung function testing. Value as a clinical monitoring tool awaits many more longitudinal measurements.

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**F-212 | Lung Ultrasound and Computed Tomography in Cystic Fibrosis Children - A Comparative Study**

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**Background:** Because of frequent exacerbations and pulmonary deterioration in cystic fibrosis (CF), the radiological exposure to chest X-ray and CT scan is frequent in patients with CF, with subsequent potential secondary effect, although also required. Lung ultrasound is,
ABSTRACTS

Currently, a useful method of evaluation in multiples diseases such as: pneumonia, pleural effusion, interstitial syndrome or pulmonary fibrosis; therefore, the use of LUS in CF would be of interest. Aim of the study: Evaluation of thoracic ultrasound utility in CF exacerbations.

Methods: Fifty CF patients were included in the study and monitored for 2 years of age. Lung ultrasound was performed every 3 months, at clinical and biological evaluation. CT scan was performed during exacerbations and for stable patients, every 2 years timetable (aged over 8 years). Ultrasound was performed using a linear high frequency 8 to 12 MHz probe, using a score based on specific artifacts which quantified the presence of consolidation, interstitial syndrome, saccular bronchiectasis and pleural effusion. CT was interpreted using the Bhalla scoring system, independently of the LUS score. Pearson’s correlation was used for the evaluation of the relationship between LUS score and CT.

Results: Median CT Bhalla score was 14.3 ± 4.5, and the average LUS score = 5.13 ± 1.2, consistent for moderate morphological lung injury. A good correlation was found in patients with increased LUS (> 4) and CT score, R = 0.75, P < 0.001. There was no reliable correlation between the lung ultrasound score and CT, therefore, validation of the LUS-CF score (R = 0.37, P = 0.26) was impossible with the currently identified artifacts. For patients in acute exacerbations, alveolar-interstitial syndrome described by multiple B-line artifacts and the presence of lake signs quantifying cystic bronchiectasis were accurately identified by LUS and confirmed by CT.

Conclusion: Lung ultrasound might be considered for detection of extensive lung changes in children with CF; but would not be recommended for incipient structural alterations, such as small bronchiectasis and air trapping. LUS could be used for fast and safe assessment in CF pulmonary exacerbations.

F-220 | Diagnostic Value of Sputum Cultures in Children under 2 Years of Age with Cystic Fibrosis and Other Chronic Productive Lung Diseases

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Background: Airway infection and ensuing inflammation may be important in infants with non-CF Chronic Productive Lung Disease (CPLD). As for Cystic Fibrosis (CF), prompt detection of specific pathogens could enable directed treatment and slow pulmonary deterioration. However, acquisition of sputum from the very young is challenging, as they do not expectorate. Bronchoalveolar lavage is invasive and therefore not used frequently. We routinely collect sputum for bacterial cultures from non-expectorating infants with chronic lung disease and a productive cough in the clinic setting. Airway clearance by an experienced physiotherapist and oropharyngeal suction promotes coughing of pooled secretions to above the larynx for acquisition of sputum (‘deep suction’). In non-productive infants or when culture results are negative, salbutamol and 4.5% hypertonic saline inhalation is delivered before physiotherapy and suction (‘induced sputum’).

Aims: 1. To describe bacterial culture results achieved by deep suction or induced sputum in infants under 2 years of age. 2. To compare bacterial cultures in CF and non-CF CPLD during routine clinic visits versus pulmonary exacerbations.

Methods: Medical records were retrospectively reviewed for infants aged 0 to 2 years with CF or CPLD, who had at least 2 sputum cultures and were treated at the Schneider Children’s Medical Center Pulmonary Institute between 2010-2016. Collected data included microbiological culture results, clinical status, and antibiotic treatment.

Results: Ninety-eight infants (16 with CF) were evaluated. A total of 534 cultures were acquired, 201 from CF infants (12 (2-23), median (range) per infant), and 333 from non-CF CPLD infants (3 (2-21), median (range) per infant). Age at first culture was 3.8 (1-19.5) months for CF and 10.4 (0.5-22) months for CPLD. Three hundred ad sixty-one cultures (68%) were positive for any bacteria. Of all positive cultures, 171 (47%) were acquired during pulmonary exacerbations, and 194 (53%) during routine follow-up. Pseudomonas aeruginosa was positive at least once in 46% of patients (56% CF and 44% non-CF CPLD, P = 0.42). More infants with CF compared to CPLD had positive cultures for Staphylococcus aureus (75% vs. 34%, P = 0.004), Klebsiella oxytoca (31% vs. 7%, P = 0.016) and Pseudomonas species (31% CF and 4% CPLD infants, P = 0.003). One CF and 7 CPLD infants had ESBL-resistant bacteria. No MRSA or multi-resistant Pseudomonas were identified. Chronic P. aeruginosa (Leeds’ criteria) was rare: 0/16 CF and 6/82 CPLD, mostly following prolonged hospitalization. In neither group was there a correlation between culture results and pulmonary exacerbations versus routine visits.

Conclusions: Airway infection is common in infants with CF and CPLD. Bacterial flora appeared to differ between these patient groups, perhaps confounded by more frequent cultures in CF patients. Staphylococcus aureus was more common in CF infants and may be an early marker for this disease. Interestingly, Pseudomonas aeruginosa was common in both CF and CPLD but chronic infection was rare and bacteria were not multi-resistant. Prompt diagnosis and aggressive treatment when required may have decreased chronic carriage and may improve clinical outcome. Our findings are retrospective and a prospective study is warranted.

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

G-67 | Respiratory Disorders in Children with 22q11 Deletion Syndrome: A Retrospective Study

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Objective: 22q11.2 deletion syndrome (22q11.2 DS) is characterized by a large variety of clinical presentation and many degrees of severity. Respiratory disorders are not part of the classic description of the disease, yet they are often a secondary manifestation of the various known disorders. Asthma and atopy are also described in this population, as well as respiratory tract disorders. The objective of this study was to identify the various respiratory disorders presented by a cohort of children with 22q11DS.

Methods: A retrospective cohort of 10 patients with BOS aged 3.4 to 12.3 years (median 6.4) at the time of the SCT were included. Lung function parameters were investigated over a period of 1.0 to 13.5 years (median 3.54). In total, 213 available lung function tests were evaluated and longitudinal changes in lung function parameters were analyzed.

Results: There were three variations of progression noted. Three out of 10 patients developed a significant progressive deterioration of their BOS despite steroid pulses and maximal conservative therapy with FAM (Fluticason, Montelukast, Azithromycin). Two patients died; one patient received a lung transplant. Four out of 10 patients developed a chronic progression with severe but stable lung function impairment showing a combined restrictive and obstructive pattern with hyperinflation (FVC < 60%, FEV1 < 50%, FVC/FEV1 < 70 and RV/TLC > 150%). Three out of 10 patients presented with typical signs of BOS on computed tomography (CT) such as bronchial wall thickening and mosaic pattern of perfusion, and in broncho-alveolar lavage (BAL) with neutrophils > 70%, and responded well to steroid pulses. Their lung function parameters improved to normal values during the course of the disease.

Conclusion: Our results indicate that BOS leads towards a progressive, chronic lung disease and is related to an increased overall mortality and morbidity. Important elements of treatment involve early and accurate detection, as well as specific and individualized therapeutic concepts to optimize the long-term outcomes in SCT survivors with BOS.

G-193 | Impact of HIV and Antiretroviral Drug Exposure on Lung Growth and Function over 2 Years in an African Birth Cohort

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Background: HIV-exposed uninfected (HEU) infants have poorer health outcomes compared to HIV-unexposed (HU) infants, including increased risk for respiratory disease. Previously we found that lung function soon after birth was altered in HEU infants, but the longer-term impacts of HIV and/or antiretroviral (ARV) drug exposure on lung function are not known.

Objectives: We aimed to assess the impact of HIV and ARV exposure on lung growth and function over the first 2 years of life.

Methods: Infants enrolled antenatally in the Drakenstein Child Health study between 2012-2015 had lung function measured using tidal breathing and multiple breath washout at 6 weeks and 2 years. Maternal HIV diagnosis was established during pregnancy using routine testing and HIV-infected women received ARV therapy as per Western Cape Prevention of Mother To Child Transmission guidelines at the time; CD4 counts were collected. Infants were tested for HIV using PCR and antibody testing. The association between HIV and ARV exposure and lung function during 2 years was assessed using linear regression, adjusted for BMI for age Z-score, sex, ethnicity, socioeconomic status (SES), and birth weight using linear regression.
ABSTRACTS

Background: Tungs' Taichung Metro Harbor Hospital images to evaluate the volumes and systolic function of the ventricles. Before and after Nuss Operation for Pectus Excavatum in Children.

Methods: Between 2014 and 2018, a total of 14 (12 male, 2 female) patients, age 12.2 +/- 4.8 years, height 145.4 +/ - 29.2 cm, weight 35.9 +/- 13.7 kg with pectus excavatum underwent echocardiography before and after chest wall correction with the Nuss procedure. The volume ratios of the right to left ventricles and the systolic functions of the left ventricle were calculated by transthoracic echocardiography.

Results: The volume ratios of the ventricles increased from 0.39 +/- 0.13 to 0.52 +/- 0.26, p-value 0.04. The ejection fraction of the left ventricle increased from 74% +/- 6.4% to 76.2% +/- 7.1%, p-value 0.39.

Conclusions: Cardiac volumes of both ventricles increased significantly and the ejection fraction of the left ventricle maintained within normal ranges after the Nuss operation for pectus excavatum in children.

I-11 | The Nationwide Survey of Mycoplasma Pneumoniae Infection in Children throughout Japan in Recent 10 Years

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Background: Recently, we experienced a Mycoplasma pneumoniae (MP) infection pandemic and an increase in the rate of Macrolide-resistant (MR) isolates in Japan.

Objective: It is necessary to understand the recent aspects of MP infections among Japanese children.

Material and Methods: We enrolled children with suspected MP infections who visited 85 institutions throughout Japan since March 2008 in whom samples were collected. Informed consent was obtained from the parents of the patients. MR isolates were defined by sequencing of domain V of the 23s rRNA gene of MP. Furthermore, we also examined the MICs of 7 antimicrobial agents for the isolates and the distribution trend of MP P1genes.

Results: From 2008 to 2017, a total of 1702 MP isolates were obtained. The annual number of isolates reached its peak (598) in 2012 and increased in 2015 and 2016 again. The overall detection rate of MR isolates was 69.3%. The annual rate of the latter reached its peak (81.8%) in 2012. It has since decreased to 8% in 2018. Almost all MR isolates had the A2063G point mutation. There was no isolate resistant to quinolone and tetracycline agents. Furthermore, the detection rate of type 1 of MP P1genes was approximately 50% in the outbreak of 2015-2016, whereas it was more than 90% in the outbreak of 2011-2012.

Conclusion: In these 10 years, outbreaks of MP infections have occurred twice in Japan. However, there were differences in the rate of MR isolates and the distribution of MP P1genes among the isolates between the two outbreaks. The annual MR rate of MP infections reached its peak (81.8%) in 2012 and thereafter it has been decreasing to 8% in 2018.

I-12 | Cardiac Volumes and Systolic Function Before and after Nuss Operation for Pectus Excavatum in Children.

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Background: Pectus excavatum results in compression of the heart and may compromise cardiac function. The changes in cardiac volumes of the ventricles and systolic function in children after Nuss operation have been less reported. Echocardiography is noninvasive and can provide images to evaluate the volumes and systolic function of the ventricles.

Results: A total of 1036 infants had at least one lung function measurement and were followed over 2 years, 226 (22%) were HEU; 535 (52%) male, 560 (54%) black African ancestry, 330 (33%) mothers smoked during pregnancy, 775 (71%) household tobacco smoke exposure. Nine hundred and ten (88%) infants had lung function tested at 6 weeks and 743 (72%) children at 2 years. The majority of HEU infants were black African (93% vs. 43% HU, P < 0.001), HEU infants had less household smoke exposure (69% vs. 81%, P = 0.01), lower SES (P = 0.001) and had higher BMI z-score at 2 years (P = 0.001) compared to HU; other demographics were similar.

At 6 weeks, HEU infants had higher tidal volume compared to HU (1.1mL, CI, 0.02; 2.2, P = 0.045). Amongst the HEU infants, those whose mothers had triple therapy ARVs had lower expiratory flow ratios, tPTEF/tE, compared to those whose mothers had zidovudine (AZT) only (-0.26, CI -0.4; -0.1, P < 0.001). At 2 years, tidal volume differences were no longer seen, but HEU infants had a higher lung clearance index compared to HU (0.12, CI, 0.02; 0.23, P = 0.019). Low antenatal maternal CD4 count was associated with mild lung function impairment at 2 years of age. More severe maternal immune compromise contributes to lower lung function. The impact of ARVs on lung growth warrants further investigation. Ongoing surveillance of respiratory health is important in HEU.

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8 | NEUROMUSCULAR AND CHEST WALL DISEASES (INCLUDING SIDS)

H-192 | Cardiac Volumes and Systolic Function Before and after Nuss Operation for Pectus Excavatum in Children.

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Background: Pectus excavatum results in compression of the heart and may compromise cardiac function. The changes in cardiac volumes of the ventricles and systolic function in children after Nuss operation have been less reported. Echocardiography is noninvasive and can provide images to evaluate the volumes and systolic function of the ventricles.

Results: A total of 1036 infants had at least one lung function measurement and were followed over 2 years, 226 (22%) were HEU; 535 (52%) male, 560 (54%) black African ancestry, 330 (33%) mothers smoked during pregnancy, 775 (71%) household tobacco smoke exposure. Nine hundred and ten (88%) infants had lung function tested at 6 weeks and 743 (72%) children at 2 years. The majority of HEU infants were black African (93% vs. 43% HU, P < 0.001), HEU infants had less household smoke exposure (69% vs. 81%, P = 0.01), lower SES (P = 0.001) and had higher BMI z-score at 2 years (P = 0.001) compared to HU; other demographics were similar.

At 6 weeks, HEU infants had higher tidal volume compared to HU (1.1mL, CI, 0.02; 2.2, P = 0.045). Amongst the HEU infants, those whose mothers had triple therapy ARVs had lower expiratory flow ratios, tPTEF/tE, compared to those whose mothers had zidovudine (AZT) only (-0.26, CI -0.4; -0.1, P < 0.001). At 2 years, tidal volume differences were no longer seen, but HEU infants had a higher lung clearance index compared to HU (0.12, CI, 0.02; 0.23, P = 0.019). Low antenatal maternal CD4 count was associated with mild lung function impairment at 2 years of age. More severe maternal immune compromise contributes to lower lung function. The impact of ARVs on lung growth warrants further investigation. Ongoing surveillance of respiratory health is important in HEU.

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10 | EPIDEMIOLOGY, ENVIRONMENTAL RISKS, PREVENTION, SOCIOECONOMIC COST, PUBLIC HEALTH RESOURCES
I-32 | Effect of Multi-Ethnicity and Ancestry on Prevalence of Allergic Disease

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Background/purpose: Differences exist among racial and ethnic groups in the prevalence and severity of allergic diseases. However, influence of population admixing on allergic disease has not been studied. We examined the effect of population admixing on the occurrence of allergic disease.

Methods: We reviewed the data of 68,043 adolescents who participated in the 11th Korea Youth Risk Behavior Web-based Survey, which provides a sample that is representative of the entire Korean middle school and high school student population. Multi-ethnic status was determined by using parental country of birth and prevalence of asthma, allergic rhinitis (AR), and atopic dermatitis (AD) was determined by questionnaire.

Results: Multi-ethnic adolescents accounted for approximately 0.9% of the total adolescents. Prevalence of asthma was significantly higher in the multi-ethnic group compared to the non multi-ethnic group while that of AR and AD was significantly higher in the non multi-ethnic group compared to the multi-ethnic group. Parental region of country at birth showed a significant difference in prevalence of allergic disease. Univariate analysis found that urbanity, perceived economic status (PES), parental region of country at birth, and environmental tobacco smoke (ETS) showed a significant odds ratio (OR) in asthma, AR and AD. Body mass index (BMI) showed a significant OR in asthma and AD. After adjusting for urbanity, PES, BMI and ETS, multiethnicity showed a significantly lower OR in AR and AD.

Conclusion: Population admixing appears to have a significant effect on the prevalence of allergic disease. Further study will be needed to clarify the effect of population admixing on prevalence of allergic disease.

I-51 | Chronic Wet Cough in Aboriginal Children: When Is a Cough Not Just a Cough?

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Background: Chronic wet cough, which is prevalent in Indigenous children, is the most common symptom of bronchiectasis and its precursors. Early recognition of chronic wet cough leading to prompt and appropriate treatment may potentially prevent progression to bronchiectasis. Therefore, timely health seeking for chronic wet cough by families, and its effective management by health practitioners is potentially important to prevent development of bronchiectasis.

Purpose: To identify the barriers to and enablers for timely health seeking for chronic wet cough by families, and optimal management by health practitioners, for chronic wet cough in Aboriginal children.

Method: A qualitative study was conducted in two communities (one remote town and one very remote community) in the Kimberley region of northern, Western Australia, of which 43% of the population is Aboriginal. Data were gathered through individual semi-structured in-depth interviews and focus groups to ascertain:

1. Aboriginal family knowledge and beliefs about chronic wet cough in children and to identify the barriers and enablers to seeking health care.
2. Health practitioner knowledge of chronic wet cough and chronic lung disease in Aboriginal children and to identify barriers and enablers to effective management.

Results: Forty Aboriginal family members participated. The three key barriers identified were: (i) ‘Cough normalization’ i.e. 70% of participants considered chronic cough as normal (with 53% of participants’ previous interactions with doctors informing participants’ understanding of chronic cough), (ii) lack of health literacy information and (iii) a sense of disempowerment (belief that no medical action would be taken and inability to challenge doctors). The key enabler described was the provision of culturally appropriate health literacy information. All participants reported that they would seek help for chronic wet cough once they were informed that it could signify underlying disease. Furthermore, families suggested that improved health practitioner knowledge of chronic wet cough would facilitate health seeking by parents.

Thirty-seven health practitioners participated. Key barriers to optimal management of chronic wet cough were: (i) limited training in assessment and management of chronic wet cough, (ii) normalization of cough in children by health practitioners, and (iii) prioritization of acute presentations and competing better known chronic conditions. Key enablers were (i) improving practitioners’ knowledge and expertise in managing chronic wet cough, (ii) easy access to clear clinical practice guidelines, (iii) improving health practitioners’ cultural competence when working with Aboriginal families, and (iv) health system changes to facilitate longitudinal patient care.

Conclusion: Knowledge about chronic wet cough and its implications is not widely appreciated amongst families and health practitioners in remote Western Australia. Culturally appropriate health information for families, training for health practitioners, easy to access clinical practice guidelines and a health service model for effective longitudinal patient care is needed to improve early detection and effective management of chronic wet cough. These measures have the potential to prevent bronchiectasis in Aboriginal children.

Reflections: Results may potentially apply to other settings. There is a need to study knowledge about chronic wet cough in other populations, particularly indigenous communities and their health practitioners.
I-58 | Epidemiological Trends of Children Requiring ICU Care in Taiwan: A Retrospective Population-Based Analysis

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Background: More than 99.5% of people living in Taiwan are covered by a national health insurance. Children younger than 18 years account for 20–25% of the general population, but the birth rate of newborns has gradually been getting lower during the past decade. Analysis on the changing patterns of children requiring intensive care is important for future children’s medical policy plan. This study aimed to investigate the epidemiology of children treated in intensive care units (ICUs) in Taiwan from 2000 to 2013.

Method: Systematic random samples from the Taiwan’s National Health Insurance Research Database were analyzed. Using the 5% inpatient data claims during 2000 to 2013, children with records of ICU hospitalization were enrolled and divided into different age groups. The related age, diagnosis, cost, seasonality, and mortality rate were analyzed and compared to adults.

Result: A total of 14,727 (1,195 ± 117 cases/month) children having ICU records were enrolled, including 9,628 (57.6%) boys and 7,099 (42.4%) girls. Among them, infants (0-11 months old) were the highest population (60.2%), and their most common diagnoses were neonatal respiratory problems, preterm birth/low birth weight, and jaundice. Small children (1-5 years old, 19.6%) and bigger kids (6-11 years old, 8.4%) had similar disease patterns, and congenital cardiac/vascular anomaly, respiratory failure/insufficiency, and pneumonia were common diagnoses. Adolescents (12-17 years old, 11.1%) had a markedly higher diagnostic rate in traumatic cranial hemorrhage than the other age groups. The top ICU hospitalization season was summer. The ICU mortality rate of children was around 4%-6% and had a decreasing trend. From 2000 to 2013, the children’s ICU hospitalization rate significantly declined; however, the adults’ ICU hospitalization rate obviously increased. As a result, the ratios of children’s ICU care significantly declined from 14.6% to 6.9%.

Conclusions: Children’s ICU care needs in Taiwan gradually declined from 2000 to 2013. Infants are the largest population to have ICU care. Preterm births, neonatal respiratory or congenital cardiovascular diseases accounted for top ICU diagnoses, although traumatic brain injury rose in adolescents. Upgrading children’s ICU care by targeting diseases of different age groups is important in any nation with an aging population.

I-61 | The Effect of Mechanical Air Purifier for Improving Allergic Symptom Scores of Allergic Children

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Rationale: The air quality and pollution in the air is completely dependent on the surroundings one lives in. Capturing ourselves indoor during the high level of pollution also needs to be readdressed since indoor air is usually dirtier than the air outdoors, due to trapping of air contaminants inside. Allergic Children are most vulnerable as they are most likely to stay indoors for longer durations. This study aimed to evaluate the change in allergic symptoms in allergic children by using an air purifier.

Methods: Forty-five allergic children were recruited from the Hanyang University Guri Hospital Pediatric Allergy Clinic (18 children with atopic dermatitis, 18 with allergic rhinitis, 9 with asthma). A Samsung air purifier was set up in the subject’s family room and operated with filter-on for 28 days as acting day and filter-off for 28 days as control with an average 14 hours/d (8–24 hours/d) since September 2018. Allergic symptom scores were self-checked on a smart cellular phone by the subject’s parents as Atopic dermatitis: SCORAD; allergic rhinitis: total 4 nasal symptom score (T4NSS); Asthma: Asthma symptom score (ASS). At same period, the level of the PM10, PM2.5, pollens and NO2, SO2, O3 were measured and recorded daily for air quality.

Results: The mean improved rate for SCORAD was 15.16%, T4NSS was 28.86%, ASS was 50.7% at the filter-off phase of the air purifier phase than at the filter-on phase. There was no significant correlation between allergic symptom scores and the level of air pollutants and pollens in this period although showed a lag-effect trend between them.

Conclusion: Allergic symptom scores were improved by using a mechanical air purifier set up in the home of allergic children.

I-68 | The Effects of Air Pollution and Meteorological Factors on Asthma Exacerbation in Taiwan: A Bidirectional Case-Crossover Analysis Model

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Background: Urbanization is an important cause for asthma increase, and some may be attributed to increased outdoor air pollution. Although many studies have identified the individual effect of single pollutants, they often mask the health effect of the mixture overall. In the real world, dynamic changes in air pollutants and meteorological factors always coexist simultaneously. Thus, a comprehensive study was carried out to study the influence of air pollution and meteorological factors on asthma acute exacerbation (AE).
Material and method: The Emergency department visit for asthma AE data (ICD 9 code 493.xx) were collected from the claims data of 1 million subjects randomly selected from 23 million insurants registered from 2005 to 2013 in Taiwan from the National Health Insurance Research Database. Complete monitoring data for the air pollutants (SO2, NO2, O3, CO, PM2.5 and PM10) and meteorological factors (relative humidity, rainfall, and daily average temperature) were collected from 74 Environmental Protection Agency monitoring stations of the Taiwanese government. In the present study, each ER visit for asthma AE was defined as case day. In bidirectional control samplings, the same weekdays 1, 2 or 3 weeks before and after ER visit for asthma were defined as the control days. Multiple correlation coefficients (R) (multiple regression analysis) were used to explain how much of the variance in the ED visits could be explained by a given set of air pollutants.

Result: As the study cases were divided as male and female, a 1 ug/m3 increase in the 48-h averages of PM2.5 and a 1°C increase in temperature were associated with asthma ER visit [OR=1.004 (95%CI, 1.000–1.008) and 0.986 (95%CI, 0.979–0.994) respectively] for male patients. A 1 ppb increase in the 48-h averages of O3 and a 1°C increase in temperature were associated with asthma ER visit [OR=1.003 (95%CI, 1.000–1.007) and 0.985 (95%CI, 0.976–0.993) respectively] for female patients. As the study cases were divided according to their age, increase in temperature was a protective factor for asthma ER visit with a 1°C increase in temperature associated with OR=0.981 (95%CI, 0.971–0.991) and 0.985 (95%CI, 0.975–0.994) for the pediatric group and young adult group, respectively. Each 1 ug/m3 increase in the 48-h averages of PM2.5 was associated with asthma ER visit for patients older than 65 years old (OR=1.008 (95%CI, 1.003–1.014).

Conclusion: In Taiwan, asthma AE is closely related to low temperature and indicated air pollution. There is an obvious bias if only a single air pollutant is being considered and neglects the influence of meteorological factors in studying the effects of the environment on asthma. With the result of this study, we can predict asthma exacerbation precisely according to individual age, gender and local air pollution/meteorological conditions. In days with high risk for asthma exacerbation, patients with asthma should avoid/decrease outdoor activity, dress warmly and maintain inhaled corticosteroid therapy.

I-117 | Identification of Criterion Values for Endotracheal Suctioning Using a Motion Capture System

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With the increasing numbers of children with home-ventilators in the community, the quantification of proficiency to evaluate the skill of endotracheal suctioning has attracted much attention to provide safe and efficient care. The purpose of this study is to identify criterion values to evaluate the proficiency of endotracheal suctioning skills between expert nurses and nursing students, using a motion capture system. Twelve expert nurses from two institutions and twelve nursing students from a university were recruited in this study. The maximum anteflexion angle, the path length and fixation time of dorsum manus were measured by a motion capture system (Perception Neuron, Noitom, USA) during endotracheal suctioning on a simulator. After measuring their performance, participants were questioned using the Japanese version of the National Aeronautics and Space Administration Task Load Index (NASA-TLX). Permission from the ethical committee was obtained before commencing this study (17-81). A total of 21 valid data from 11 nurses and 10 nursing students were obtained. The mean completion times of expert nurses and students were 84.15[s] and 115.30[s], respectively. As a result of independent t-test, a significant difference was found between the two groups (P=0.00028). The average of anteflexion angle of nurses was 29±8.05[deg] and the students’ was 34±10.68[deg] without significant difference (P=0.153). As for the total path length of dorsum manus, there was a significant difference in their left hands (P=0.01), but no statistical significance was found in their right hands (P>0.05). The fixation time of dorsum manus were 327.2[s] for nurses and 59.66[s] for students in their right hands, and 24.2[s] and 39.85[s] in their left hands. In NASA-TLX scores, there were significant differences regarding time pressure (P=0.004), anxiety (P=0.02), stress (P=0.028), and satisfaction of their performance (P=0.007).

However, while the path length of the right dorsum manus was not statistically significant, there was a significant difference in completion time between the two groups. The reason considered was that their left hand was their nondominant hand, while their dominant hand needed to be kept clean to touch an aseptic suction catheter. Therefore, novice participants were unfamiliar with manipulating suctioning equipment with their left hand, which appeared as a difference in their proficiency. Their fixation time of right hands occupied approximately 50% of their average completion time, whereas the percentage of fixation time within the completion time was about 40% for the nurse group. Given the fact that the NASA-TLX score revealed that the student group was time-pressured and unsatisfied about their performance, the prolonged fixation time might play an important role in cognitive activity for them. In conclusion, we identified three possible criterion values: the performance time, the path length of the left dorsum manus, and fixation time of the dorsum manus in both hands, to measure the proficiency of endotracheal suctioning skills. Further study is required to determine the sufficient level of proficiency to provide safe endotracheal suctioning, including accuracy, avoidance of patient pain, hygienic manipulation of the catheter, and location of equipment to prevent adverse events in endotracheal suctioning.
Endotracheal suctioning is recently provided not only in hospitals but also in community settings. The provision places for such invasive procedure have expanded, including special-need schools in particular. It is easily imagined that endotracheal suctioning is a stressful health-maintaining technique for family caregivers or school teachers until acquiring its high-risk characteristics. This study, therefore, aims to compare the learning outcome in the 2D/3D Computer Graphic (3D CG) animation as one of the training methods of endotracheal suctioning skill. Thirteen experienced nurses from three institutions and twelve nursing students from a university participated in this study. These participants were asked to watch a 2D video of an experienced nurse performing endotracheal suctioning on a training simulator, or 3D CG animation which is able to enlarge areas of interest (AOIs) and rotate virtual camera angles as a visual stimulus. The position of the participants’ heads was fixed on a head holder in front of the display. Simultaneously, their eye movement was tracked by a head-mounted eye-mark recorder (EMR-9, NAC Image technology Inc., Japan) with a world camera (62[deg] horizontal angle of view) and binocular cameras. The sampling rate was 60[Hz]. Obtained data were analyzed by EMR-dFactory (version 2.7.0, NAC Image technology Inc., Japan). The gaze fixation was defined as less than 2[deg] within 100[ms]. Afterwards, impression regarding watching the digital content to learn the procedure of a nursing skill was assessed by an original self-reported questionnaire. Excluding the data of Ns.5 and St.1, in whom the estrangement with other measurement results was remarkable, data from 12 nurses and 10 nursing students were analyzed. After the eye-mark was computed, analysis for frequency distribution of fixation point movement velocity was conducted. Contrary to the previous study which concluded that the novice group tended to be unimodal, bimodality of eye trajectory velocity with two peaks at 0 to 29 [deg/s] and 75 [deg/s] was found in all of the four groups. An independent t-test revealed no significant differences in the two nurse groups who watched 2D video or 3D CG. There was no significant difference in the two student groups who watched 2D video or 3D CG. From post-performance questionnaire responses, benefits of 3D CG were reported that the function of a virtual camera improved the accessibility to AOIs by screen transition, whereas operation was difficult, so they could not realize the effect of learning. Advantages of 2D video was described that it is easy to concentrate because the device was familiar, while there was a negative impression that it was hard to observe AOIs compared to 3D CG. There was no significant difference between the groups who watched 2D video or 3D CG animation in the frequency distribution of fixation point movement speed analysis. However, considering the unignorable potential of 3D CG animation as a training tool, we concluded that defining visual criteria for assessing learning outcome of digital contents requires more research in the future.

The aim of this study is to compare the level of endotracheal suctioning proficiency between experts and novices, using an eye-mark recorder.

A head-mounted eye-tracking device (Pupil, Pupil Lab, USA) was used to capture eye movement of the participants. Twelve experienced nurses from three healthcare facilities who had more than 3 years of experiences of suctioning, and twelve nursing students from a university who had no experience of providing suctioning for real patients, participated in a simulation scenario of a patient with endotracheal intubation. We utilized cephalothorax realia with a simulated upper respiratory tract from mouth, nose, to a tracheal bifurcation, which did not represent any biological/pathological reactions of the human body. While the participants performed endotracheal suctioning, their completion time, gaze fixation frequency and gaze fixation duration were measured, followed by the percentage of fixation duration against the completion time, and the frequency distribution of fixation point movement velocity was calculated. The sampling rate was 60[Hz]. The gaze fixation was defined as less than 2[deg] within 100[ms]. After performing endotracheal suctioning, the participants were asked to fulfill a Japanese version of the National Aeronautics and Space Administration Task Lord Index (NASA-TLX) survey. Data were analyzed by MATLAB (2014a, USA), SPSS(version 22.0, USA), and Microsoft Excel (Home and Business 2016, USA). Approval from the ethical committee was obtained before commencing this study (17-81-2).

Average completion times in the nurse group and the student group were 88.2[s] and 112.3[s]. As a result of independent t-test,
there was a significant difference ($P = 0.006$) between the two groups. The values for gaze fixation frequency were 63.6(right) and 67.3(left) for the nurse group, and 88.8(right) and 83.4(left) for the student group ($P = 0.004$right), $P = 0.04$left). Gaze fixation duration of the nurse group was 55.4[s]right and 54.4[s]left, and 80.7[s]right and 88.5[s]left for the student group, with significant differences between the two groups ($P = 0.03$right), $0.03$left). Percentages of fixation duration against the completion time were 62.8%(right), 61.6%(left) in the nurse group, and 71.9%(right) and 71.7%(left) in the student group. The graph of frequency distribution of fixation point movement velocity was unimodal with a peak at 0 to 29 [deg/s] in both groups, which was constrative of the characteristics of expert nurses’ bimodal eye movement speed in our previous study.

As for the result of NASA-TLX, there was no significant difference between the two groups.

The completion time, gaze fixation frequency, gaze fixation duration could be referable visual quantitative criteria for skill assessment of endotracheal suctioning. There were no significant differences in percentages of fixation duration against the completion time and analysis of frequency distribution of fixation point movement velocity; however, factors which differentiate the results from the previous study have to be confirmed. Given the fact that the NASA-TLX did not vary depending on the participants' clinical experience, the workload might have been equally high in the unfamiliar environment of a laboratory. Further studies will be required to determine the sufficient level of proficiency to provide safe endotracheal suctioning before putting it into practice in pediatric patients in the future.

**I-140 | Clinical and Diagnostic Aspects of Prolonged and Chronic Cough in Children**

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The diagnostic search of prolonged and chronic cough in children presents difficulties, because there are many different respiratory and extrapulmonary diseases as its causes. **Aim:** to determine the clinical structure and causes of prolonged and chronic cough in children.

**Patients and methods:** 272 children aged from 2 to 17 years with prolonged (from four to 8 weeks) ($n = 109$) and chronic cough (more than 8 weeks) ($n = 163$) were examined. Cataract diagnosis lasted from 6 to 18 months. The control group included 60 healthy children. All patients underwent history and examination, as well as surveys of parents and/or patients with specially designed questionnaire, including the score of the main characteristics of cough (dry/wet, frequency, intensity and others). According to indications, the following were taken: chest X-rays, consultations with specialists, in-depth examination in a specialized hospital or diagnostic center. Statistical analysis was carried out with the help of a package of computer programs «Microsoft Excel 2010», «Statistica v. 10.0». The examined children with prolonged and chronic cough, along with acute respiratory tract infections (ARTI) (in 45%), had a high frequency (in 43%) of occurrence of allergic respiratory diseases (ARD) (allergic rhinitis, bronchial asthma) ($P > 0.05$). Bronchial asthma (BA) including its cough variant was diagnosed in 29% and in 8% respectively of children with prolonged and chronic cough. The frequency of occurrence of BA increased with patient age. Other, rarer causes of prolonged and chronic cough (chronic bronchitis; whooping cough; psychogenic, neurogenic cough; gastroesophageal reflux disease; foreign body airway obstruction) were found in 12% of our patients. In clinical structure of the prolonged cough (from four to 8 weeks), ARTI prevailed (upper ARTI or exacerbation of the chronic upper respiratory tract infections in 25% and lower ARTI in 40%) in contrast to chronic cough (more than 8 weeks), during which the frequency of allergic genesis of the disease increased (allergic rhinitis in 18% and BA in 34%).

Our research proved that a longer cough (regardless of of its genesis) was found in patients with negative predisposing factors and their combination: passive smoking; unfavorable environmental conditions; recurrent respiratory tract infections ($P < 0.05$). Prolonged and chronic cough was further promoted by previously delayed diagnosis of the disease, insufficient treatment, late consultation with a doctor ($P < 0.05$). Furthermore, there were more frequently observed recurrent episodes of prolonged or chronic cough in the examined children with the presence of comorbid disease (chronic upper respiratory tract pathology of the infectious/ allergic genesis) in contrast to patients without comorbidity ($P < 0.05$). Thus, the multifactorial causes of prolonged and chronic cough in children necessitate the development and introduction of informative diagnostic algorithms into clinical practice. This will help reduce the time of diagnostic search, enable early start of treatment and preventive measures and improve prognosis and quality of life of patients.

**I-173 | Effects of Environmental Tobacco Smoke Exposure on Urinary Cotinine Level and Lung Function Test in Children**

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**Background:** The Global Youth Tobacco Survey 2014 in Indonesia showed that 57.3% of students are exposed to environmental tobacco smoke, which causes inflammation of respiratory tracts and a decrease in lung function. Urinary cotinine can be used as a biomarker for cigarette smoke exposure.
Objectives: To examine the effects of environmental tobacco smoke exposure on urinary cotinine level and lung function test in children.

Methods: Subjects were children aged 6 to 17 years in the Clinical Practice Research Database and linked to Hospital Episode Statistics with at least one asthma record between 2011-2015. Four hierarchical groups were defined: treated asthma [with baseline asthma medications], severe asthma [above + Global Initiative for Asthma Step 4/5], severe refractory asthma [SRA; above + Global Initiative for Asthma Step 4/5], and eosinophilic SRA [above + blood eosinophils ≥ 150 cells/µL]. Exacerbations and healthcare resource use during the one-year follow-up period were described.

Results: The treated asthma group included 32,893 patients, of which 2,711 (8.2%) had severe asthma and 265 (0.8%) had SRA. The mean age in the treated, severe and SRA groups was 12.1 years, 13.4 years and 12.6 years, respectively. The eosinophilic SRA group included only 8 children, likely driven by the fact that only 3% of the SRA group had a multivariate analysis was adjusted for age, BMI for age Z score, gender, ethnicity, maternal HIV status and socioeconomic status.

Results: Between July 2012 and Sept 2017, 910 (female: 48%; HIV-exposed: 21%; Black African: 76.8%) six-week, 784 (86%) 1-year and 744 (82%) 2-year infants were tested. More than half (53%) of the children had postnatal ETS exposure. Postnatal ETS exposure was associated with an average 3% decrease in RR (0.03 (95% CI -0.00, 0.06)), increased LCI (0.09 turnovers (95% CI, 0.01, 0.16)) and decreased TV (-1.59mL (95% CI -2.81 - -0.37)) over 2 years. Of the IAP measures, particulate matter (PM10) was associated with reduced TV (-4.60 mL (95% CI -8.51, -0.69) at 2 years and benzene (VOC) with a decrease in FENO (-0.27 (95% CI -0.44, -0.11)) over 2 years.

Conclusion: Environmental exposures from tobacco smoke and IAP in early life had a significant impact on lung function over 2 years. Reducing early-life environmental exposures, particularly from tobacco smoke, may improve lung function trajectories.

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I-216 Early-life Exposure to Indoor Air Pollution or Environmental Tobacco Smoke: Impact on Lung Function in First 2-Yrs Of Life in an African Birth Cohort


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Early-life environmental exposures may impact on lung growth and function. This study longitudinally investigated the impact of indoor air pollution (IAP) and environmental tobacco smoke (ETS) exposure on lung function over 2 years in a South African birth cohort study.

Methods: Mother-infant pairs enrolled in the Drakenstein Child Health Study (DCHS) were followed from birth through 2 years. IAP exposure (particulate matter, nitrogen dioxide or volatile organic compounds (VOC)) were measured at an antenatal and postnatal home visit. Maternal and infant urine cotinine measured ETS exposure. Lung function measured at 6 weeks (6-10 weeks), 1 year (11-14 months) and 2 years (23-26 months) of age included respiratory rate (RR), lung clearance index (LCI), tidal volume (TV), functional residual capacity (FRC), exhaled nitric oxide (FENO) and expiratory flow ratios (tPTEF/tE ratio). Mixed effect models with random subject effects explored the impact of demographics and postnatal exposures on lung function during the first 2 years of life. The number of cigarettes per day (OR= 34.71). There were significant differences between urinary cotinine level with number of smokers (P = 0.027) and number of cigarettes per day (P = 0.037). No association was found between cigarette smoke exposure and lung function test. There was a significant difference in school absenteeism between the case group and control group; P = 0.004; OR= 6.00 (CI, 95% 1.42-25.33).

Conclusions: Children exposed to environmental tobacco smoke have higher urinary cotinine levels than nonexposed children. Factors such as number of smokers and number of cigarettes per day may affect urinary cotinine levels.

Keywords: children; cigarette smoke exposure; urinary cotinine level; lung function test.

I-225 Burden of Severe Asthma in Children in the English Primary Care Setting

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Background: Real world data on the health care burden of severe asthma in children are limited.

Aim To describe exacerbations and health care resource use among children with asthma in England.

Methods: We included children aged 6 to 17 years in the Clinical Practice Research Database and linked to Hospital Episode Statistics with at least one asthma record between 2011-2015. Four hierarchical groups were defined: treated asthma [with baseline asthma medications], severe asthma [above + Global Initiative for Asthma Step 4/5], severe refractory asthma [SRA; above + baseline exacerbations], and eosinophilic SRA [above + blood eosinophils ≥ 150 cells/µL]. Exacerbations and healthcare resource use during the one-year follow-up period were described.

Results: The treated asthma group included 32,893 patients, of which 2,711 (8.2%) had severe asthma and 265 (0.8%) had SRA. The mean age in the treated, severe and SRA groups was 12.1 years, 13.4 years and 12.6 years, respectively. The eosinophilic SRA group included only 8 children, likely driven by the fact that only 3% of the SRA group had a
valid eosinophil test result, and therefore the eosinophilic SRA group was not analyzed further. During follow-up, 3.9%, 10.8% and 42.6% of the treated, severe and SRA groups had at least one asthma exacerbation. In the 30 days after the first asthma exacerbation, 4.4% treated, 8.2% severe and 16.8% of the SRA group had >1 asthma hospitalization; and 2.4% treated, 3.8% severe and 7.1% of the SRA group had >1 record for an asthma accident and emergency department visit. Most children also had >1 general physician visit within 30 days after the first asthma exacerbation (73.2%, 77.1%, and 81.4% in the treated, severe, and SRA groups, respectively).

Conclusions: This study demonstrates that the burden of asthma exacerbations and health care resource use in children with asthma increases with increased asthma severity, thus highlighting the potential unmet need for specific treatments in subgroups with more severe disease.

Funding: GSK [PRJ3070].

10 | INVESTIGATION AND DIAGNOSTIC TESTS

J-53 | The Use of WristOx2 in the Diagnosis of Obstructive Sleep Apnea (OSA) in Children

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Background: Polysomnography (PSG) is a gold standard for obstructive sleep apnea (OSA) diagnosis; however it is complex, labor intensive and expensive. Overnight pulse-oximetry is an alternative diagnostic tool but its feasibility amongst the pediatric age group is debatable. Our study aimed to test the reliability and accuracy of pulse-oximetry performed by WristOx2 for OSA diagnosis and its severity.

Method: A cross-sectional study was performed in children aged 1 to 18 years with a clinical suspicion of OSA referred to the pediatric sleep lab at the University of Malaya Medical Center between 2014 and 2018. The WristOx2 (Nonin 3150) was simultaneously applied along with PSG (Cadwell, USA). The pulse oximetry studies were scored using a validated McGill Oximetry Score. Using the PSG as the "gold standard", the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for the pulse-oximetry.

Results: 163 patients were recruited with a mean age of 9.3 ± 3.5 years and predominantly male (65%). WristOx2 accurately diagnosed OSA in 139 children (86%) when compared to the PSG (95% CI, 0.72, 0.88). The WristOx2 had a sensitivity of 89% (95% CI= 0.81, 0.94), specificity 95% (95% CI= 0.86, 0.98), PPV 96% and NPV 84%. WristOx2 had 100% sensitivity (95% CI= 0.93, 1.00) for moderate-to-severe OSA diagnosis and 76% specificity (95% CI= 0.59, 0.89) for mild OSA diagnosis. The corresponding area under the receiver operator curve for OSA diagnosis was 0.92 (95% CI, 0.86, 0.96). There was also good correlation of SpO2 nadir between PSG and WristOx2 (r= 0.83).

Conclusion: Pulse-oximetry by WristOx2 is a reliable tool for obstructive sleep apnea (OSA) diagnosis in children.
Introduction: Bronchoalveolar lavage (BAL), an important tool in the assessment of the lower respiratory tract, can be obtained during flexible bronchoscopy as well as non-bronchoscopically. There are relatively little data in healthy children and no data that compared these techniques. In 100 children without respiratory disease, we described (i) the BAL differential cellular count and its correlation with age, and (ii) compared the differential cytology between non-bronchoscopic BAL (NB-BAL) and bronchoscopic BAL (B-BAL).

Methods: Children who underwent B-BAL or NB-BAL, with no history of chronic cough and no acute respiratory infection in the preceding 4 weeks were included. BAL was obtained according to European Respiratory Society guidelines. For B-BAL, a sterile normal saline solution in three aliquots of 1 ml/kg (maximum 20 ml) was instilled into the right middle lobe (first and third aliquots) and lingula (second aliquot) and the return was suctioned into a mucus trap. The first and second aliquots were pooled for microbiological examination, while the third aliquot was used for cytology. For NB-BAL, with the child's head turned to the left, an 8F catheter was inserted through the endotracheal tube until it was wedged. Sterile normal saline (1 ml/kg, maximum 20 ml) was instilled and collected for microbiology examination. A further 1 ml/kg (maximum 20 ml) was instilled and the second collection was utilized for cytology.

Results: The median age of the total cohort (42 B-BAL and 58 NB-BAL) was 7.4 years (range 8 days to 16.6 years). However, the NB-BAL group was significantly older (8.2 years, IQR 5.4-12.5 years, vs. B-BAL 3.3 years, IQR 0.9-9 years). In the pooled grouped, the median total cell count was 10.4 x10^4 per millilitre (IQR 5.7-18.2x10^4), macrophage (89.5%, IQR 82.3-93%), lymphocytes (5%, IQR 3-10%) and neutrophils (4%, IQR 2-7%). The total cell count and lymphocyte percentage were inversely correlated with age while the macrophage percentage was positively correlated with age. In univariate analysis, macrophage percentage was significantly higher in NB-BAL (91%, IQR 87-94%) compared to B-BAL (85%, IQR 78-90%) with lower lymphocyte percentage (NB-BAL 4%, IQR 2-6%) versus B-BAL (10%, IQR 4-13%)). However, when adjusted for age using regression statistics, these differences were not significant.

There was no significant difference in the total cell count (NB-BAL 9.3x10^4/mL, IQR 4.5-15.3x10^4/mL versus B-BAL 11.8x10^4/mL, IQR 8-22.1x10^4/mL) and neutrophil percentage (NB-BAL 4.5%, IQR 2.8%-7% versus B-BAL 3.5%, IQR 1.8-8%) between the two groups. There was no significant difference in the differential cytology with age in both B-BAL and NB-BAL.

Conclusion: NB-BAL provides comparable information on the cellularity components of BAL when compared to B-BAL and should be considered an alternative. As age influences cellular differential count, age-matched data are required for comparative studies on BAL in children.
Background: Spirometry is an essential tool for assessing patients with lung disease. However, it necessitates cooperation and thus, it cannot be performed in infants. One of the established alternative techniques in infants is the raised-volume rapid thoraco-abdominal compression technique (RVTCT) which uses a compression tent to squeeze the chest forcefully after inflating the lungs to near total lung capacity (TLC). Although it is an acceptable method, it is far from being perfect since it is not easy to perform. Obtaining the raised-volume passive expiration curve (RVPE) from passive deflation of the lungs from TLC is an easier technique (Figure 1). However, to our knowledge, data obtained from the RVPE curve were not assessed for their ability to estimate expiratory airway function in infants.

**Aim:** To compare data collected from the RVPE flow-volume curves with those of the RVTCT and investigate the ability and ease of creating technically valid curves.

**Methods:** A retrospective study investigating the RVPE and the RVTCT curves in infants that were tested at Hadassah hospital during the years 2011-2015. Data were gathered for: FVC ( Forced Vital Capacity), FEV0.5, FEV0.75 (Forced Expiratory Volume at 0.5 and 0.75 seconds, respectively), and for the following flows: peak flow (PF), and the flows at 50%, 75% and 85% of the FVC (FEF50%, FEF75%, FEF85%) and the respective parameters for all of the above parameters on the RVPE loops (table 1).

**Results:** Of 166 tests meeting the inclusion criteria, 35% did not have valid RVTCT curves, as opposed to 8.4% of the RVPE group. In 107 tests with valid curves, only a third of the trials ended in a valid RVTCT curve, compared to 70% of RVPE loop trails. Correlations:

![Figure 1](image.png)

**Correlations:** The flow at certain Percentage of Forced Vital Capacity

**Conclusions:** RVPE is easier to perform and correlates reasonably with the RVTCT.

**Table 1: Raised-Volume Forced vs Passive expiration techniques and their correlation**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RV-Passive Curve</th>
<th>RV-Forced Curve</th>
<th>Pearson Correlation (r)</th>
</tr>
</thead>
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<td>FVC</td>
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<tr>
<td></td>
<td>PEV 0.5 sec</td>
<td>FEV 0.5 sec</td>
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<td></td>
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<td></td>
<td>PEV 1 sec</td>
<td>FEV 1 sec</td>
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<tr>
<td>Flow*</td>
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<td>Forced-PF</td>
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<tr>
<td></td>
<td>PEF 50%*</td>
<td>FEF 50%**</td>
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<tr>
<td></td>
<td>PEF 75%*</td>
<td>FEF 75%**</td>
<td>0.714</td>
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<td>PEF 85%*</td>
<td>FEF 85%**</td>
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<tr>
<td>Relations</td>
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<td>FEV 0.5/FVC</td>
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</tbody>
</table>

J-157 | Agreement between Tuberculin Skin Test and Interferon-Gamma Release Assay for the Diagnosis of Latent TB Infection among under Fifteen-Year-Olds

**Objective:** To verify the concordance between tuberculin skin test (TST) and interferon-gamma release assay (IGRA) results for the diagnosis of latent tuberculosis infection (LTBI) in individuals aged up to 15 years old.

**Methods:** In this cross-sectional study, we recruited immunocompetent, HIV-negative subjects exposed to smear-positive adult index cases with pulmonary TB. TST was performed with the purified protein derivative (PPD) RT23 (Statens Serum institute, Copenhagen, Denmark), whereas IGRA was performed through QuantiFERON® TB Gold in Tube (QFT-GIT; Qiagen, Hilden, Germany). All procedures were performed according to manufacturers’ recommendations by an experienced professional, blinded to clinical and radiological findings. TST was considered positive if induration > 10 mm and QFT-GIT
when value of the TB antigen minus nil control was > 0.35 IU / ml and > 25% of nil value. Agreement between the results of the TST and QFT-GIT tests were assessed through Kappa statistics.

Results: Among the 42 children evaluated, 22 (52.4%) were girls, 15 (35.7%) were under five when exposed to index cases, 26 (61.9%) were children or grandchildren of the index cases and 30 (71.4%) were exposed to the index case more than 1 day per week during the symptomatic period and before treatment with antituberculous drugs. Eleven out of the 42 studied patients (26.2%) had a positive result to TST and/or IGRA; none of them had active TB. Overall, the simple percent agreement between TST and QFT-GIT was 95.2%, while Kappa value was 0.87 (P < 0.001, 95% CI, 0.57-1.0). Specifically for under-fives, agreement between the two tests was slightly lower (simple percent 93.3% and Kappa= 0.84 (P = 0.001, 95% CI, 0.34-1.0).

Conclusion: As the level of agreement between TST and IGRA was quite high, both tests might be used for the diagnosis of LTBI in children at the onset of the symptoms. However, the same cannot be said for the under fives; therefore, better diagnostic tools are needed for this age group.

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J-159 | Relationship between Malocclusion and Airway Volume of Children in The Mixed Dentition Period

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Objective: The aim of this study was to evaluate the influence of malocclusion to upper airway volume in children during the mixed dentition period.

Methods: From 2014 to 2018, 39 patients in the mixed dentition period (at the age of 8-10 years) who underwent cone beam computed tomography at our dental clinic were included in the study. Children for whom malocclusion treatment had already been initiated were excluded. The upper airway volume was defined as the total volume of nasopharynx and oropharynx as measured with SICAT AIR. Malocclusion was classified according to the anterior dentition into the following groups: crowding group (n = 7), protrusion group (n = 10), deep bite group (n = 11) and crossbite group (n = 11). The upper airway volume was compared among these groups. Statistical significance of differences among the groups was tested by the Mann-Whitney U-test.

Results: The upper airway volume (mean ± SD) was 13921.7 ± 4037.8 mm³, 11847.8 ± 4288.0 mm³, 10654.5 ± 3368.8 and 9617.2 ± 2898.5 mm³ in the three groups, respectively. The upper airway volume was reduced in the order of simple crowding group > protrusion group > deep bite group > crossbite group. Furthermore, the reversed occlusion group’s volume was significantly lesser than the crowding group’s volume (P < 0.05).

Discussion: Our results indicate that upper airway volume in the protrusion and deep bite and crossbite groups is lesser than in the crowding group. This is probably due to severe malocclusion caused by lowering of the tongue position owing to disturbed nasal respiration in the presence of reduced upper airway volume.

Conclusion: We suggest that malocclusion in children is associated with upper airway stenosis.

J-164 | Profiles and Determinants of Nasal Microbiota in Healthy Chinese Toddlers

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Background: Upper airway microbiota undergoes rapid evolution during the first 2 years of life, which may alter host susceptibility for respiratory tract infections and airway allergies. In contrast to microbiome in infancy, there is limited data on upper airway microbiota composition of healthy toddlers. This study investigated the profiles and determinants for nasal microbiota in Chinese toddlers.

Methods: Flocked nasal swab samples were collected at baseline from subjects who participated in a nutritional intervention study (registration identifier: NTR4779), which were stored at -80°C until analysis. DNA isolated by mechanical lysis was subjected to Illumina sequencing of the V4 region of the 16S rRNA gene. Samples with less than 6000 bp reads in amplicon sequencing were excluded from further analysis. Possible associations between host factors and nasal microbiota composition were analyzed using non-supervised and supervised statistical methods.

Results: A random subset of 160 participants aged 18.2 ± 4.9 months, with 72 (45%) being males, were identified for this microbiome analysis. One hundred and forty-three (89.4%) children were ever breastfed for 4.0 ± 4.7 months. Forty-five (28.1%) children had passive smoking exposure. Based on DNA quantity and PCR quality, 94.4% of samples were eligible for microbial analysis. Following feature selection by abundance and coefficients of variation, we identified seven dominant bacterial genera that included Corynebacterium, Dolosigranulum, Moraxella, Streptococcus, Staphylococcus, Haemophilus and Helcococcus. These genera were also observed in deep nasopharyngeal swabs of Dutch children (Biesbroek et al, 2014; Bosch et al, 2016). We observed considerable heterogeneity of these microbes in nasal samples. Subjects’ age accounted for 0.72% of the variance seen in microbiota composition (P = 0.005). However, none of the following factors significantly explained the variation in microbiota composition: gender, breastfeeding ever, presence of siblings, daycare attendance, history of neonatal problems, occurrence of allergic diseases and passive smoking exposure.
**Tracheobronchomalacia in Young Children**

Tomography Imaging Is Useful for the Diagnosis of

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**Background:** Post-bronchoscopy fever in children is a commonly described complication (14.2%-48%). Risk factors for fever are well described and include young age and abnormal BAL findings. However, anesthetic choice as a risk factor for fever has not yet been reported.

**Objectives:** The aim of our study was to explore the role of sedative agents as a risk factor for fever during the 24 hours after the procedure. Additional risk factors were investigated as well.

**Methods:** A retrospective analysis of files of immunocompetent children that underwent elective bronchoscopies during the period of 2013-2017 in Safra’s Children’s Hospital was conducted, and a statistical analysis was performed.

**Results:** One hundred and thirty children were enrolled, 56.15% of patients were treated with Sevoflurane. Post-bronchoscopy fever occurred in 23.85% of cases, 35.62% of patients receiving Sevo-flurane developed post-bronchoscopy fever compared to 8.77% in the non-Sevo-flurane group (RR= 4.06, CI [1.66-9.91], P = 0.05). Multivariate analysis of the data (comorbidities, sedation choice, age, indication for performing the procedure, BAL performed and its findings, post-prematurity, FTT, and medications) suggested that only Sevo-flurane and young age were statistically significant risk factors for fever. Chronic treatment with Montelukast was found to be a protective factor against fever.

**Conclusions:** We conclude that post-bronchoscopy fever is probably an inflammatory noninfectious process. Sevo-flurane is a significant risk factor for developing post-bronchoscopy fever by generating such inflammation. The same mechanism may also explain why Montelukast has a protective role.

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**Fever Post Flexible Bronchoscopy – Finding the Usual Suspect**

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**Introduction:** Tracheobronchomalacia (TBM) is not a common disease, although several studies have reported that TBM is more prevalent than previously thought. Severe airway malacia is usually recognized and diagnosed in early infancy; on the other hand, cases that are not severe are often misdiagnosed. Flexible bronchoscopy (FB) is the gold standard for the diagnosis of TBM. However, this procedure is invasive and requires sedation and special techniques, thereby limiting its use. Alternatively, dynamic four-dimensional computed tomography (4D CT) imaging is potentially a noninvasive modality. This study compares the findings of 4D CT with those of FB in the assessment of TBM.

**Aim:** To assess the accuracy of 4D CT in detecting TBM in young children.

**Methods:** Fifteen patients underwent 4D CT and FB at the Department of Pediatric Pulmonology and Allergy of Osaka Women’s and Children’s Hospital from April 2015 to December 2018. TBM was retrospectively reviewed as present or absent in 3 anatomic segments: trachea and the right and left main bronchi. TBM was defined as > 50% reduction of the airway lumen.

**Results:** The study population comprised 15 patients (8 males and 7 females) with ages ranging from 1 month to 5 years (median: 9 months). The most common presenting symptom was recurrent wheezing. Eleven patients were diagnosed with airway malacia from the FB findings. Among the others, 1 patient had gastroesophageal reflux disease, 2 patients had complete tracheal rings, and 1 was idiopathic. The overall diagnostic accuracy of 4D CT compared to FB was 91% (41/45 possible segments). The agreement was not different between that for the trachea and the left and right bronchi. 4D CT indicated no false-positive results.

**Conclusions:** 4D CT is a highly accurate and reliable noninvasive imaging modality for evaluating TBM in young children.

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**Sonographic Characteristics of Consolidation in Children**

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**Background:** Lobar pneumonia is a serious infectious disease and causes severe morbidity and morbidity in children. Conventionally, radiological imaging is the test of choice for diagnosing pneumonia and follow-up. Our objective was to determine the clinical application of chest sonography in pediatric patients with particular emphasis on sonographic characteristics in consolidation in lobar pneumonia in children.

**Method:** The study was conducted comparing chest sonography in 35 children from birth to 18 years of age suspected of having lobar pneumonia in a tertiary-teaching hospital. All ultrasound examinations were conducted using a 3 to 8 MHZ probe. Chest sonography was performed by 2 authors (KSH and CWT). Chest sonography was interpreted independent of the radiographic findings. We included 35...
patients who had the final diagnosis of lobar pneumonia. All of these patients had conventional clinical examination plus chest radiography and chest sonography.

**Results:** A total of 35 patients were included, ranging between 4 months to 18 years old with a mean and standard deviation of 5.3 ± 3.1 years old. Affected lobes were respectively; 3 on the right upper, 7 on the right middle, 10 on the right lower, 4 on the left upper and 11 on the left lower lobe. Sonographic signs that indicated lobar pneumonia were consolidation in the individual lung lobes. Cases with lobar pneumonia and consolidation showed scattered air bronchogram. There was no air entry with mixed fluid and tissue density, loss of nature curvature of lung surface with shrinkage of lung tissues.

**Conclusion:** Chest ultrasonography is a useful, safe and accurate diagnostic tool for evaluating children with lobar pneumonia and could well delineate consolidated lung in the affected lobes.

11 | THERAPEUTIC PROCEDURES

K-50 | Outcomes of Home Positive Airway Pressure (PAP) in Management of Obstructive Sleep Apnea in a Pediatric Unit in Hong Kong

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**Aim:** To study the characteristics of pediatric patients who had initiated nocturnal Positive Airway Pressure (PAP) for treatment of OSAS and to assess the outcomes of PAP therapy.

**Methods:** Retrospective review of clinical data of patients aged 1 month to 18 years having initiated PAP for treatment for OSAS in the pediatric unit of a public hospital in Hong Kong. Treatment outcomes of polysomnographic parameters and symptoms pre- and post-therapy were analyzed and patient’s adherence was evaluated.

**Results:** Forty-five patients having initiated PAP during January 2009 to December 2016 were included. There was an increasing number of patients being initiated on PAP therapy for treatment of OSAS over the years. The study population was predominantly male with two-thirds over 12 years old. Craniofacial or syndromal conditions were mostly present in young children less than 5 years old while obesity was more common in adolescents. Of the treated patients, 75.6% had allergic rhinitis. Comparing symptoms before and within 6 months after PAP trial, there were significantly less patients with complaints of habitual snoring (95.6% vs. 8.9%, P < 0.01) and excessive daytime sleepiness (42.2% vs. 11.1%, P < 0.01). There was significant improvement in PSG parameters with mean OAHI decreasing from 21.5±18.5/hour TST to 1.6±1.9/hour TST (P < 0.05) and mean SpO2 (oxygen saturation) nadir increasing from 80.6% ±10.4% to 90.9%±5.7% (P < 0.05) after PAP therapy. Within 6 months of follow up, 57.8% of the patients adhered to PAP satisfactorily while the adherence dropped to 37.8% at the time of the latest follow-up. Satisfactory usage established before 6 months was associated with favorable long-term outcomes of satisfactory usage or cessation of therapy due to improvement at the latest follow-up (chi square test P = 0.008). The commonest reported reason for non-adherence was due to nasal obstruction.

**Conclusion:** Nocturnal PAP is an effective treatment option for OSAS especially in children with comorbid conditions. Our findings of high prevalence of coexistence of allergic rhinitis and complaints of nasal obstruction warrant further investigations on management strategies to improve adherence in our local population.

K-93 | Implantation, Management and Long-Term Outcomes of Tracheobronchial Stent with Flexible Bronchoscopy in Infants < 5 kg: A 14-Year Experience

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**Background:** Tracheobronchial (TB) lumen narrowing may require prolonged positive-pressure ventilation, endotracheal tube intubation or even surgical interventions. Therapeutic flexible bronchoscopy (TFB) of balloon-expandable metallic stent (BEMS) placement and subsequent management with forceps, laser and balloon dilatation are less invasive and may be helpful. This study aimed to analyze the placement, follow-up management with TFB and long-term outcomes in small infants with BEMS.

**Methods:** This retrospective study reviewed the medical records and associated TFB videos of infants with a maximum BW of 5.0 kg who had TB BEMS placement from January 2005 to December 2018 at our institution. All these TFB procedures were supported with a novel Noninvasive ventilation of nasopharyngeal oxygen with intermittent nose closure and abdominal compression.

**Results:** Forty-three BEMSs were placed in 26 infants. The mean BW and mean age were 4.0 ± 0.8 kg and 4.9 ± 2.7 months, respectively. There were 21, 9 and 13 stents located in trachea, carina and mainstem bronchi, respectively. Seven infants with 13 stents died without obvious stent-related mortality. Among them, 12 stents in 8 children were successfully retrieved by rigid endoscopy. At placement, the diameters of the 11 remaining tracheal and 11 remaining bronchial stents were 7.5 ± 1.1 (4–10) and 5.4 ± 0.9 (4–8) mm, respectively. These implanted BEMSs could be gradually and significantly (P < 0.01) expanded. At the end of this study, all the remaining 18 stents in 12 infants could be kept functional. The diameters of the 11 remaining tracheal and 11 remaining bronchial stents were 9.7 ± 2.0 (8–14) and 7.0 ± 1.4 (4–10) mm, respectively.

**Conclusion:** BEMSs are practical and effective in select small infants with benign TB narrowing and can be safely implanted and managed with TFB, and finally retrieved by rigid endoscopy.
Keywords: balloon dilatation; balloon-expandable metallic stent; flexible bronchoscopy; nasopharyngeal oxygen with intermittent nose closure and abdominal compression.

K-97 | Single Port Video-Assisted Thoracoscopic Surgery as an Option for Pediatric Primary Spontaneous Pneumothorax, a Single Center Experience

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Background: Primary spontaneous pneumothorax (PSP) is a significant clinical problem in pediatric populations. Patients with recurrent PSP or persistent air leakage require video-assisted thoracoscopic surgery (VATS) for bullectomy and pleurodesis. Compared to conventional triple-port VATS (TP-VATS), single port-VATS (SP-VATS) has become a trend in adult populations owing to a smaller surgical wound, less pain and a more rapid recovery period. The aim of this study is to evaluate the clinical effectiveness of single port VATS for pediatric patients with primary spontaneous pneumothorax.

Methods: We retrospectively reviewed pediatric patients (age less than 18 years old) who received VATS for bullectomy and pleurodesis for recurrent PSP between January-May 2015 to September 2018 at the China Medical University Children’s Hospital. The surgical outcome of conventional TP-VATS and SP-VATS were compared and analyzed.

Results: A total of 63 surgeries were performed in our institute, including 12 cases of TP-VATS and 51 of SP-VATS. The patients’ median age was 16±1.15 years old, and 92.3% patients were male (Male to Female ratio = 12:1). The site of the pneumothorax was 62.9% at the left side, 32.3% at the right side, and 4.8% at both sides. The operation time (109.3±23.9 for TP-VATS - 62.9% at the left side, 32.3% at the right side, and 4.8% at both sides) was not significantly different between these two groups. The ipsilateral recurrence rate was 39.2 minutes for SP-VATS, P = 0.258) and postoperative hospital stay (3.1±0.87 vs. 3.57±1.01 days, P = 0.251) were not significantly different between these two groups. The ipsilateral recurrence rate was slightly higher in the TP-VATS group compared to the SP-VATS group (33% vs. 13.7%, OR= 2.36, P = 0.095) The median recurrence time after surgery was longer in TP-VATS than in SP-VATS (188 [156.3 - 294.8] days vs. 141.5 [74.5-245.5] days, P = 0.096). Females were more likely than males to have ipsilateral recurrence in the SP-VATS group (M:F = 10.4% vs. 40%, OR= 5.73, P = 0.124).

Conclusion: SP-VATS is as effective as TP-VATS for treating pediatric patients with recurrent PSP. Both groups have similar operation time and postoperative hospital stay; nevertheless, SP-VATS is associated with lower recurrence rate and longer recurrence time.

K-195 | Endobronchial Foreign Body- An Important Cause of Respiratory Symptoms in Children and its Management by Flexible Bronchoscopy

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Introduction: Foreign body (FB) aspiration in the airway is a common occurrence in the pediatric age group; however, it is not always diagnosed (especially in radiolucent FB) due to nonspecific symptoms of varying severity. Often the symptoms are subtle and mistaken for other more common conditions such as pneumonia and asthma and does not respond as expected to standard therapy and presents a diagnostic challenge.

Aim: This study aimed to emphasize the importance of considering endobronchial foreign body as a cause of persistent or recurrent respiratory symptoms in children and to outline the clinical evidence of the utility and feasibility of flexible bronchoscopy for endobronchial FB management in children.

Methods: This prospective study was performed on children (aged 6 months to 6 years) having recurrent or long standing, non-resolving or partially resolving respiratory complaints who underwent flexible bronchoscopy for suspected FB from July to December 2018 in a tertiary care hospital in Bangladesh. History, clinical, radiological, bronchoscopic findings and immediate effect after bronchoscopy were analyzed.

Results: Among a total of 11 children, only 18.2% (n = 2) had a definite history of FB aspiration. The most frequent symptom was paroxysmal cough (72.7%) followed by wheezing, stridor and recurrent pneumonia. FB was found in 54.5% (n = 6) of children and removed successfully by Dormia basket in 5 children and 1 by grasping forceps. The most common (n = 3) FB was peanut. Other foreign bodies were a plastic Tasbih bead, a pencil torch light filament and a custard apple seed. Respiratory symptoms improved after removal of foreign bodies in all cases. During the procedure, transient hypoxia developed in 2 children which was alleviated by temporary cessation of the procedure.

Conclusions: The possibility of foreign body aspiration should be considered in any child who presents with persistent or recurrent respiratory symptoms. Flexible bronchoscopy is documented as a crucial diagnostic and safe therapeutic tool for foreign body management in the pediatric age group.
Acute, female BALB/c mice were intraperitoneally sensitized with ovalbumin on days 1, 2 and 3, and received intranasal OVA challenges on days 14, 17, 21, 24 and 27. The sensitized mice were divided into different groups according to the course of designed airway changes. FIP-fve groups of sensitized mice received 200μg of FIP-fve on days 1 to 14 (pretreatment) and the other groups of sensitized mice received the same drug on days 14 to 27 (posttreatment). In the chronic model, the mice were intraperitoneally sensitized with ovalbumin on days 1, 2 and 3, and received intranasal OVA challenges on days 14, 17, 21, 24, 27, 60, 69, 71, 73, 74 and 75. However, FIP-fve groups of OVA-treated mice were given FIP-fve. The pretreated groups were given FIP-fve on days 1 to 14 and days 45 to 60. The post-treated groups were given FIP-fve or a corticosteroid on days 14 to 28 and days 60 to 75.

Results: According to the results, TGF-β, TNF-a, IL-8, IL-17, CXCL-1, CXCL-10, CCL-17 and CCL-22 were highest in the chronic stage during acute and chronic stages of asthma. Moreover, in the FIP-fve groups, Th2 cytokines and TNF-a, IL-8, IL-17, TGF-β, CXCL-1, CXCL-10, CCL-17 and CCL-22 were decreased significantly while IL-22 increased significantly in the FIP-fve groups during the chronic stage.

Conclusions: There are many different immune responses in the different stages of asthma. Therefore, our findings could be the marker to distinguish between acute or chronic stage in asthma. However, FIP-fve can improve asthma through immune regulation not only in acute, but also in chronic stages. Hence, FIP-fve might be an alternative therapy that can be used in the different stages in allergic airway diseases such as asthma.
Introduction: Community-acquired pneumonia can be complicated by empyema thoracis. Prompt diagnosis and management will influence the outcome. We intend to compare the management of empyema thoracis in Malaysia to local and international guidelines.

Methods: Retrospective descriptive study of children diagnosed with community-acquired pneumonia complicated by empyema thoracis, who were admitted to Penang Hospital (northern regional tertiary hospital with Pediatric Respiratory services), Malaysia from October 2017 to October 2018. Adherence to the standards for diagnosis, investigation and management were analyzed.

Results: Fifteen patients were reviewed, of which 86% (13/15) were less than 5 years old. Approximately 53% (8/15) presented before Day 5 of illness and only 40% (6/15) received outpatient antibiotics. Most patients were diagnosed with empyema thoracis based on the chest radiograph during the first week of illness (67%, 10/15 cases, median: Day 5 of illness). All patients were subjected to thoracic ultrasound for confirmation and staging of effusion by the second week of illness (Median: Day 8.5 of illness). Chest drainage was performed in 67% (10/15) of patients, however, first insertion was at median Day 10 of illness due to late presentation. Urokinase was administered in 47% (7/15) of patients with a failure rate of 57% (4/7). They were unsuitable for urokinase intervention due to late presentation and referral or clinically unstable upon diagnosis. Most patients underwent open lateral thoracotomy and decortication (73%, 11/15 cases) with prolonged median hospital stay of 21 days (range 14 - 52 days) while those who had successful urokinase therapy had a median hospital stay of 16 days (range 14 - 23 days). This may be due to late presentation, unsuccessful urokinase therapy and inaccessibility of Video Assisted Thoracoscopic Surgery (VATS) in Penang Hospital. One patient recovered with only antibiotic therapy (without any urokinase or surgical intervention).

Conclusion: Empyema thoracis is associated with high morbidity but rarely mortality. There were various limitations in our center which eventually led to surgical management of empyema thoracis. In the presence of a Malaysian consensus guideline, educational courses need to be reinforced to ensure better understanding, proper implementation and improve outcomes.

Objective: To determine the correlation of Fingertip Portable Pulse Oximetry versus Arterial Oxygen Saturation Result of patients with Pediatric Community-Acquired Pneumonia ages 2 months to 18 years old seen at the Emergency department of a Tertiary Government Hospital.

Setting: QCGH Medical Center.

Subjects: All pediatric patients aged 2 mos. - 18 years seen at the QCGH - Emergency department presented with PCAP C & D.

Methods: O2 saturations of patients with PCAP C & D using only one MD FS20A brand of Fingertip PPO and ABGs were obtained and recorded. O2 saturations by Fingertip PPO and arterial oxygen saturation were then compared using Pearson’s correlation coefficient.

Statistical Analysis: SPSS version 10 for Windows was used. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean ± SD were generated. Analysis of the different variables was performed using Pearson’s correlation and McNemar test.

Results: A total of 168 subjects were included. Mean age was 2.94 years. Mean RR was 58.41. There was a strong positive correlation of 0.72 noted in the comparison of the results of O2 saturation pulse oximeter and arterial blood gas result as proven by the p value of < 0.001. The oxygen saturation reading of Fingertip PPO was comparable with arterial oxygen saturation. As oxygen saturation in fingertip PPO increased, arterial oxygen saturation result also increased or vice versa.

Conclusion: This study showed a direct correlation between the O2 saturation obtained from Fingertip Portable Pulse Oximeter with that of the oxygen saturation in arterial blood gas.

Keywords: O2 saturation, portable pulse oximeter (PPO), SaO2.
and all children were assessed for serum zinc levels. The primary outcome was the prevalence of serum zinc deficiency. Children having zinc deficiency were recruited for the study of the effect of oral administration of zinc 20 mg for 2 weeks. The secondary outcomes were incidence and duration of acute upper respiratory and acute lower respiratory infections per child-year and side effects after giving zinc therapy.

**Results:** There was no significant difference with regard to mean age, weight, height and modified Kuppuswamy classification of family status between zinc deficient and non-zinc deficient groups. There was a significant difference in mid arm circumference between zinc deficient and non-zinc deficient groups. Also the number of episodes of acute upper respiratory infections (AURI) and mean duration of acute respiratory infection (ARI) was significantly different in the two groups. There was no significant difference in acute lower respiratory infection (ALRI) episodes in the two groups. After zinc supplementation in zinc deficient children, there was a significant decrease in the number of episodes of AURI, ALRI and mean duration of ARI at 6 months after supplementation as compared to the preceding 6 months before supplementation.

**Conclusion:** This study sheds light on the efficacy of short course prophylactic zinc supplementation in reducing the burden of ARI among zinc deficient children. Future studies should assess the effectiveness of delivering prophylactic zinc supplementation at scale, comparing the feasibility and cost benefit of short course and continuous regimens.

**M-151 | Acute Respiratory Distress Syndrome in Pediatric Septic Shock**

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**Background:** Acute Respiratory Distress Syndrome (ARDS) is a serious complication of sepsis and septic shock. This syndrome increases the mortality rate of sepsis. The exact diagnosis and treatment of ARDS contribute to a reduction in mortality from hypoxia and from sepsis in general.

**Objectives:** To describe the ARDS characteristics in children with septic shock at a teaching hospital in Viet Nam.

**Methods:** A descriptive prospective study of ARDS in children from 2 months to 15 years old with septic shock between 10/2008 and 4/2011 in the emergency department and intensive care unit at Children’s Hospital 1 in Ho Chi Minh city, Viet Nam. Septic shock was diagnosed according to criteria of the International Pediatric Sepsis Consensus Conference in 2005. We used the Berlin definition to recruit ARDS cases with at least 2 samples of blood gases separated by 12 to 24 hours showing a ratio of \( \frac{\text{PaO}_2}{\text{FiO}_2} \leq 300 \text{ mm Hg} \). We excluded patients with congenital heart disease and heart failure.

**Results:** Eighty-three children were included. Males represented 48.5%, average age was 31.7 ± 4 months. The rate of ARDS was 39.8%. The mortality rate in children with this syndrome was 78.8%. Septic shock with ARDS had a higher mortality rate than septic shock without this syndrome (26%). Most children with this syndrome were in the moderate and severity range (78.8%); 81.8% were ventilated. The tidal volume was 8.3 ± 1.6 ml/kg and average PEEP was 8.6 ± 2.2 cmH2O, the medium FiO2 was 90.7 ± 16.4 %; 36.4% of cases had a tidal volume of 8 to 10 ml/kg. There were no differences in tidal volume, PEEP and FiO2 between survivor and non-survivor cases.

**Conclusions:** ARDS had a high prevalence in pediatric septic shock and the mortality rate among septic shock cases with this syndrome is still very high.

**Keywords:** septic shock, acute respiratory distress syndrome
other combinations of congenital airway problems. All cases (n = 16) of foreign body aspirations were also successfully retrieved by FB. The number of procedures increased every year, 2 in 2012, 23 in 2013, 62 in year 2014, 96 in 2015, 126 in 2016 to 177 in 2017, and 104 in 2018.

Conclusion: Flexible bronchoscopy is a very helpful tool in the management of pediatric airway problems. There is an increasing need for the procedure. We must start and improve the procedure in Indonesia to enhance the comprehensive management of childhood airway problems.

Keywords: airway problems, pediatric flexible bronchoscopy, diagnostic, therapeutic tools, complication.

M-170  |  Sociodemographic Features and Diagnosis of Tuberculosis in Nigerian Children

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Background: The World Health Organization recommends that bacteriological confirmation of TB should be sought whenever possible as indicated by clinical presentation. This is however not usually possible due to the paucibacillary nature of childhood TB and the difficulty in getting sputum from young children. In Nigeria at present, the diagnosis of TB in children is made using the TB score chart which is based on clinical findings.

Objective: To assess the sociodemographic features and the diagnostic methods of childhood tuberculosis in Nigerian children.

Methods: This was a retrospective cross-sectional study. Data were extracted from the case notes of children managed for tuberculosis in the Pediatric ward and the DOTs clinic of UUTH from January 2013 to December 2017. Information extracted from the case records included the patients’ epidemiological data, duration of illness, signs and symptoms, TB score, chest radiograph findings and microbiological diagnosis. Pulmonary tuberculosis was defined as a symptomatic child with: (1) bacteriologically-confirmed tuberculosis, (2) radiologically-confirmed tuberculosis, or (3) probable tuberculosis (as defined). Probable TB was defined as a TB score > 7 and a good clinical response to antituberculosis treatment in the absence of bacteriological confirmation or radiological certainty. Radiologically-certain TB was defined as agreement between two independent radiologists that the chest X-ray indicated certain tuberculosis and a TB score 1 to 6 in the absence of bacteriological confirmation and a good clinical response to antituberculosis treatment.

Results: Thirty-three patients met the criteria for TB as defined in this study. The total inpatients from January 2013 to December 2017 were 3276, while the total number of respiratory cases for this period was 1307. Therefore, the prevalence of TB was 1% and 2.5% of the total ward admissions and respiratory admissions respectively for the period studied. Most patients (56%) were in the 0 to 5 year age group, with a predominance of males (72%). Ten patients (31%) had a positive history of contact with an adult with chronic cough and 30 patients (94%) had BCG vaccination. Cough (72%) was the commonest symptom recorded with a mean duration of 13 weeks, followed by weight loss (63%) and fever (63%). Pallor (47%) was the commonest clinical sign, followed by lymphadenopathy (44%). Nine patients (28%) had abnormal chest signs. Two patients (7%) had a positive sputum AAFB result, geneXpert was positive in the gastric aspirate sample of one patient and negative for all the sputum and lymph node aspirate results. The chest radiograph was suggestive of TB in 21 (84%) patients while TB-HIV coinfection was present in nine (29%) patients. Tuberculin skin test (Mantoux) measurement ranged from 0-23mm with a mean ± SD of 10±7.8. Nine (53%) of the patients had a Mantoux result of 10mm and above. The TB score ranged from 6 to 17 with 96% of the patients having a TB score of seven and above.

Conclusions: The microbiological confirmation of TB in Nigerian children is grossly inadequate and the TB score chart and TB algorithm is still the preferred method of TB diagnosis in Nigerian children.

M-185  |  Characteristics of Community-Acquired Pneumonia in Children: Experience from a Tertiary Unit in a Lower Middle-Income-Country

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There is a paucity of data regarding childhood pneumonia in Asia and this is more so in South Asian countries such as Sri Lanka.

The objective of the study was to describe the outcome of the children admitted with acute community-acquired pneumonia to a tertiary unit in the country.

This is a retrospective study conducted in children who presented to the professorial pediatric unit of the Teaching Hospital, Peradeniya from March 1st 2016 to August 30th 2017, fulfilling diagnostic criteria for community-acquired pneumonia requiring in-hospital care.

Results: The study population included 127 children, aged between 1 month and 14 years; 58% were girls and 42% boys. There were 42, 69 and 15 patients in the age categories of 1 month to 1 year, one to 5 years and more than 5 years respectively. Bronchopneumonia was diagnosed in 47% of patients while 44% had lobar pneumonia. Atypical pneumonia
was diagnosed in 3%. The diagnosis of the remaining patients was undetermined lower respiratory tract infection. All patients fulfilled the admission criteria and were treated according to the unit guidelines which are based on British Thoracic Society guidelines and Infectious Diseases Society of America (IDSA) pediatric guidelines. Accordingly, antibiotics had been changed to second line agents if there was no/inadequate response by 48 to 72 hours. This included addition of azithromycin or clarithromycin and addition of vancomycin to cover atypical organisms and resistant pneumococcal infections respectively.

In our sample, 35% (44) of patients responded to first line antibiotics including cefuroxime, cefotaxime, ceftriaxone or co-amoxiclav according to unit policy, 52% (66) required second line antibiotics and 13% (17) needed treatment beyond second line agents due to complications.

According to the unit policy to transfer to ICU which is based on IDSA guidelines, 2% of the patients needed intensive care. HDU care was given for 38% of patients who required supplemental oxygen to maintain pulse oximetry above 92%.

Analysis of length of hospital stay indicated that 25% of the patients were discharged by the 4th day and 61% were hospitalized for 5 to 9 days. There was no mortality among the patients evaluated.

Conclusions: This retrospective analysis revealed that childhood community-acquired pneumonia is associated with significant morbidity and is an economic burden. The majority (65%) needed therapy beyond first line antibiotics which may indicate significant antibiotic resistance.

Reflections and proposals: The study sheds light on indirect evidence of significant antibiotic resistance and the need for surveillance data on drug sensitivity and a national policy on antibiotic use. Moreover, it highlights the importance of introduction of the pneumococcal vaccine to the national program of immunization.

M-190 | Association between Early Hospitalization Due to Human Metapneumovirus Infection and Asthma Symptoms during School Age in Costa Rica

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Wheezeing episodes due to viral infections that occur early in life have been identified as risk factors for the development of asthma in childhood. Human Metapneumovirus (hMPV) is one of the most frequently detected viruses in children under 2 years of age in Hospital Nacional de Niños of Costa Rica.

Objective: This study aimed to determine the prevalence of recurrent wheezing and asthma in a group of children with a history of hospitalization due to low respiratory tract infection by Metapneumovirus.

Methods: We performed a cross-sectional study that included all patients that were hospitalized before the age of two, and tested positive for hMPV in the immunofluorescence of nasopharyngeal aspirate, between 2008 and 2011. A telephone questionnaire was performed to inquire about the prevalence of wheezing episodes and diagnosis of asthma of these patients at the age of 6 to 11 years.

Results: a total of 65 children were reached to complete the questionnaire. The prevalence of asthma in this group was 41.5%, with up to One-third of the children being male (66%). We found that 66% of the patients reported having at least one other episode of wheezing in the first 12 months after discharge. The mean age of hospitalization was 7.3 months, and 81.4% were younger than 1 year of age. We did not find an association between younger age at the time of hospitalization, prematurity or secondhand smoke exposure and asthma diagnosis at school age. The children who were exclusively breastfed in the first 6 months of life were found to have a lower prevalence of asthma later in childhood (OR= 0.3, CI, 95%, 0.1-0.9). On the contrary, children that used antibiotics in the first 2 years of age had a higher prevalence of asthma (OR= 3.2, CI, 95%, 1.1-10.7). We found a high percentage of patients who were exposed to secondhand smoke at home at the time of hospitalization (35.3%) and during pregnancy (47.6%), yet we could not demonstrate an association with the diagnosis of asthma. Up to 32.3% of the patients of school age reported having respiratory symptoms during exercise, and 30.7% had nocturnal symptoms.

Conclusion: The prevalence of asthma in children with a previous respiratory infection by hMPV is very high, and twice of that reported nationwide (21.9%). Other associations found were that children who used antibiotics in the first 2 years of life had a higher prevalence of asthma, while breastfeeding resulted in a preventive association. The prevalence of secondhand smoke found in this study exceeds the latest reported prevalence in the country (19.7%).

M-214 | Etioclinical Profile of Recurrent and Persistent Pneumonia in Children

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Introduction: Recurrent and persistent pneumonia is one of the common reasons for referral and continues to be a major challenge. There are limited data on underlying causes of persistence or recurrence of pneumonia in children. This study aimed to ascertain the etiology and clinical profile of recurrent and persistent pneumonia in tertiary level hospitals in Dhaka city.

Methods: A descriptive cross-sectional study conducted in admitted recurrent and persistent pneumonia patients in tertiary level hospitals in Dhaka City during June 2015 to May 2016. Among the enrolled
population, 100 recurrent and persistent pneumonia patients were finally studied and analyzed after completing the inclusion criteria. Recurrent pneumonia was defined as 2 or more episodes of pneumonia in a single year or 3 or more episodes ever, with radiographic clearing between occurrences. Persistent pneumonia was defined as features of lower respiratory tract infection with radiological evidence of infiltrates or consolidation in lungs persisting for 30 days or more, despite receiving antibiotics for minimum 10 days. The following investigations such as CXR, CBC with film, TB screening, CRP, blood culture, USG of chest, HRCT, bronchoscopy, contrast swallow of esophagus in T position, stool for fecal fat, sweat chloride test, serum IgG, IgA, IgM level, T-cell, B-cell marker, echocardiography, pleural fluid study, X-ray PNS, saccharine test were performed according to cases. Patients were followed-up regularly.

Results: Among 100 cases, 66 were male and 34 female, ages ranging from 2 months to 14 years with a mean age of 3.92 ± 3.75 years. Seventy-six (76%) were recurrent pneumonia and 24 (24%) were persistent pneumonia. Etiology of recurrent and persistent pneumonia was determined in 83 cases. The most common causes of recurrent pneumonia were recurrent aspiration (21%: GIT aspiration -18.4% and foreign body aspiration -2.6%), cystic fibrosis (19.7%), pulmonary tuberculosis (7.9%), congenital heart disease (6.6%) and immunodeficiency (3%). The most common causes of persistent pneumonia were recurrent aspiration (37.5%: GIT aspiration -20.8% and foreign body aspiration -16.7%), pulmonary tuberculosis (12.5%), congenital cystic adenomatous malformation of the lung (4.2%), interstitial lung disease (4.2%) and cystic fibrosis (4.2%). Less common causes were immunodeficiency, cerebral palsy, spinal muscular atrophy, Down syndrome, bronchopulmonary dysplasia, BOOP, bronchial asthma.

Conclusion: Aspiration pneumonia, cystic fibrosis, pulmonary tuberculosis, congenital heart disease and immunodeficiency, congenital cystic adenomatous malformation of the lung and interstitial lung disease are common causes of recurrent and persistent pneumonia.

14  |  CLINICAL CASES

O-21  |  Esophageal Duplication Cyst Presenting with Stridor in a Child with Congenital Pulmonary Airway Malformation: A Rare Case Report

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Background: Esophageal duplication cyst (EDC) is a rare developmental aberration arising from the embryonic foregut. It may remain asymptomatic but produces a mass effect on surrounding organs if it rapidly enlarges. Congenital pulmonary airway malformation (CPAM) is a congenital lung malformation with an unknown chance of developing symptoms. Here we report a rare case of a esophageal duplication cyst with CPAM.

Case summary: A 16-month old boy with type 2 CPAM presented progressive stridor and was admitted to our hospital because of pneumonia. The patient responded poorly to antibiotics. A chest X-ray showed consolidation in the left upper lobe with tracheal right side deviation. Chest computed tomography (CT) revealed a cystic lesion 3.3 cm in size in the superior mediastinum. During the surgery, we found an isolated cystic lesion located between the trachea and bilateral carotid arteries. The cyst was completely removed and some yellowish turbid fluid was exuded when the cyst was incised. Microscopically, the cyst was lined by squamous epithelium (90%) and ciliated columnar epithelium (10%). The cyst wall presented predominantly of smooth muscle, with an absence of mucus gland, cartilage, thyroid follicle, lymphoid tissue, or thymic tissue. Finally, pathological diagnosis was confirmed as an EDC. The postoperative course was uneventful and the patient was discharged as such. One month later, at outpatient clinic follow-up visit, the patient no longer had stridor.

Conclusion: To the best of our knowledge, this is the first case report of EDC with left side type 2 CPAM. Our patient is also the only known case to recover well without lobectomy of CPAM. Despite the rarity of esophageal duplication cyst, a chest CT scan should be considered for children with persistent stridor, as well as CXR findings of the trachea deviated by a mass lesion in the mediastinum, especially for those with CPAM.

O-5  |  Resolution of Periodic Breathing in a Child with Idiopathic Pulmonary Arterial Hypertension

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Central sleep apnea (CSA) and periodic breathing are unusual findings described in pediatric patients with congestive heart failure. However, CSA has not been reported in children with pulmonary hypertension. We hereby report on a 10-year-old girl with idiopathic pulmonary arterial hypertension (IPAH) who had frequent central events in a periodic breathing fashion seen in her polysomnography, which was normalized following medical treatment leading to improvement of the pulmonary pressures.

This case supports the importance of PSG in pediatric patients with IPAH, not only to exclude OSA as a potential cause but also to assess for the presence of PB. We also show that the presence of PB might be a sign of disease severity and can be a marker of response to medical treatment. Prompt diagnoses and management of IPAH would improve SDB in this vulnerable population and might lead to a favorable prognosis.
O-23 | Suppurative Chronic Bronchitis in a Child Revealing Stat1 Heterozygous Gain of Function

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Introduction: We report the case of a 2-year-old female with suppurative chronic bronchitis associated with esophageal candidiasis revealing a rare genetic disease, recently described: heterozygous STAT1 gain of function.

Case Report: E. 2 years old, with no personal or family past history and no inbreeding, was referred for feeding difficulties (anorexia and crying for first 6 months), with failure to thrive associated with persistent wet cough since the age of 6 months and persistent mouth candidiasis (despite prolonged adequate treatment). Clinical examination found crackles in the left inferior lobe with folds candidiasis. Chest radiograph (fig 1) showed left inferior opacity consistent with partial atelectasis. Fiberoptic bronchoscopy showed thick and diffuse secretions, predominantly in left bronchial tree. Bronchoalveolar lavage was inflammatory (79% of neutrophils) with 10(8) Haemophilus influenzae. Gastroesophageal endoscopy revealed esophagitis with erythema with white deposits, consistent with candidiasis (confirmed by biopsies). The main etiologies of chronic suppurative bronchitis were ruled out: sweat test, immunological test (NFS, Ig G,A,M; IgG1-4), barium swallow, pH-meter were normal. CT scan (fig 2) showed partial atelectasis of the lingula, medial segment of the middle lobe, anterobasal segment of the right inferior lobe and bronchiectasis of the anterior segment of the right upper lobe. Because of the association of bronchiectasis and persistent candidiasis, complementary immunological tests were performed: lymphocytic phenotyping showing mild T and NK lymphopenia, with B lymphocytosis; the search for mutation on the STAT1 gene was positive (heterozygous gain of function C.1154C-T ex in exon 4 STAT1 gene).

Discussion: Heterozygous STAT1 gain of function mutations was first described in 2011. Since then, over 50 mutations were described. It is responsible for more than 50% of chronic mucocutaneous candidiasis (CMCD). The largest case series identified 274 patients(1): symptoms started around 12 months and were heterogeneous: cutaneous and airways, with mainly Staphylococcus and Pseudomonas) viral, mycobacterial infections. They touched upper and lower airways, responsible for bronchiectasis in 20% of cases. Autoimmunity can be present in 40% of cases. Morbidity is severe, and mortality is premature (cancer, cerebral aneurysm). In cases of chronic suppurative bronchitis and/or bronchiectasis, heterozygous STAT1 gain of function mutations should be searched (after excluding current etiologies), especially if associated with candidiasis.


O-28 | Tuberculosis in Children Presenting with Chylothorax

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One-third of the world’s population is estimated to be infected with Mycobacterium tuberculosis. Tuberculosis (TB) is endemic in many Sub-Saharan African countries. The burden is further made worse by the HIV scourge. The number of children with TB and its attendant complications, is equally on the rise. TB can mimic many diseases ranging from infections to malignancies. Among pleuro-pulmonary TB complications, exudative effusion is more common while chylothorax is rare and thus easily missed especially if no classical milky appearance.

We present two children from a TB endemic region, with microbiologically confirmed TB presenting with parapneumonic effusion containing chyle, that were misdiagnosed initially as pleural empyema. Tuberculous pleural effusion occurring with chylothorax is uncommon. The first case is a 12-year-old girl who presented with localized left-sided chest pain and parapneumonic effusion and a previous liver transplant and long-term intravenous catheter, who
was on chronic immunosuppressive therapy. The second case was a 10-year-old boy who was HIV-exposed but uninfected and presented with symptoms of severe complicated pneumonia with right-sided pleural effusion. These cases are instructive as they bring to the fore the importance of a full investigation of pleural fluid in suspected TB disease, and thus assist in correct diagnosis and prompt effective management.

**Q-40 | Two Pediatric Cases of Pneumocystis jirovecii Pneumonia Diagnosed by Polymerase Chain Reaction (PCR) of Gastric Lavage**

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Pneumocystis jirovecii causes respiratory infections in patients with cellular immunodeficiency. These infections are severe, with a mortality rate of 100% without treatment. Detecting P. jirovecii by bronchoalveolar lavage (BAL) or lung biopsy is the gold standard for PJP diagnosis, but these techniques are not always applicable in children because of their high invasiveness. To date, there are no reports, to our knowledge, on using gastric lavage PCR to diagnose PJP. We report two cases in which P. jirovecii was identified by gastric lavage PCR and was treated appropriately.

**Case 1** was a 1-year-old preterm, low-birth-weight male infant with Down syndrome who had undergone operation for necrotizing enterocolitis and was being administered central venous nutrition. He was started on prednisolone for pericardial effusion because of post-pericardiotomy syndrome when he was 7 months old and had been in an NICU for a year. On the day of onset of PJP, he required increased oxygen levels, and infiltrative shadows were observed in both lung fields on chest radiography. Further, his (1–3)-D glucan (BDG) levels were elevated. P. jirovecii was detected on gastric lavage polymerase chain reaction (PCR), and trimethoprim-sulfamethoxazole was administered for 3 weeks, following which his condition improved.

**Case 2** was an 8-month-old preterm, very-low-birth-weight male infant who was under central venous nutrition because of digestive tract disease. He was under treatment with hydrocortisone for 5 months because of refractory hypoglycemia and had been in an NICU. On the day of PJP onset, he showed increased oxygen demand, and chest radiography showed infiltration in both lung fields. Further, his BDG level was elevated. P. jirovecii was detected on gastric lavage PCR, and trimethoprim-sulfamethoxazole was administered for 3 weeks, following which his condition improved.

**Discussion:** About 10%-30% of immunocompetent children carry P. jirovecii in their respiratory tract, and this percentage, depending on the underlying disease, is 60%-70% in immunosuppressed patients. Therefore, when P. jirovecii is detected, it is important to distinguish infection from colonization. In these two cases, we suspected PJP on the basis of the clinical symptoms, backgrounds, BDG levels, and observations from image examination, and P. jirovecii was detected on gastric lavage PCR analysis. The patients’ condition improved after definitive therapy. To our knowledge, there has been no report of PJP diagnosis by gastric lavage PCR to date, and this diagnostic technique may be useful if it is difficult to collect lower respiratory tract specimens. Both patients had cellular immunodeficiency because of long-term steroid administration, although prophylactic treatment with trimethoprim-sulfamethoxazole for PJP had not been administered. This suggests the necessity of prophylaxis.

**Conclusion:** Gastric lavage PCR in suspected cases of PJP helps confirm PJP diagnosis in children with mild-to-moderate airway symptoms or in whom invasive examination is difficult. PJP prevention should be considered in long-term steroid users.

**Q-44 | Esophageal Lung - A Rare Cause of Recurrent Pneumonia in Children**

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We are reporting a 7-month-old boy, who was previously hospitalized with recurrent monthly pneumonia since birth until presentation to a regional tertiary center with pediatric respiratory services in Penang, Malaysia. He had persistent right middle and lower lobe opacities on chest radiograph which were attributed to collapse consolidation. Right lung hypoplasia was suspected by our unit. Computed tomography of the thorax and pulmonary angiogram demonstrated right lung hypoplasia, hypoplastic right pulmonary artery, partial anomalous left pulmonary artery and possible esophageal bronchus. Bronchoscopy showed absent right bronchus with no fistula while esophagoscopy showed a fistula from the esophagus which was suspicious of right main bronchus. The diagnosis of esophageal lung was secured. Right pneumonectomy was performed due to a short and hypoplastic right bronchus. He was discharged with no respiratory support and was well during subsequent follow-up. Esophageal lung is a rare cause of congenital pulmonary bronchopulmonary foregut malformation and scarcely reported in the literature. Although rare, children with recurrent pneumonia and persistent opacities on chest radiographs who are unresponsive to conventional medical treatment should be evaluated for congenital bronchopulmonary malformation. Anastomosis of esophageal lung to normal
tracheobronchial tree is a treatment option, though lobectomy or pneumonectomy may be considered in severe hypoplasia or abnormal vasculature. Both surgical options offer excellent outcomes.

O-62  |  Early Diagnosis of Infantile Laryngeal Cyst by Flexible Bronchoscopy

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Congenital stridor is not a rare condition in infants. Although laryngomalacia accounts for 70%-80% of congenital stridor in infants, the possibility of other etiologies should be kept in mind. We herein report a case of laryngeal cyst in a 3-month-old boy who suffered from stridor breathing sounds since one-month-old accompanied with poor feeding and failure to thrive. Bronchoscopy and head and neck CT revealed one 1.1x1.3 cm laryngeal cyst at midline and another 6 mm cyst inferior to the epiglottis. The patient underwent CO2 laser marsupialization and the pathology showed mucocutaneous tissue with cyst lined by stratified squamous epithelium. The breathing pattern was smooth after the operation and his growth curve caught up later. Early flexible bronchoscopy diagnosis can rescue the failure to thrive of this condition. Epidermoid cyst, thyroglossal cyst, and vallecular cyst should be considered in the differential diagnosis of congenital laryngeal cyst.

O-74  |  Severe Obstructive Sleep Apnea Caused by Lingual Tonsil Hypertrophy after Adenotonsillectomy in a 2-Year-Old Girl with Nemaline Myopathy

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Background: Pediatric obstructive sleep apnea (OSA) caused by adenotonsillar hypertrophy is common. Adenotonsillectomy (AT) is the first line treatment to improve OSA in most children. However, there is a possibility that compensatory enlargement of other tonsils occurs after AT, and it can cause OSA again. There are few reports evaluating risk factors for OSA relapse after AT. We present the case of a 2-year-old girl with congenital myopathy who had relapse of severe OSA caused by compensatory sublingual tonsil hypertrophy a year later after the first AT.

Case Report: A 22-month-old girl with nemaline myopathy who had been cared with noninvasive ventilation (NIV) at home underwent AT because of OSA caused by adenotonsillar hypertrophy. After the AT, her symptoms of OSA improved. However, when she was 34 months old, she had a relapse of severe OSA. She could not breathe intermittently while sleeping and presented cyanosis with oxygen saturation nadir < 80% in spite of NIV care. A laryngeal endoscopy revealed sublingual tonsil hypertrophy above the epiglottis, and a tracheotomy was scheduled. However, before the operation, she suffered from aspiration pneumonia and went into cardiopulmonary arrest caused by mucous suffocation in spite of the management with NIV in an intensive care unit. She was recovered with immediate cardiopulmonary resuscitation with tracheal intubation and mechanical ventilation. After this episode, a tracheotomy was performed and symptoms of OSA improved. She was discharged without neurological sequelae and has been cared with all-day mechanical ventilation at home.

Congenital muscle diseases in young children can be a risk factor of relapse of OSA by compensatory enlargement of other tonsils after AT. High-risk patients should be evaluated repeatedly with a laryngeal endoscopy after AT to detect compensatory enlargement of other tonsils.

O-75  |  Lipoblastoma: A Rare Cause of Acute Mediastinal Syndrome

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Mediastinal syndrome has become increasingly recognized as the use of diagnostic imaging increases. A lipoblastoma is a rare, benign, rapidly growing tumor that develops principally (and asymptomatically) on the extremities during infancy. We report a 6-month-old male infant with a presentation of acute bronchiolitis with respiratory distress. Sudden onset of cyanosis with respiratory failure and emergent intubation occurred 3 days after admission. X-ray showed a mediastinal mass unexpectedly. Subsequent chest CT revealed a tumor located in the upper posterior mediastinum, which anteriorly displaced the esophagus and the trachea, and entrapped the descending aorta. Exploratory thoracotomy was performed by pediatric thoracic and cardiovascular surgeons for complete excision. The pathological report revealed lipoblastoma. The patient’s respiratory condition improved and extubation was performed 4 days after operation. He had no need for further chemotherapy and no recurrence of tumor in the 4 years follow-up.

O-87  |  Repetitive Respiratory Wheezing Due to Pulmonary Artery Sling

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An 8-month-old female infant was admitted to our intensive care unit with the initial presentation of acute bronchiolitis with
respiratory failure requiring intubation. After extubation, recurrent wheezing and stridor was noticed. Echocardiography showed an abnormal left pulmonary artery arising from the right pulmonary artery. With the impression of pulmonary sling, an esophagogram also showed a narrow esophagus with anterior indentation. Bronchoscopy revealed tracheal stenosis. The chest CT revealed aberrant left pulmonary artery with sling between the trachea and esophagus. In addition, stenosis of the distal trachea and right main bronchus was found due to external compressions by the pulmonary artery, vertebral body and azygos vein. Due to recurrent wheezing and failure to thrive, surgery was performed at the age of 2 years old. Left pulmonary artery reconstruction with sliding tracheoplasty was performed. After operation, the clinical course was uneventful and the patient was discharged 2 weeks after surgery.

O-88 | Intra-tracheal Mesenchymal Stem Cell Therapy in an ARDS Patient with Juvenile Myelomonocytic Leukemia Supported by ECMO

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Acute respiratory complications occur frequently during the early phase of leukemia, and the most severe form is acute respiratory distress syndrome (ARDS). Leukemia-related complications and documented infections are the most frequent etiologies of ARDS. Extracorporeal membrane oxygenation (ECMO) allows for ultraprotective ventilation to minimize ventilator-associated lung injury and enable injured lung parenchyma to heal. Mesenchymal stem cells (MSCs) have shown promising therapeutic effects in preclinical models of both ARDS and sepsis. Poor outcome is usually accompanied in immunocompromised patients with hematological malignancies, and usually worsens with ECMO-related major bleeding, cannula infection, and ventilator-associated pneumonia (VAP).

We herein report a 6-year-old girl with immunocompromised status and ARDS. She was rescued by ECMO, exogenous surfactant supplementation, and intratracheal mesenchymal stem cell therapy. Her underlying disease was juvenile myelomonocytic leukemia (JML). ARDS developed soon after JMML being diagnosed. She was initially rescued by ECMO, but lung conditions did not gain much improvement for months despite aggressive ventilatory care and exogenous surfactant use. Mesenchymal stem cell therapy was then considered after full discussion with the family and obtaining approval from the institutional review board for human trial. We administered intratracheal mesenchymal stem cell therapy via fiberbronchoscopy once per week for three consecutive weeks. After the 3rd course, her oxygen demand decreased from 100% to 50%-70% to maintain the oxygen saturation higher than 85%. The general perfusion and vital signs showed short-term improvement after the intratracheal mesenchymal stem cell therapy. However, the patient eventually expired after an episode of irreversible ventilator-associated pneumonia and septic shock. This therapeutic experience highlights the potentially beneficial effects of intratracheal mesenchymal stem cell therapy to treat immunocompromised ARDS cases who are already under ECMO support.

O-94 | A Life-Threatening Congenital Pulmonary Airway Malformation in a Very Low Birth Weight Premature with Giant Patent Ductus Arteriosus

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This very low birth weight premature male baby was born by cesarean section due to twin delivery, premature rupture of membranes, at the gestational age of 26 weeks and 1 day. The patient weighed 1,100 gm, the Apgar score at one and 5 minutes was 6 and 8, respectively. He had respiratory distress since birth, and the initial diagnosis was premature with grade III respiratory distress syndrome (RDS) and neonatal sepsis. RDS persisted after surfactant use, and high frequency oscillatory ventilation (HFOV) was applied since birth for desaturation, subcostal retraction, and grunting. Significant patent ductus arteriosus, 1.9 mm with left to right shunt when the patient was 3 days old, surgical ligation was carried out after 2 days of ibuprofen treatment without proper response. Multiple cystic lesions were well visualized in the left lower lung before and after PDA ligation. Respiratory distress was persistent. The chest radiograph showed progressively prominent multiple cyst lesions in the left lower lung. Congenital pulmonary airway malformation (CPAM) was highly suspected. Because of sudden onset of frequent desaturation and hypotension when the patient was 10 days old, emergent open chest surgery was performed. CPAM was excised by the pediatric surgical team Partial lung lobectomy was carried out. The surgical specimen consisted of multiple lung cysts and confirmed the diagnosis of type 2 CPAM. The postoperation course was uneventful, he was discharged with good condition.

Conclusion and reflection: CPAM, previously known as congenital cystic adenomatoid malformation (CCAM) is a congenital disorder of the lung. It occurs in approximately 1 in every 30,000 newborns. Unlike type 1, type 2 congenital pulmonary airway malformation is more difficult to detect prenatally and should be taken into consideration when facing an infant with persistent respiratory distress.
Tracheal Agenesis with Esophagobronchial Fistula: Fatal Congenital Anomalies and Challenging Intensive Care

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Tracheal agenesis (TA) is extremely rare and usually fatal. Complete or partial absence of the trachea below the larynx can be found, and a tracheoesophageal fistula may exist. There is usually no prenatal symptom, but other congenital anomalies are commonly found. We present a low-birth-weight male infant (gestational age 36 weeks; birth weight 2100g) born with respiratory distress. Physical and radiological examination disclosed single umbilical artery, bilateral malalignment of thumbs, sacral dimple, and hemi vertebra. Difficult intubation was noted soon after birth. After being transferred to our center with an intubated endotracheal tube, flexible bronchoscopy was performed and found it was an esophageal intubation. A blind pouch at the subglottic level of the trachea without a fistula was observed. Diagnosis by computed tomography (CT) with 3D-reconstruction revealed TA (Floyd type II) with a small esophago-branchial (EB) fistula at the lower esophagus and linked to the right upper bronchus. At the age of 3 days, esophageal ligation and gastrostomy were performed. At the age of 21 days, with the assistance of 3D-printing simulation and esophageal ligation and gastrostomy and tracheoplasty were executed. The cervical esophagus was end-to-end anastomosed to the larynx. After dividing and excision of the EB fistula, the proximal end of the lower thoracic esophagus just above the fistula was end-to-side anastomosed to the right main bronchus. The distal end of the lower thoracic esophagus was ligated. However, pneumothorax, anastomosis dehiscence and repair, narrowing of anastomosis, collapse of esophageal-consisted airway, and bilateral pulmonary atelectasis developed in the following 2 weeks. Flexible bronchscopy aid balloon dilatation and stent implantation were planned. However, massive air-leak to mediastinum and peritoneum, shock and disseminated intravascular coagulation (DIC) occurred. Finally, this neonate passed away with Do-Not-Resuscitate (DNR). The whole clinical course revealed strong interprofessional collaborative practices in pediatric intensive care. In addition to traditional intensive care, the technique of 3D-printing to assist surgical reconstruction, maintaining ECMO on a 2-kg neonate, and flexible bronchoscopy for both diagnostic and therapeutic interventions all played important roles in trying to save this infant’s life.

In conclusion, TA should be considered during difficult tracheal intubation of a newborn baby with respiratory distress. Flexible bronchoscopy, CT scan and surgical interventions for diagnosis and management are suggested. Further updated techniques for effective therapy are required to improve the outcomes.

Surfactant Deficiency in a Late Preterm Neonate: A Rare Presentation

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Introduction: Surfactant protein deficiency is a rare congenital pulmonary disease in neonates which is difficult to diagnose. It may be caused by different types of gene mutations. Among these, surfactant protein C deficiency shows variable presentation and prognosis.

Case Presentation: This neonate presented as a late preterm (gestational age: 36 4/7 weeks) who was transferred to our intensive care unit due to respiratory distress developed after birth. Maternal and birth history were uneventful. Physical examination showed bilateral coarse breathing sounds with subcostal retraction.

Initially, nasal CPAP (continuous positive airway pressure) was provided for respiratory support; however, intubation was finally performed with high-frequency oscillation use due to fluctuating
respiratory condition. Series of chest plain film showed progressive diffused infiltration, while high-resolution computed tomography showed bilateral ground glass appearance. In combination of her clinical features and image presentation, lung biopsy was performed due to the high suspicion of diffuse lung disease. Oral steroid and azithromycin was administered but her improvement was poor. We did not administer Hydroxychloroquine because of her G6PD (glucose-6-phosphate dehydrogenase) deficiency. Recurrent ventilator-associated pneumonia was noted which needed several types of antibiotics. At 3 months of age, a tracheostomy was performed. Lung transplantation was offered to the family but they decided to proceed with mechanical ventilation use. Due to worsening of clinical condition and resistance to medication treatment, she received palliative extubation after full discussion with her family at the 5th month. A blood sample was collected for genetic testing before the patient passed away.

Result and Discussion: The biopsy result showed interstitial widening with type II pneumocyte hyperplasia and pulmonary alveolar proteinosis. Next generation sequencing (NGS) and DNA sequence analysis showed heterozygous mutation of codon 39 (c.115G>T, p.Val39Leu) on SFTPC gene. Surfactant protein C deficiency was confirmed.

A number of cases have been reported in surfactant protein C deficiency worldwide. Each of them feature different mutation sites, disease onset, clinical presentation, treatment and prognosis. In our patient, she had early onset of respiratory distress with rapid progression which needed maximal ventilation support to maintain her respiration at the end. Also, experimental hydroxychloroquine was held due to her underlying disease. These are the main differences compared with previous literature.

O-122 | Can Plumbing Be an Effective Solution for a Systemic Problem?

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Introduction: Kaposiform lymphangiomatosis (KLA) is an aggressive lymphatic vascular anomaly with morbidity and mortality due to pericardial and pleural effusions. Mean interval between diagnosis and death was 2.75 years in a large case study. Treatments including Sirolimus, Avastin, Corticosteroids and Vincristine have limited success. Magnetic resonance intranodal lymphangiography has revolutionized imaging of the “forgotten third circulation”, improving our understanding of lymphatic diseases and paving the way for a new treatment modality, lymphatic embolization. We present a 7-year-old girl with KLA whose pleural effusion stabilized following two lymphatic embolization procedures.

Case Report: Our patient presented at 2 years with recurrent severe non-pulmonary infections. Chest radiographs showed prominent diffuse reticular opacities despite the absence of respiratory symptoms or signs. Comprehensive immunology and rheumatology investigations were normal, as were exhaled and nasal nitric oxide, ciliary biopsy, bronchoscopy and lavage, echocardiography and oxygen saturation at rest, on exertion and overnight. A chest CT showed thickening of interlobular septae with preservation of parenchymal architecture. A bone scan showed reduced uptake at L4, as well as T10 and the left clavicle in keeping with “vanishing bone disease”.

By 5 years of age, tachypnea had developed with radiographic disease progression. A thoracoscopic lung biopsy showed diffuse proliferation and dilation of lymphatic channels within the pleura and interlobular septa typical of lymphangiomatosis, associated with spindle cell proliferation with admixed red blood cells, typical of the kaposiform variant.

Following the lung biopsy, an ipsilateral pleural effusion developed and progressed over subsequent months despite Propranolol and Sirolimus treatment, to occupy the entire left hemithorax (Figure 1A).

MR lymphangiography showed huge left lymphatic collaterals draining into the left lung and pleural space. Lymphatic embolization resulted in significant reduction in lymphocyte and triglyceride drain output. However, the effusion recurred over the following months. A repeat MR lymphangiogram showed clear improvement in the interstitial changes of the right lung. However, additional lymph vessels draining into the left lung and pleural space were identified. A second lymphatic embolization was performed, following which only a small amount of pleural fluid returned. This has been unchanged for 3 years (figure 1B), with excellent functional status under maintenance treatment with Sirolimus alone.

Discussion: In our patient, MR lymphangiography followed by targeted lymphatic embolization procedures aborted aggressive progression of a lymphatic pleural effusion. Although KLA is a systemic proliferative disease, our case demonstrates that this "mechanical approach" might change the natural course of the disease.

A) Chest x-ray before lymphatic interventions (May 2015) showing a large pleural effusion with mediastinal shift. B) Chest x-ray following two lymphatic embolization procedures employing glue and coils. A small left pleural effusion and right sided port-a-cath are seen. Prominent interstitial lung markings visible throughout. (June 2018)

O-127 | Endobronchial Carcinoid Tumor: A Pediatric Case. Concepcion, Chile

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ABSTRACTS

Lung carcinoid tumors start in neuroendocrine cells, a special type of cell found in the lungs or gut. They are sometimes classified by where they form in the lung, central or peripheral. There are 2 types of lung carcinoid tumors: typical and atypical. Rarely, they release sufficient hormone-like substances into the bloodstream to cause symptoms. The present case is an adolescent Chilean boy, 13 years old. He suffered four obstructive bronchitis episodes during 2017 diagnosed as asthma. He was started with fluticasone + salmeterol twice a day, salbutamol SOS and desloratadine daily. Despite the treatment, he had weakness, wheezing, cough which was sometimes bloody. No family history of hemorrhagic disease. In August 2017, the patient attended the emergency service because of hemoptysis. He was admitted into the hospital. Pulmonary tuberculosis was suspected. He stayed at the pediatric service for 1 week. He was stabilized; he was sent home to complete the tests as outpatient. TB infection and atypical bacterial infections with Ziehl-Neelsen tests were negative. The chest X-rays were reported as normal. PCR in bronchial secretion for atypical and TB mycobacterium were negative. Respiratory viruses were (-). Bacterial cultures in bronchial secretion (-). Blood culture was (-). Blood cell count and Shilling formula were normal. A chest computed tomography with contrast confirmed an endobronchial hypervascular tumor in intermediate bronchi. The fiber-optic bronchoscopy confirmed the tumor. The biopsy was performed by open lung surgery, there were no lymph nodes involved. The middle lobe and the right lower lobe were excised because of obstruction of the lumen, with failure of re-expansion. The biopsy was negative for atypical cells, confirming neuroendocrine tumor grade I: Positive immunohistochemical staining for Chro-mogranin (Cg) and Synaptophysin, (+) TTF1, (+) Ki67, (−) Keratin AE1/AE3. No possibility for octeocride test before or after surgery. The boy is now under control in oncology, pediatric pulmonology, endocrine unit and continues with respiratory rehabilitation exercises.

O-131 | ABO-incompatible Lung Transplantation in Infants with Surfactant Protein Deficiencies

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Surfactant dysfunction disorders can present as severe diffuse lung disease of the newborn, leading to progressive hypoxemic respiratory failure and are often fatal in early infancy. Lung transplantation is the only definitive therapy for these patients however, limited availability of suitable donors and high waitlist mortality often prevent transplantation. One strategy to increase organ availability for infants is to perform ABO-incompatible (ABOi) transplants, a strategy that was previously established in infant heart transplantation. We performed the world’s first successful ABO-i lung transplantation in an infant (Grasemann H et al, Am J Transplant. 2012;12:779-81). We report here on the Hospital for Sick Children experience of three consecutive infant ABO-i lung transplantations for surfactant dysfunction disorders. All three patients are alive and current follow-up ranges from 7.5 to 2.5 years.

Of the three patients, two had genetically confirmed surfactant protein-B deficiency and one had a diagnosis of ATP binding cassette subfamily A member 3 (ABCA3) deficiency. All received a double lung transplant and the surgeries were performed on cardiac bypass. Donor/recipient blood groups were B-/A1+ in one, and A+ /O+ in two patients. An intraoperative plasma exchanges of 1.5 times the infant’s blood volume was the only preparatory procedure performed. Isohemagglutinins were monitored before transplant and regularly during follow-up. Immunosuppressive therapy included basiliximab (induction) on day 0 and day 4 post-op, methylprednisolone, and mycophenolate mofetil. Tacrolimus was added at post-op day 5 to 7. All patients remained on relatively low-doses of triple maintenance immunosuppressive therapy. Investigations to monitor lung grafts during follow-up included surveillance bronchoscopy with
bronchoalveolar lavage (BAL) and transbronchial lung biopsies, radiographs and computed tomography of the chest, infant pulmonary function testing (IPFT) and multiple breath washout (MBW) technique to determine the lung clearance index (LCI). None of the three transplant recipients experienced any episode of severe infection, acute cellular rejection (ACR) of the graft or Bronchiolitis Obliterans (BO).

Our experience suggests that ABO-i lung transplantation for severe surfactant dysfunction disorders is a suitable therapeutic option resulting in long term survival. ABO-i lung transplantation should also be considered for other fatal diffuse lung diseases in infancy.

O-149 | A Case of Obstructive Sleep Apnea Successfully Treated with Rapid Maxillary Expansion

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Background: Adenotonsillectomy (AT) is the first-line treatment for obstructive sleep apnea (OSA) due to adenotonsillar hypertrophy (ATH) in children. However, craniofacial abnormality (CA) is also a known cause of OSA in children. AT has no effect on OSA caused by CA, although rapid maxillary expansion (RME) is reported to be useful for it.

Objectives: Herein, we report the case of a patient with OSA likely due to CA that was successfully treated with RME.

Case Report: A 7-year and 1-month-old boy visited our dental clinic with a chief complaint of malocclusion. Constricted maxilla and mandible with open bite, retruded maxilla, and tongue thrust were the pediatric orthodontic findings observed. An anterior cross-bite and open bite associated with maxillary hypogrowth was diagnosed. A medical interview revealed the presence of snoring, apnea and chest retraction during sleep. Computed tomography scan indicated the presence of moderate ATH. OSA was suspected and out-of-center sleep testing (OCST) was performed on two consecutive nights. Respiratory event index (REI) were 24.2/h and 17.0/h on nights 1 and 2, respectively; nadir SpO2 were 70% and 76%. As a result, severe OSA was diagnosed. Since his family did not wish for AT, RME was performed. Snoring and retractive breathing during sleep disappeared 3 weeks after the start of RME, and 8 months later, OCST was performed again on two consecutive nights. REI had improved to 5.7/h and 3.7/h on nights 1 and 2, respectively, and nadir SpO2 had improved to 81% and 85%.

Discussion and Conclusion: No evidence on the usefulness of RME for OSA in children has been established. However, RME was useful for OSA likely due to moderate ATH and CA in this patient, suggesting that tongue space expansion by RME can be a useful therapeutic method for OSA.

O-150 | Gorham-Stout Disease - Two Case Reports

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Gorham-Stout disease is also known as vanishing bone disease. It is a rare disease of unknown etiology characterized by progressive osteolysis and proliferation of lymphatic vessels. We report 2 cases of Gorham-Stout disease presenting with recurrent chylothorax and lytic bone lesion.

Case 1: 12-year-old boy presented with recurrent episodes of right chylothorax for 6 weeks needing chest tube drainage. Radiological imaging showed vanishing right scapula with abnormal right clavicle, humerus and ulna. Bone biopsy was performed but unfortunately the result was inconclusive. Lymphoscintigraphy revealed normal finding. Child was treated with total parenteral nutrition, sirolimus and propranolol in which the child responded well to treatment.

Case 2: 8-year-old boy presented with multiple lytic bone lesion involving the lower cervical and upper thoracic spine and massive left pleural effusion for 3 months. Left chest tube drainage showed presence of chyle. He underwent two bone biopsies, however the result was inconclusive. He was treated with total parenteral nutrition, sirolimus and propranolol but unfortunately response to treatment is poor. He still has persistent left chylothorax despite good adherence to treatment.

In conclusion, diagnosis of Gorham-Stout disease should be considered in children presenting with recurrent chylothorax and bony abnormalities.

O-152 | High-frequency Oscillatory Ventilation in Treating Severe Pediatric ARDS Caused by Pneumocystis jiroveci Pneumonia and Multiple Viral Infections

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Pediatric acute respiratory distress syndrome (PARDS) is one of the most challenging conditions in treating critical infants and children. There is still no conclusive recommendation regarding the ideal ventilator mode to treat PARDS. High-frequency oscillatory ventilation (HFOV) is considered as an alternative ventilator mode for patients with moderate-to-severe PARDS. The risk of mortality of PARDS is thought to be more related to underlying disease processes than the ventilator mode. Sepsis due to various infections is a common cause of PARDS. Pneumocystis jiroveci pneumonia (PJP) is a life-threatening opportunistic infection. It is relatively common in immunocompromised patients, including HIV-
infected population, infants born preterm or having poor nutritional status.

We present a 2-month-old female infant with fever, cough, and vomit for 4 days. She was transferred to our medical center due to rapid progression to PARDS within 1 day, and her throat swab CMV PCR test revealed positive. Her chest radiograph showed bilateral white-out, and very high ventilator settings were required to maintain oxygenation. Cardiac disease was excluded by ultrasonography. Intravenous ganciclovir, broad-spectrum antibiotics, and methylprednisolone were given, but the gas exchanges were still poor (oxygenation index = 31 at 38 hours after hospitalization). HFOV was then applied (FiO2 = 1.0, MAP = 20 cmH2O, amplitude = 30 cmH2O, frequency = 10, I time = 33%). After using HFOV, the lungs were recruited and the settings could be weaned down gradually. Intravenous immunoglobulin was given for suspected viral sepsis. Since tracheal aspirate was positive to toluidine blue O stain, PJP was also highly suspected and intravenous trimethoprim-sulfamethoxazole was started. Two days later, high CMV viral loads from urine were detected. In addition, multiple respiratory viral antigen tests from the respiratory aspirates were positive, including parainfluenza virus, rhinovirus, and corona virus. Otherwise, bacteria culture from sputum, tracheal aspirate, urine and blood all revealed negative results. This patient was successfully extubated 72 hours later. Tracing back her history, this infant was under good nutritional status, having negative SCID test and no repeated or opportunistic infection since birth. Maternal anti-HIV combo was negative. Immune status was examined, but there was no significant finding.

In conclusion, this successful therapeutic experience highlights the potential role of HFOV in infants with severe PARDS when the underlying disease is adequately treated. Furthermore, PJP and CMV infection may be taken into consideration in infants with PARDS.

Q-163 | Successful Thrombolysis of Neonatal Pulmonary Artery Thrombosis


Introduction: Pulmonary artery (PA) thrombosis in neonates is rare. The true incidence is probably underestimated because of its varying presentations, ranging from mild respiratory distress to acute right-heart failure and cardiovascular collapse. The standard of management of life-threatening thrombotic events in neonates is not established. The options include use of anticoagulation therapy alone and addition of thrombolytics. We report a case of a neonate with symptomatic PA thrombosis successfully treated with recombinant tissue plasminogen activator (RTPA).

A full term neonate male was born by normal vaginal delivery and had birth weight of 2.5 kg. Antenatal history was significant for gestational diabetes, arterial hypertension. In 6 hour after birth infant developed Streptococcus.agalacticae sepsis successfully treated with combination of ampicillin and gentamicin through the venous umbilical catheter.

On day of life nine, the infant suddenly developed severe respiratory distress with severe hypoxemia (SpO2 37%), acute
cianosis with lethargy and poor perfusion. The patient was reassigned to NICU for high-frequency oscillation ventilation. Anti­
shock therapy was started according to the accepted protocol. Echocardiography revealed a structurally normal heart. Right
ventricle was dilated to 20mm, with the intraventricular septum bowing into the left ventricle. Right ventricular pressure was
lreated to 60 mmHg. Floating thrombus was detected in the
outflow tract of RV. It extended in the trunk of the PA (21mm x
4mm). (Fig. 1). The diagnosis of pulmonary thrombosis was made, and anticoagulation therapy with low-molecular-weight heparin (LMWH) was started. Infant’s clinical status did not improve. The patient’s condition was critical. It was decided to start thrombolytic therapy
with RTPA (Tenecteplase “Metalyse”) 0.2 mg/kg. Dose was repeated after 6 hours. The follow-up echocardiogram after 6 hours showed
thrombus size reduction from 21 mm to 4.5 mm. PA pressure was
near normal. Thrombolytic therapy was stopped and replaced with
continuous intravenous heparin therapy for 72 hours followed by
subcutaneous LMWH.

Thrombolytic therapy complicated with the development of
bilateral intraventricular hemorrhage. The formation of occlusive
hydrocephaly was excluded by brain MRI.

At the 30 day of life patient was discharged. Echocardiogram
demonstrated completely dissolved thrombus with normalization of
pulmonary pressure. Cranial ultrasound showed partial lysis of
trombotic masses. Daily LMWH heparin was continued for 3 months.

Genetic analysis showed homozygous polymorphisms in genes of
inhibitor of the activator of a plazminogen (PAI-1) and a platelet
collagen receptor.

Follow up at the age of two years showed no residual or
recurrent thrombus in the PA or other systemic vessels. His
neurologic status now is normal.

Conclusion: PA thrombosis is a rarely reported complication in
neonates. Considering the potentially lethal nature of pulmonary
embolism, pediatricians and neonatologists should maintain a high
degree of suspicion for thrombotic events in infants with sudden
inexplicable deterioration in cardiorespiratory status. In our case
thrombolysis was a life-saving treatment.

O-168 | Treatment of Recurrent Respiratory Papillomatosis - Pediatric Case Report

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Introduction: Recurrent respiratory papillomatosis is rare condition
usually caused by human papilloma virus (HPV) types 6 and 11. It
occurs in children younger than 5 years. HPV attacks the mucosal
basal layer and induces cellular proliferation. Papillomatosis is very
often predilected to the larynx but may be present anywhere in the
respiratory tract. Purpose of the case was to show the course of the
disease after using different therapeutic options.

Case Report: 19-month-old child, male, admitted to the Institute for
Child and Mother Care Belgrade, for dysphonia, stridor, shortness of
breath and tachypnea worsening during cry, physical activity and at
night. Child was without fever at all times. Two months before onset of
symptoms, he often vomited after meals. Antenatal history was
insignificant. This was the second child from the second pregnancy,
vaginally delivered on time with birth weight of 3800 grams, birth length
55 cm, vaccinated on time with proper psychomotor development. There
were no respiratory symptoms in the neonatal period. Family history
was unremarkable. On admission: body weight 10 kg (P5), using auxiliary
respiratory muscles, and audible inspiratory stridor, without fever or
cyanosis. RF 38/min, SpO2 96%. Remainder of the physical examination
was normal. Laboratory analyses (CBC, biochemistry, CRP) were in the
reference range. Chest X-ray: areas of lung consolidation were observed
as scattered opacification in the right lower lobe and around the hilum.

Barium swallow test showed dilatation of the distal two thirds of the
thoracic segment of the esophagus and extended evacuation and
retention of contrast. Lymphoid hyperplasia of the hypopharynx with
obstruction of supraglottis and glottis with tumor masses were seen on
flexible fiberoptic bronchoscopy. Biopsy of the papilloma was performed
and HPV type 11 was identified. Esophagoscopy showed papilloma on
the anterior wall of the upper esophagus. After admission to hospital,
treatment with Acyclovir was started with little success. Several
excisions using carbon dioxide laser failed to prevent spread of papilloma
to trachea and bronchi. After the episode of severe respiratory distress,
urgent tracheostomy was performed and interferon (IFN) 2α was
introduced, without significant improvement. Laryngeal microdebrider
was then applied for the treatment of laryngeal and intra-tracheal
lesions. The intervention required simultaneous use of flexible endo-
scope to visualize the lesions and rigid instrument to introduce the
debrider. The “Shaving-off” of the papillomas reduced their number and
dimensions in both trachea and bronchi. Radical improvement was seen
only after antiviral Cidofovir had been intralesionally injected into
remaining papilloma of larynx, trachea and bronchi with the needle
commonly used for aspiration biopsies.

Conclusion: The treatment of recurrent juvenile papillomatosis is
challenging especially in case of metastatic disease and even more in
little child where the dimensions of the airways limit the choice of
instruments. We present the successful use of microdebriderment and
intralesional injection of cidofovir in the treatment of laryngo-
tracheo-bronchial papillomatosis in a two-year old.

O-171 | Clinical Presentation and Management of Pediatric Parapneumonic Pleural Effusion in Limited Resources Country: A Case Series

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Parapneumonic pleural effusion remains a common complication in lung infection. The presence of parapneumonic pleural effusion denotes an increase in morbidity, mortality and also hospital length of stay in pediatric patients. Despite the current development of diagnostic tools and treatment, limited resources countries still find it difficult to provide these modalities.

Case presentation: We report four cases of parapneumonic pleural effusion in pediatric patients. The patients’ ages (2 male, 2 female) ranged from 1 to 10 years. Three patients presented with dyspnea as their chief complaint and only one patient had chest pain as a chief complaint. The diagnosis of parapneumonic pleural effusion was established from clinical findings and chest radiography. Three patients had necrotizing pneumonia and one of them had already been treated with antituberculosis drugs 2 months before admission. Upon the patients’ arrival in the emergency department, we performed pleural fluid analysis and culture. We managed these patients with antibiotics and nonoperative surgical procedure in most cases. Broad spectrum antibiotics were already administered in all cases before they were referred to our hospital. All of the pleural fluid culture results were sterile due to prior administration of antibiotics. Chest tube insertion was performed on the first day of admission in all cases: two patients had only chest tube drain placement, one patient had chest tube insertion and fiber-optic bronchoscopy and one patient had chest tube insertion followed by open thoracotomy and decortication.

Conclusion: The clinical presentation of parapneumonic pleural effusion may vary in each case. Management of parapneumonic pleural effusion in limited resources country is becoming much more challenging and more patient-specific. Most cases of parapneumonic pleural effusion that we reported here have favorable outcomes.

Keywords: Parapneumonic pleural effusion, pneumonia, limited resources country.

O-182 | **Pulmonary Artery Pseudoaneurysm in Pediatric Infective Lung Diseases – A Case Report**

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Introduction: Pulmonary artery pseudoaneurysm (PAP) is a rare condition that may occur in association with congenital cardiovascular anomalies, infection, trauma, neoplasm, or vasculitis. Presentations range from a silent lesion incidentally found in imaging studies to severe life-threatening hemoptysis. We report two cases of PAPs in pediatric infective lung diseases.

Case Report: Patient A was an 18-month-old girl with Down syndrome, congenital hypothyroidism, small patent ductus arteriosus and anorectal malformation who presented with persistent fever and cough for 2 weeks post stoma closure. On examination, she was tachyypneic with a respiratory rate of 50 breaths/minute and subcostal recessions. Her blood investigations showed a drop in hemoglobin from 12g/L to 8.8g/L. Nasopharyngeal culture grew fast bacilli, and a culture later grew Mycobacterium tuberculosis confirming the diagnosis of pulmonary tuberculosis. He was commenced on antituberculous medications on day three of admission. However, his hemoptysis persisted and worsened despite over 2 weeks of treatment and his hemoglobin dropped from 8.8g/dL to 6.4g/dL requiring blood transfusion. A CT angiography revealed a pseudoaneurysm and multiple adjacent cavitating lesions over the left upper lobe with no feeding vessel seen. In view of the potential high mortality and morbidity, and increased technical complexity of interventional management due to the underlying comorbidities, he was treated conservatively. The hemoptysis resolved after 4 weeks of anti-TB treatment and he was subsequently discharged home. A follow-up CXR 3 months later showed resolving pseudoaneurysm.

Conclusion: Although pulmonary artery pseudoaneurysms are uncommon, knowledge of their existence and association with infective lung diseases is important. Recognition of unusual abnormalities on imaging studies can lead to early diagnosis and treatment. Diagnosis is often made by CT angiography and embolization is the treatment of choice.

O-183 | **Middle Aortic Syndrome Presenting as Pulmonary Edema, 3-Month-Old Boy: Case Report**

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Coarctation of the aorta (CoA) is a congenital malformation of the aorta that is a relatively common defect. However, middle aortic syndrome (MAS), an uncommon condition characterized by
segmental narrowing of the distal descending, thoracic or abdominal aorta, is rare. We herein report a case of MAS presenting as seizure and difficult breathing.

A three-month-old boy came to the emergency department with seizure clustering and difficult breathing. Although seizures stopped with intravenous administration of Diazepam and Thiamylal, respiratory condition was unstable. Chest X-ray revealed cardiomegaly and congestive lung. Ultrasound cardiography (UCG) was conducted for assessment of cardiac function. UCG identified a decrease in left ventricular ejection fraction (36%) and moderate atrioventricular valve regurgitation. There was no stenosis in the descending thoracic aorta. However, his echocardiogram identified segmental narrowing of the abdominal aorta, which caused cardiac hypofunction. His upper limb BP was 118/76 mm Hg and lower limb BP was 77/44 mm Hg. The cause of the seizures was considered to be posterior reversible encephalopathy syndrome (PRES). Since surgical operation was necessary, he was transferred to a tertiary referral children’s hospital. At 10-months old, catheter surgery for intravascular stenosis was performed successfully. Vasculitis, such as Takayasu’s arteritis, can be stated as a differential diagnosis; however, finding of vasculitis was all negative. One year after initial presentation, the patient was fine.

This report describes a rare case of CoA, MAS. Chest X-ray and UCG could result in leading to diagnosis, even if it does not appear to be a cardiovascular disease based on symptoms.

O-184 | Primary Empyema Due to Streptococcus Mitis Infection: A Common Disease by an Unusual Etiology

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Introduction: Community-acquired pneumonia is one of the most common respiratory infections in children. Epidemiology and etiologies have changed among the last decades and new pathogens have emerged recently. Some cases may present with unusual clinical features and evolve to complicated pneumonia. We present the case of an 8-year-old boy who presented with chest pain and was diagnosed with empyema caused by Streptococcus mitis (S. mitis) secondary to an odontogenic infection. This is the first case of empyema caused by this agent in our center.

Case Report: An 8-year-old boy with no past medical history, presented with 3 weeks of right-sided chest pain that radiated to right shoulder. No fever, respiratory symptoms or history of trauma were recorded. Initial diagnosis by Orthopedics was a musculoskeletal pain treated with anti-inflammatory medications without improvement. Subsequently, he was admitted at the emergency department with persistent chest pain for further investigations.

Chest X-ray showed an extensive right pleural effusion and ultrasound described a right basal consolidation with a pleural effusion of 353ml. Pleural fluid sample obtained by thoracentesis was purulent with exude characteristics and a chest tube was inserted for drainage.

Due to these findings, a thoracic CT scan was performed and revealed atelectasis of the right lung and severe loculated pleural effusion with fluid-filled cavities in the right middle and lower lobes. Since the patient was stable, a conservative management was preferred and empiric IV antibiotics, cefotaxime and clindamycin, were started. After 7 days of treatment, pleural fluid culture was positive for S. mitis. S. mitis was sensitive to ampicillin, thus treatment was completed with 10 days of ampicillin and 7 days of cefotaxime and clindamycin with a satisfactory outcome.

Considering that S. mitis is an innocuous commensal organism of the oropharynx, skin, and gastrointestinal and genitourinary tracts, we looked for primary infection sites. The origin of the infection was a cavity in the third lower molar that extended to the root. The patient had a history of a dental procedure 4 weeks before diagnosis.

Discussion: Empyema in children may develop with different
Bovine tuberculosis has been identified as the most frequent cause of sputum-positive tuberculosis in adults in the study area. The authors concluded that the use of ethambutol for pulmonary tuberculosis is not currently effective in eliminating the risk of drug resistance. The study results suggest that the use of ethambutol for pulmonary tuberculosis may not be sufficient to prevent the development of drug-resistant tuberculosis. 

**O-194 | Cutis Laxa: A Case Report**

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**Background:** Cutis laxa (CL) is a rare disease, a heterogeneous group of genetic and acquired connective tissue disorders caused by mutations in the elastin and fibulin-5 genes. Congenital forms of cutis laxa are more common than acquired disease. Autosomal dominant, autosomal recessive and X-linked recessive patterns have been described, with the recessively inherited form being the most frequent and most severe. Cutis laxa is characterized by a generalized reduction in the amount and size of elastic fibers and fragmentation and disruption of their normal arrangement, progressive looseness of the skin associated with abnormalities of other organs and structures containing elastic tissue such as lung, vasculature or gastrointestinal tract. The most clinical feature is loose and pendulous skin, sagging of the cheeks, or prematurely aged appearance. This disease is often associated with severe internal complications such as emphysema leading to cor pulmonale and death in the first few years of life. Emphysema in autosomal dominant CL is caused by heterozygous elastin gene mutations. Cutis laxa shows increased lung compliance and decreased stiffness of lung tissue. Combined effects of these processes lead to the development of an emphysematous pulmonary phenotype in CL.

**Case:** An 8-month-old girl presented with cough and shortness of breath, inguinal lump, weight loss, sagging in almost entire part of the body. There had a history of recurrent episodes of cough and breathlessness since age of 4 months, with an increase in the frequency and severity of the episodes in the last weeks. The patient has a sister with the same condition who already passed away. On examination, the child had fever, tachypnea, dyspnea with intercostal and subcostal retractions. The respiratory rate was 55/min, heart rate 105/min, and SaO2 was 95% using 2% of oxygen supplementation. Weight and height were 5.7 kg (<-2DS) and 66 cm (0–2DS), the nutritional status was malnourished. The face had a senile appearance with sagging cheek, pendulous ear lobes and lax skin. There were rales and retractions on chest examinations; the cardiovascular system was normal. There were umbilical hernia and inguinal hernia. The laboratory findings showed anemia, leukocytosis and increase in C-reactive protein. Other examinations such as electrolyte, thyroid hormone, renal and liver function were within normal limits. A chest X-ray showed bilateral emphysema, pneumomediastinum. Echocardiography showed normal...
the neurodevelopment of the patient by brain MRI. The MRI ventilation support since birth, we decided to make an assessment of was treated under NIV support. After 9 months of mechanical ventilation was performed and the patient was transferred to the neonatal intensive care unit. After 3 months of mechanical ventilation was 1500 g. Because of respiratory distress syndrome, endotracheal tube to guarantee the safety of the respiratory system; (2) The neonatal MRI-ventilator which includes NIV mode is too expensive and requires a well-trained respiratory therapist to operate the MRI-ventilator. We believed that once we well-prepared the MRI-ventilator, infants with VD who are receiving NIV support could undergo MRI more safely. By sharing this case experience, we hope the profession of neonatal respiratory therapy could receive more attention. 

Keywords: neonatal magnetic resonance imaging; bronchopulmonary dysplasia; ventilator dependency; noninvasive ventilation.

O-213 | Chronic Hypoxemia and Recurrent Epistaxis: Connecting the Dots

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Introduction: Osler-Weber-Rendu syndrome or hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by epistaxis, mucocutaneous telangiectasia with systemic manifestations due to visceral telangiectasia and arteriovenous malformations (AVM). Pulmonary arteriovenous malformations (PAVMs) are found in up to half of patients, commonly presenting with hypoxia, and can lead to fatal embolic and hemorrhagic complications.

We present two cases that were diagnosed after multiple consultations: Case 1. A 2-year-old girl presented with a history of recurrent episodes of cyanosis during her first months of life, worsening respiratory symptoms and poor exercise tolerance. She was assessed on several occasions by a general practitioner (GP) who did not consider that further investigations were necessary. She also had recurrent epistaxis and was being followed by the local ENT specialist who considered the episodes as normal. At the age of two, she was admitted to her local hospital with a LRTI, cyanosis and persistent low oxygen saturation levels (70%). She was treated with antibiotics, but given her slow improvement she was referred to our center for further workup. On examination, she presented with failure to thrive, general cyanosis, multiple telangiectasia in oral cavity and nostrils, and clubbing fingers. Initial chest X-ray showed...
Fever, Cough and Tachycardia in a CF Toddler

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Background: Children with cystic fibrosis (CF) have frequent respiratory exacerbations, therefore the occurrence of cough and fever in a CF child raises the suspicion of an acute infectious event, while in a non-CF child this fever/cough association would suggest a pneumonia. What about the presence of tachycardia, which would suggest a different diagnosis, from myocarditis or hyperthyroidism. We herein present the case of a 3-year-old girl with cystic fibrosis with frequent acute cough, persistent fever and tachycardia attacks.

Methods: A 3-year-old girl was diagnosed with cystic fibrosis in infancy, because of a Pseudo-Blottert syndrome. The child's evolution was very good, with good clinical and biological status, normal pulmonary lung function described by a normal lung clearance index and germ-free cough swab and negative induced sputum. She was monitored according to the national Romanian guidelines every 3 months in the regional CF center and annually at the national center, by clinical and biological investigation. No CT or bronchoalveolar lavage was performed until age of 3 years.

Results: In evolution, her mother noticed episodes of tachycardia 5 months before the actual admission, supposed secondary to play or hospital anxiety, without any electrical ECG alteration. Four months before admission, she had a mild exacerbation associated with insignificant chest X-ray findings and she received intravenous cephalosporin. After 1 month, she started to productively cough and fever, with a relatively strong persistence despite AINS. Her first CT scan showed left lower lobe pneumonia with pleural effusion and antiseptosomal with anti-MRSA antibiotics were initiated. The evolution was initially good, with fever reduction and reduced cough intensity and frequency. After 2 weeks, the biochemistry showed the persistence of an elevated ESR and CRP; she was referred to the national CF center. At admission, she was started on vancomycin with the suspicion of a resistant Streptococcus pneumoniae and inflammatory indices decreased and the ‘wait and see’ attitude was adopted, without the repetition of CT. Another cardiology evaluation was performed for a new tachycardia episode and a reduced cardiac partial movement was noticed. The lung ultrasound revealed the presence of a large vascularized tumor located in the left lower lobe, without signs of consolidation or pleural effusion. The biopsy revealed an Askin tumor with costal debut.

Conclusion: Not every cough or fever in a child with cystic fibrosis signifies an exacerbation; likewise, not every apparent consolidation with pleural effusion is a pneumonia. A more incisive investigational approach should be considered in a CF child with persistent inflammation.
Background and significance: It is estimated that 4800 children living in the USA are currently supported by mechanical ventilation at home. In spite of advances in technology, the mortality rate of 27.5% and 21% remains high. Previous studies identified a knowledge gap in the responses to emergencies in the home. Therefore care providers need to know the types of home emergencies and how to respond appropriately in the home setting.

Purpose / aims of the study: The Children’s Hospital of Los Angeles (CHLA) approached regional home clinicians and formed an advisory panel to address HMV emergency management.

Methods: We consulted 28 clinicians who are HMV clinical experts: 9 home respiratory care practitioners, 9 home health clinical nurses, 3 parents, 2 pulmonologists, 4 hospital nurse clinicians and 1 inpatient respiratory care practitioner. Phase I: the experts participated in an online survey, recalling the emergencies they had encountered in their career. Phase II: the expert advisory panel gathered for a one-day focus group workshop to discern all the emergency scenarios and responses in detail.

Data collection procedures: The final curriculum is a summation of the most commonly encountered home emergencies recalled by this expert panel with 412 years of experience. Home emergencies were recalled; they were categorized according to the type of emergency scenarios. In post data analysis, the expert panel shared clinical experience on each scenario via the modified Delfi method.

Results: Ninety-two HMV emergency scenarios were recalled. Data were categorized into 16 emergency situations. The expert panel deliberated on 1) the emergency situation 2) the immediate response 3) the possible causes and 4) pearls – the collective sharing of experiences on these encounters.

<table>
<thead>
<tr>
<th>Tracheostomy Related Issues</th>
<th>Ventilator Related Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucous plugging High-pressure alarm</td>
<td>Tube slipped out of the stoma Low pressure alarm</td>
</tr>
<tr>
<td>Tube is disconnected High minute volume alarm</td>
<td>Inability to suction Low minute volume alarm</td>
</tr>
<tr>
<td>Large volume of secretions High respiratory rate alarm</td>
<td>Bleeding from the trach Disconnect alarm</td>
</tr>
<tr>
<td>Ventilator disconnected</td>
<td>Ventilator stopped with no warning</td>
</tr>
<tr>
<td>Water in the circuit</td>
<td>Ventilator power resources</td>
</tr>
</tbody>
</table>

An example of the presentation of the emergency scenario:

<table>
<thead>
<tr>
<th>Situation</th>
<th>Possible Causes</th>
<th>Immediate Responses</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to suction through the trach tube.</td>
<td>Trach tube is ill-fitted. Trach tube is too short or too long. Trach tube is blocked by mucous plugs. Granulation tissue below the end of the tube. Abnormal anatomy (tracheal shelf, severe scoliosis).</td>
<td>Assess the child. Assess the reason for the alarm. Suction the trach tube. Reposition the child and suction again. Re-assess the child. Secure the trach tube snugly Change the trach tube.</td>
<td>If an inline suction catheter is used, switch to the open suctioning method. Generous amount of normal saline if mucous plug is suspected. Ready to change trach tube. Make sure the trach size is correct: neonatal vs. pediatrics. Reposition trach tube and attempt to suction again if positional tube is suspected. Be ready to go to ED or call 911 for advanced management. Knowing patient’s volume baseline will help in determining a possible plug due to a much lower read-out on the ventilator screen.</td>
</tr>
</tbody>
</table>
Sixteen emergency situations will be presented in detail using the above format.

**Conclusion:** A training module for care providers (especially home health nurses and parents) on HMV emergencies is now available; we have the type of home emergencies and the proper responses. This study study is a creative approach to developing the HMV emergency curriculum and implementing the training program in Southern California. We hope to share our experience with the CIPP participants.

**N-2 | Curriculum Development and Training of Pediatric Home Mechanical Ventilation Emergencies for Home Care Providers**

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**Background and significance:** Of the more than 9.4 million children in the United States with special health care needs, few present with more challenges than those faced by children requiring home mechanical ventilation (HMV). It is estimated that 4800 children living in the USA are currently supported by mechanical ventilation at home.

In spite of advances in technology, the mortality rate of 27.5% and 21% remains high. Home health nurses did not perform well in studies related to emergency-based scenarios on tracheostomy management and ventilator alarms. Inpatient care providers do not have complete data of emergency reports at home.

**Purpose/aims of the study:** We recognized that a curriculum developed by stakeholders at all levels was needed to address the types of emergencies encountered outside the hospital setting and what the response should be. As each state/hospital might have a different approach to the type of tracheostomy tube and ventilator for their HMV patients, we implemented a regional approach to collect data from local experts to create a curriculum for home care providers.

**Methods:** We invited 28 experts who are HMV home clinical experts from inside and outside the hospital: 9 home respiratory care practitioners, 9 home health clinical nurses, 3 parents, 2 pulmonologists, 4 hospital nurse clinicians and 1 inpatient respiratory care practitioner to participate. These experts were asked to recall the emergencies they had encountered in their career and consensus was reached via the modified Delfi method.

**Data collection procedures:** The final curriculum is a summation of the most commonly encountered home emergencies recalled by this expert panel with 412 years of experience. Home emergencies were categorized according to the type of emergency scenarios. In post data analysis, the advisory expert panel discussed the home emergencies in detail.

**Results:** Ninety-two HMV emergency scenarios were recalled. Data categorized into 16 emergency situations. The expert panel deliberated on 1) the emergency situation 2) the immediate response 3) the possible causes and 4) pearls – the collective sharing of experiences on these encounters. The tracheostomy and ventilator home emergency curriculum for home health nurses was finalized.

- Mucous plugging
- Tube slipped out of the stoma
- Tube is disconnected
- Inability to suction
- Large volume of secretions
- Bleeding from the trach
- High pressure alarm
- Low pressure alarm
- High minute volume alarm
- Low minute volume alarm
- High respiratory rate alarm
- Disconnect alarm
- Ventilator disconnected
- Ventilator stopped with no warning
- Water in the circuit
- Ventilator power resources

**Dissemination of information:** To animate participation, we will provide an incentivized program by offering the first 150 home health nurses a gift card of $20 for their participation with 1 unit of CEU. We will perform a pre and posttest to capture the knowledge gain from this educational opportunity.

**Conclusion:** We have created a curriculum for HMV emergencies. An innovative training module for HMV emergencies in Southern California is underway to train home health nurses and parents. This curriculum represents all major stakeholders addressing home emergencies for pediatric HMV patients outside the hospital settings.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Possible Causes</th>
<th>Immediate Responses</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding from the trach</td>
<td>Dryness. Irritation from aggressive suctioning. Infection. Ill-positioned trach tube. Granulation tissue beyond the end of the tube.</td>
<td>Assess the child. Suction the trach tube gently. Use cold normal saline drops to clear airway. Change the trach tube. Call 911 if airway is still not patent.</td>
<td>Distinguish between blood-tinged mucus vs. frank bleeding from the trach tube. Bleeding non-stop necessitates ED visit. Clear coagulated blood by trach tube or circuit change. Seek advice of physician for possible antibiotics or flexible endoscopy. For bleeding from dryness: switch to a heated wire circuit. Check room temperature for condensation/rain out phenomenon.</td>
</tr>
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**N-6 | The Prevalence of Obstructive Sleep Apnea among Obese Toddlers and Preschool Children**

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**Purpose:** Obstructive sleep apnea (OSA) is a common disorder estimated at 1%-5% in school-aged children. With the obesity prevalence reaching staggering rates globally, OSA in obese adolescents is estimated to be 4 to 5 fold higher than their lean peers. There is a paucity of data regarding obesity-related OSA in children 6 years and less. This is particularly relevant as OSA is associated with neurocognitive deficits. The aim of this study is to evaluate the prevalence of OSA among obese toddlers and preschool children and further to determine what other factors may be associated with the presence of OSA.

**Methods:** A retrospective study involving children <6 years, identified from two Canadian pediatric tertiary care centers who had an in-lab polysomnography (PSG). Obesity was defined by a BMI of >95th percentile for age and gender or a z-score of >2. OSA was diagnosed if the obstructive apnea-hypopnea index (OAHI) was greater than 2 events per hour.

**Results:** There were 60 participants included; the mean age was 4.4 years (standard deviation [SD] +1.7), mean BMI z-score was 3.0 (SD +1.2). Of these, 22/60 (36.6%) had OSA. Compared with the non-OSA group, the OSA group had a higher Epworth sleepiness score (P = 0.03) and were more likely to snore (P = 0.01).

**Conclusions:** Young obese children should be assessed for OSA. A history of snoring and daytime sleepiness may be useful indicators to facilitate triage for a PSG, especially in resource-limited settings.

**Clinical Implications:** Early identification and targeted interventions for OSA in this vulnerable group will likely improve downstream health including neurocognition.

**N-29 | To Compare the Efficacy of Nebulized Salbutamol and Nebulized Adrenaline and any Added Advantage of Nebulized Hypertonic Saline in Bronchiolitis**

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The present study "Comparative study of nebulized beta 2 agonist, nebulized adrenaline and any added advantage of 3 % hypertonic saline in bronchiolitis" was undertaken to assess the efficacy. A total number of 150 patients (50 patients in each group) were examined below 24 months of age. Group A was nebulized with salbutamol, group B was nebulized with adrenaline and similarly, group C was nebulized with 3% hypertonic saline. Comparison of mean ± S.D. of RDAI score before and after nebulization was performed in all 3 groups. In each patient from all groups (ie A, B and C), RDAI scores were recorded at the time of admission (ie at 0 minutes), at 20 minutes and 40 minutes (after nebulization) and on subsequent days. The mean value of RDAI score at admission and discharge was 10.78±1.03 and 6.58±1.54 respectively in group A. In group B, RDAI score at the time of admission and discharge was 11.20 ± 1.05 and 5.9 ± 1.61, respectively. Similarly in group C, RDAI score at the time of admission and discharge was 8.14 ± 1.80 and 3.18 ± 0.94, respectively. All the parameters before treatment had a P value >0.05 (not significant at 0 minutes.) and at the time of discharge, the p value became <0.0001 (extremely significant). Mean differences in HR, RR, RDAI SCORE and SpO2 were assessed after subsequent nebulization in all 3 groups. The post treatment values for group A (Salbutamol), group B (Adrenaline) and group C (3% Hypertonic Saline) were compared. All groups showed an increase in HR, but group B (mean difference of 14.80) showed a more increasing trend than group A (mean difference of 4.84) and group C (mean difference of 7.04) and had a P <0.05. Regarding RR, all 3 groups showed decreased RR, but group B (mean difference of 15.96) was more significant than group A (mean difference of 14.80) and group C (mean difference of 12.20) and had a P <0.05. Regarding RDAI score, all 3 groups showed improved score, but group B (mean difference of 5.3) was more significant than group A (mean difference of 4.2) and group C (mean difference of 4.96) and had a P <0.05. Similarly, all 3 groups showed improved SpO2 %, but group B (mean difference of 10.24) showed more improvement than group A (mean difference of 9.26) and group C (mean difference of 6.38) and had a P <0.05.

**Summary and Conclusion:** Clinical parameters (heart rate, respiratory rate, RDAI score and SpO2 %) in both groups were comparable before nebulization.

Nebulized salbutamol was given to group A, nebulized adrenaline to group B and nebulized hypertonic saline to group C. Different clinical parameters in the groups were compared before and after subsequent nebulization. Mean respiratory rates, RDAI scores and SpO2 (%) significantly improved in all 3 groups. However, improvement was more significant in the adrenaline group. Shorter length of hospitalization was noted in group C (Hypertonic saline).

No undesirable side effects were noted in all 3 groups.

All 3 groups showed a transient increase in heart rate, although more so in the adrenaline group.

**N-52 | Lung Function Decline in Primary Ciliary Dyskinesia**

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**Introduction/Aim:** Primary ciliary dyskinesia (PCD) is a hereditary and potentially life-threatening disease. The clinical course is heterogeneous and characterized by progressive destructive airway disease and chronic ear, nose and throat problems; other organ systems, for example the cardiovascular and reproductive system can also be affected. The estimated incidence of PCD is 1:20,000, thus, the availability of longitudinal lung function data needed to characterize the course of pulmonary disease is poor.

**Methods:** We analyzed lung function data from a European PCD registry (BESTCILIA project). The lung function course (forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC)) was analyzed by linear mixed model analyses for repeated measures (SPSS, V24.0).

**Results:** Three hundred and six spirometries in 127 patients (463.4 patient-years) with a confirmed diagnosis of PCD were evaluated. Fifty-nine patients (47.2%) were male, 61 (48.8%) had situs inversus. 45 (35.4%) patients had a defect of the outer and/or inner dynein arms, in 69 patients (54.3%) the diagnosis was confirmed genetically. Mean FEV1-z-score and FVC-z-score were -1.93 (SD 1.75) and -1.39 (SD 1.94), respectively. The mean annual decline of FEV1-z-score and FVC-z-score was 0.041 (SD 0.01) and 0.044 (SD 0.01), and for the subgroup of PCD with microtubular defects, the mean annual decline was 0.054 (SD 0.05) and 0.027 (SD 0.07), respectively.

**Conclusions:** The annual decline in FEV1 and FVC in PCD is substantial and comparable to the lung function decline in patients with cystic fibrosis. PCD variants with microtubular defects have an increased annual decline in FEV1-z-score and a decreased annual decline in FVC-z-score. This suggests that PCD subgroups have different patterns of lung function course. PCD registries are a useful tool to characterize the clinical course of PCD and PCD variants.

**N-66 | Endothelial Dysfunction in Children with Obstructive Sleep Apnea Syndrome**

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**Objectives:** Endothelial dysfunction (ED) is one of the initial pathological changes ultimately leading to atherosclerosis and consequent cardiovascular disease. Children with endothelial dysfunction are at higher risk of developing systemic and pulmonary hypertension, atherosclerosis and cardiac remodeling, with potential long-term adverse outcomes into adulthood. Obstructive sleep apnea syndrome (OSAS) has been found to cause impaired endothelial function in adults. However, the evidence in pediatric OSAS is limited. The aim of the study is to evaluate endothelial function in a large cohort of children clinically referred for suspected OSAS, and to identify risk factors contributing to the presence of ED.

**Methods:** Children aged 3 to 11 years old with habitual snoring (snoring ≥ 3 nights per week) were recruited to this study between June 1st 2015 - March 1st 2016. All subjects underwent an overnight polysomnography (PSG), as well as endothelial function testing using peripheral arterial tonometry (PAT) to derive the reactive hyperemic index (RHI). Subjects were then divided into OSAS and primary snorers (PS) groups according to their obstructive apnea-hypopnea index (OAHI).

**Results:** A total of 355 cases completed the study, with 248 children being diagnosed as OSAS, and 107 children assigned to the PS group. There were no differences in age, gender and BMI z-score between the two groups (all P > 0.05). The OSAS group had lower RHI than that of PS (P < 0.05). Univariate correlation analysis showed that RHI was linearly correlated with age, gender, OAHI, oxygen desaturation index, respiratory related arousal index, and oxygen saturation nadir. The relationship between BMI z-score and RHI was quadratic. RHI and BMI z-score were positively correlated when BMI z-score < 1.67 while negative correlated when BMI z-score ≥ 1.67 [RHI = 1.1286 + 0.0338*BMI z-score - 0.0147*(BMI z-score)^2]. Multivariate correlation analysis showed that age was independently positively correlated with RHI (P = 0.006), while BMI z-score^2 and respiratory related arousal index were negatively correlated with RHI (P = 0.03 and P = 0.004 respectively).

**Conclusion:** Children with OSAS have significant endothelial dysfunction compared with PS. Frequent arousals due to obstructive apneas and hypopneas during sleep may be a candidate risk factor for endothelial dysfunction in children with OSAS. In addition, age and BMI are also factors influencing the endothelial function in children.

**N-101 | The Study of Therapeutic Strategy for Eisenmenger Syndrome**

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**Background:** Eisenmenger syndrome (ES) refers to any congenital cardiac defect (CHD) with intracardiac communication that leads to pulmonary arterial hypertension, reversal of flow, and cyanosis. The previous left-to-right shunt is converted into a right-to-left shunt secondary to elevated pulmonary artery pressures and associated pulmonary vascular disease. It is only suggested to treat functional class (FC) III patients with ES with bosentan. In this study, we retrospectively reassessed the clinical outcome, cardiac hemodynamics, quality of life and complications in ES patients by advanced vasodilators during the long-term follow up.

**Methods:** Since 2005, we have treated adult patients with ES by utilizing add-on combination of advanced therapy including Sildenafil, Bosentan and Ventavis except traditional therapies used. During the 14-year follow-up, we regularly performed EKG, cardiac echogram,
6 minute walk testing (SMWT) and monitoring of serum BUN, BNP and creatinine. Also, cardiac catheterization and hemodynamic studies, PET study with uptake of glucose analog 2-deoxy-2-18F-fluoroglucone (18F-FDG) and pulmonary perfusion-ventilation scan were performed.

**Results:** We enrolled six patients with ES including atrial septal defect type II (3 cases), atrial septal defect type I (1 case), right atrial isomerism after total cavopulmonary connection (TCPC) (1 case) and ventricular septal defect (1 case); the male:female ratio was 3:3. Hemodynamic studies revealed that mean pulmonary arterial pressure was 52±7.3 mm Hg; pulmonary vascular resistance index was 26.1±7.9 WU*m², except the case receiving TCPC. In addition, three cases of intrapulmonary thrombus in right pulmonary artery, three cases of cerebral stroke and three cases of atrial fibrillation were found. The lung scan revealed that there were nonspecific findings noted in the ES patients with or without intrapulmonary thrombus. Very interestingly, an increased uptake of 18F-FDG in the right ventricle was noted in three cases. Subsequently, there were two mortalities because of right ventricular failure.

**Conclusion:** Pulmonary scintigraphy did not delineate the intrapulmonary thrombus in ES. There is a relationship between metabolic changes and ventricular dysfunction in the right ventricle, compared with the left ventricle, in ES. Some of the AT agents (eg, bosentan, inhaled prostacyclin and oral sildenafil) have yielded improvements in exercise tolerance, and/or systemic arterial oxygen saturation in limited cases with ES. The beneficial data on specific-target pharmacologic interventions in CHD with significant PAH are still quite preliminary, and large trials are warranted. Specifically, the extrapolation of ES from adult patients should be made carefully.

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**N-112 | Influence of The Position on the In Vitro Performances of a New Spacer for Pediatric Use in a Mechanical Ventilation Circuit**

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**Statement:** In vitro drug delivery by nebulization and with a pressurized metered dose inhaler (pMDI) was shaken for 5 seconds and then fired into the spacer at a flow rate (x) relationship was $y = 0.1015x^2 + 0.8343x$ (R² = 0.9985).

**Material and methods:** In vitro Salbutamol delivery from a pressurized metered dose inhaler (Ventolin, GlaxoSmithKline, France) and a vibrating mesh nebulizer (Aeroneb Solo, Aerogen, Ireland) with the spacer were investigated in invasive mechanical ventilation circuits. The prototype was inserted in the circuit in two different positions: between the inspiratory limb and the Y piece and between the Y piece and the endotracheal tube (7 mm inner diameter for adult model and 4.5 mm inner diameter for the pediatric model). The ventilator (Evita 2 Dura, Dräger, France) was used in volume-controlled mode with adult settings (tidal volume 450mL, 15 breaths/min, ratio between inspiratory and expiratory 40/60 and Positive end-expiratory pressure (PEEP) 5 cmH2O) and pediatric settings which corresponds to a child of 15kg weight (tidal volume 150 ml, 25 breaths/min, ratio between inspiratory and expiratory 50/50 and PEEP 5 cm H2O). A filter was placed between the endotracheal tube and the test lung model (SmartLung Adult, IMT medical, Switzerland) to collect the drug. All components were tested for drug deposition. Deposited doses were quantified by spectrophotometry. All measurements were performed five times.

**Results:** The percentages of the nominal dose of salbutamol deposited on the filter with the adult model after nebulization and aerosolization, were similar when the device was located before or after the Y piece (31.87 ± 3.83 % vs. 27.03 ± 3.05 % and 30.71 ± 4.33 % vs. 27.80 ± 3.16 %). The same observations were made with the pediatric model (19.85 ± 3.82 % vs. 20.12 ± 2.36 % and 8.54 ± 2.00 % vs. 8.67 ± 2.16 %).

**Conclusion:** There is no influence of the position of this prototype in the breathing circuit on the in vitro drug delivery when using a vibrating mesh nebulizer or with a pressurized metered dose inhaler for adult and pediatric mechanical ventilation models.

**Reflection:** A clear understanding of the different parameters which could affect drug delivery during mechanical ventilation is important to optimize drug delivery. The position of the inhalation device in a circuit is a key parameter which could significantly affect drug delivery.

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**N-113 | Analysis of the Impact of a Specially Designed Annubar Probe (digithal®) Inserted into a VHC, Using IVIVC Testing Systems**

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**Statement:** Using a system for improved In Vitro - In Vivo Correlations (IVIVCs) of Inhaled Drug Products, the ability of the Annubar probe (AP) to properly analyze respiratory flow and its impact on valved holding chamber (VHC) performance were checked.

**Methods:** Aerodynamic particle size distribution (APSD) and emitted mass (EM) were measured during simulated tidal breathing using IVIVC testing systems. USP throat was connected to a Breath Simulator (BS2000, Copley) and the next generation impactor (NGI) by means of a T-piece. A constant flow through the NGI cascade impactor was balanced with a pressurized air source, resulting in simulated tidal breathing through the VHC and constant air flow through the cascade impactor. The pressurized metered-dose inhaler (pMDI) was shaken for 5 seconds and then fired into the spacer at the beginning of the inspiration. Five actuations were performed with 7 full breathing cycle intervals between puffs. Each experiment was performed five times. Respiratory flow analysis was measured during all the experiments using AP inserted into the mouthpiece of the VHC and a differential pressure sensor (SDP610, Sensirion). An electronic card linked to the sensor converted the pressure variation into a flow rate (Bernoulli’s Principle).

**Results:** Flow analysis. During inhalation, the pressure differential ($\Delta P$) vs. flow rate ($\dot{V}$) relationship was $\Delta P = 0.1015\dot{V}^2 + 0.8343\dot{V}$ (R² = 0.9985).
Abstracts

Methods: Resistance, ability to close and emitted mass of drug.

Statement: The following experiments were aimed at characterizing

Results: Valve resistance generated at low inspiratory flow rate

IVIVC measurement: APSD analysis of Ventolin (Salbutamol 100µg/ dose, GSK) was assessed in vitro using in vivo - in vitro correlation methods. For VHCs including AP, MMADs decreased slightly compared to VHC alone. No significant change in GSDs, FPD50µm and FPF (P values< 0.05) were noticed. According to these results, the mass distribution of Salbutamol remained stable with or without AP.

Conclusion: Results show that within the scope of our in vitro experiment, insertion of an Annubar Probe directly into the mouthpiece of the valve holding chamber allows a precise, instantaneous and reproducible measurement of the respiratory flow during the use of the inhalation chamber. Using the IVIVC technique, we were able to test this probe in conditions close to normal use. It was therefore pointed out that the pMDI actuation did not disturb flow measurement, and that presence of the pitot probe inside the mouthpiece did neither affect the VHC characteristics (ASPD) nor treatment delivery (EM).

Reflection: Annubar Probe inserted into a VHC mouthpiece could potentially lead to the development of new devices capable of analyzing patients’ respiratory cycles during VHC use (inspiratory and expiratory phases, inhalation flow rate, etc.). This information could instruct the patient, leading to an improvement of his/her inhalation technique over time (Kamps 2007).

N-114 | Functional Analysis of Several Valved Holding Chamber Inspiratory Valves

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Statement: The following experiments were aimed at characterizing valve operation and its impact on drug delivery, by measuring valve resistance, ability to close and emitted mass of drug.

Methods: Because different valve configurations require different mouthpiece shapes and volumes (ranging from 10.5 to 21.5 ml), six custom-built VHCs were developed differing only by their inspiratory valves and mouthpieces. The six inspiratory valves had different weights, materials and shapes. Valve resistance (cmH2O/L/s) was measured by differential pressure analysis at different flow rates (from 5 to 60 L/min). The ability of the inspiratory valve to close was determined by measuring flow rates with flowmeters placed on both mouthpiece and backpiece of the VHC for different breathing patterns (Child, Adult USP). Delivery of fluticasone propionate (Flutide 50 μg, GSK) to a filter (emitted dose, ED) was assessed for each custom-built chamber using a breathing simulator (Copley Scientific) simulating coordinated and uncoordinated pediatric use (Child USP pattern).

Results: Valve resistance generated at low inspiratory flow rate (5 L/min) varied greatly between the different valves ranging from 9.5 to 0.27 cmH2O/L/s; however as the flow rate increased, variations were reduced (3.98 to 0.43 cmH2O/L/s at 60 L/min).

The ability to close varied strongly from one valve to another: for some valves, expiratory flow did not pass through the inspiratory valve while for others, only partial closing could be achieved (85% of expiratory flow passed through the inspiratory valve). These results were confirmed by measuring the flow through the expiratory valve, maximum (100% of the initial flow rate) when inspiratory valves were completely closed. Tilting the chamber did not seem to affect this result.

ED measured with pediatric breathing parameters in coordinated and uncoordinated use was similar for four of the custom VHCs while with the other two VHCs, ED was lower.

Conclusion: Four of the six custom VHCs showed high ED even when simulating uncoordinated use. Three showed average resistance and one little resistance to low flow inhalation flow rate. All blocked exhaled air properly except one. The other two VHCs showed lower ED compared to the others. One showed little resistance to low inhalation flow rates and could only partially block exhaled air, while the other could close completely but showed high resistance to inspiration at low flow rate. Lower drug output can be explained by high resistance to low flow rate, causing poor opening of the valve at the beginning of the inspiration, and the valve not closing during expiration, causing exhalation inside the chamber.

Reflection: The main role of a VHC is to improve inhaled drug delivery. Given the preponderant role of inspiratory valves in the proper functioning of VHCs, it is essential to properly analyze their characteristics, especially at low flow rates. Inspiratory valves must function effectively To not compromise drug delivery. Therefore, it is important to consider it properly when choosing a VHC, especially for children.

N-116 | Effective Motion of Endotracheal Suctioning Catheter and Viscosity of Secretion

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Endotracheal suctioning is considered as one of the invasive nursing techniques which has a risk of hemorrhage, tracheal spasm, bradycardia and so forth; however, research regarding the effective motion of endotracheal suctioning catheter is limited. The aim of this study is to unveil the relationship between effective motion of an endotracheal suctioning catheter and viscosity of secretion.

An electric suctioning machine (Power smile, SHINEI KOGYO), a suctioning catheter (10Fr., NIPRO), two viscosities of simulated secretion (666 poise, SAKAMOTO MODEL, 0.22 poise KYOTO
The objective of this study was to determine the prognostic factors related with mortality in pediatric hemato-oncology patients admitted for pulmonary complications on the ICU.

This was a retrospective cohort study of patients below 21 years old with underlying hemato-oncologic diseases admitted for pulmonary complications at the ICU of a tertiary referral hospital in Korea between April 2009 and March 2017. Patients admitted for perioperative management or non-pulmonary complications were excluded. Demographics, laboratory parameters and clinical parameters such as Glasgow Coma Scale (GCS), the pediatric version of the Sequential Organ Failure Assessment (pSOFA) score and the Pediatric Logistic Organ Dysfunction (PELOD) score, etc., were extensively reviewed.

A total of 110 pediatric hemato-oncology patients were admitted at the ICU for pulmonary complications. The median age was 13 (IQR, 8–16) years old, and 62 (56.3%) were boys. The median duration of ICU hospitalization was 8 (IQR, 4.25–16) days, and 45 patients (40.9%) were applied mechanical ventilation. The mortality rate was 59.1% (65/110 patients). Factors with a significant association with increased mortality in a multivariable logistic regression analysis were as follows: low GCS scores, low SpO2/FIO2 ratio, low hematocrit levels, and increasing total bilirubin levels. The pSOFA score and PELOD score assessed on the third day of admission had significant discrimination for in-ICU mortality with an area under the curve of 0.87 (95% CI, 0.80–0.95) and 0.83 (95% CI, 0.74–0.92), respectively.

The GCS score, SpO2/FIO2 ratio, hematocrit level, total bilirubin level, pSOFA scores and PELOD scores are useful factors for the prediction of an increased risk of mortality in pediatric hemato-oncology patients with pulmonary complication.
age was between 1 and 2 years old. There were 68 CHD children with airway problems, including trachea-bronchomalacia, stenosis of the trachea or bronchus. Patients aged less than 1 year old had longer hospital stay than those whose age was above 1 year old. The mean PICU stay and the intubation period had a similar trend. In the comparison of groups without airway anomalies, the hospital stay in children who had hemodynamic-significant CHD or heart failure (without associated airway anomalies) was 46.6 days compared to 11.6 days in children who did not have hemodynamic-significant CHD or heart failure (without airway anomalies) ($P < 0.05$). In children with airway anomalies but did not fulfill the criteria of hemodynamic-significant CHD or heart failure had longer hospital stay (22.8 days) than those without airway anomalies but with hemodynamic-significant CHD or heart failure (10.6 days) ($P < 0.05$).

Conclusions: Patients with airway anomalies are not rare in children with CHD, although the severity varies. Lower airway anomalies were associated with longer hospital stay in CHD children who were not hemodynamic-significant or heart failure. We found that airway problem is a risk factor for prolonged hospital or PICU stay in CHD children with RSV bronchiolitis. To achieve successful and sustainable outcome in CHD children with RSV bronchiolitis, it is crucial to have early identification of concomitant airway anomalies in these children.
Immunomodulation in children with recurrent wheeze: Present knowledge and future perspective

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1 | INTRODUCTION

Chronic asthma has been shown for a number of decades to declare itself clinically in very early life, in fact mostly in the earlier preschool years. Preschool wheezing or wheezing lower respiratory illnesses (WLRIs) in infants and toddlers are frequent and typically initially triggered by viral upper respiratory tract infections (RTIs), and are associated with a high degree of inflammation and airway remodeling. Recurrent wheezing, depending on viral etiology, may significantly increase the risk of developing permanent wheeze or asthma later in life, with irreversible reduced lung function. The risk is further increased when associated with early sensitization to aeroallergens. Considering that the majority of lower RTIs begin in the upper airways (a phenomenon known as “united airways”), it is likely that an effective strategy to reduce the risk for asthma inception may be the prevention of viral upper RTIs, including colds. This can be achieved via environmental and behavioral changes or immunity-targeted strategies, including the use of vaccinations or nonspecific immunomodulators.

2 | DISEASE BURDEN OF EARLY-LIFE RESPIRATORY INFECTIONS AND THEIR SEQUELAE

The disease burden from respiratory infection is greater than that of any other cause of disease in childhood, being associated with significant morbidity and representing one of the most common reasons for unscheduled medical visits. The majority of WLRIs are caused by viruses, such as respiratory syncytial virus (RSV) and human rhinovirus (HRV) and, during early life, viral infections are the most common cause of hospitalization with varying incidence in different parts of the world. Data from the RSV Global Epidemiology Network revealed that in 2015, 33.1 million RSV-associated lower RTIs resulted in about 3.2 million hospitalizations, and 59,600 deaths in children younger than 5 years. The role of HRV emerged when a variety of studies on wheezing children showed that it is the predominant pathogen in older children and may be significant in determining the nature of postinfectious wheezing that was traditionally attributed to RSV. Infants and children who experienced severe RSV infections often develop respiratory sequelae, such as wheezing, asthma, airway hyperresponsiveness, or allergy, although a recent meta-analysis reaffirms that the association between infant RSV hospitalization and respiratory morbidity decreases with age. The impact of HRV on subsequent wheezing may be more powerful and persistent, especially in children at a high atopic risk. The interplay between increased susceptibility to HRV infection in atopic subjects, and amplification of this atopic tendency by HRV is of particular relevance, since the association of asthma at 6 years of age is especially high if children were sensitized at an age younger than 2 years.

3 | UNMET NEEDS

There is a pressing need for well tolerated early interventions to prevent RTIs and their short- and long-term complications. An attempt to modify the course of children at a high risk for asthma was made by using inhaled corticosteroids (ICS) or montelukast (MTK). ICS were effective in reducing respiratory symptoms and morbidity during the 2-year course, but failed to modify the ultimate outcome once discontinued. The efficacy of prophylactic treatment with MTK appears to be limited. Thus, preventing the advent of viral
infection or modifying its course and severity appear to be the logical best strategies. Indeed, a proof of concept study with palivizumab prophylaxis in otherwise healthy late preterm infants showed a significant reduction in wheezing days in the active group through the 1st year of life, including the period after treatment discontinuation.\textsuperscript{6} In this context of unmet need and therapeutic void, boosting the efficiency of the host immune response against viral infections by immunomodulators may prove to be effective.

4 | IMMUNOLOGICAL IMMATURETY AND ENVIRONMENTAL FACTORS

The increased susceptibility of young children to respiratory viral infections reflects a poor efficiency of the host defense mechanisms, which ultimately determines the severity of the acute presentation and its short- and long-term sequelae. Although some aspects of the immune responses are functional at birth, both the innate and the adaptive arms of the immune system are immature and undergo prolonged periods of postnatal maturation until much later in childhood (Figure 1A).\textsuperscript{7} Neonatal dendritic cells show a decreased ability to process and present antigens to T-cells, associated with a lack of functional mature T-cells expressing antigen-specific receptors and with significant proportions of T-cells undergoing apoptosis, avoiding the formation of long-lived memory cells. The ultimate result is a defective production of antigen-specific neutralizing antibodies by B-cells in response to infection. Moreover, due to the suppression of helper T (Th1) cell-like functions during pregnancy, the neonatal adaptive immune system shows a Th2 bias that tends to persist in children, increasing the high risk of developing asthma.

Postnatal maturation of the immune system is driven by environmental factors in which, as recently reaffirmed, exposure to microbial products plays a major role.\textsuperscript{8} There is clear epidemiological, clinical, and experimental evidence that living in cleaner environments increases the risk of recurrent WLRIs, allergy, and asthma. Therefore, treatments based on modulation of the immune system by derivatives mimicking the effect of bacteria are proving to be a rational approach to prevent infection and potentially regulate the Th2 responses.

5 | IMMUNOTHERAPY WITH ORAL BACTERIAL LYSATES (OBLs)

The efficacy of OBLs is related to nonspecific activation/modulation of the immune system. The mechanistic rationale for OBL use in prevention of respiratory conditions focuses on the gut-lung immune axis, indicating a central role for dendritic cells (DCs), resident in Peyer’s patches of the gut-associated lymphoid tissue (GALT).\textsuperscript{3,9} OM-85 is the best characterized OBL that shows efficacy and safety in the prevention of RTIs in children and adults, modulating the activities of immune-effector and parenchymal cells (Figure 1B).\textsuperscript{3,9} As shown for OM-85, OBL-exposed DCs trigger antigen-specific T-lymphocytes that modulate B-cell isotype switching into immunoglobulin (Ig) secreting cells by synthesis of cytokines and growth factors.\textsuperscript{9} Activated DCs and T- and B-lymphocytes reach the mesenteric lymph nodes, where they continue to mature and proliferate. They then migrate into the thoracic duct and are distributed by the systemic circulation to extraintestinal sites, including the upper and lower respiratory tract. A polyclonal activation of the immune system follows, which involves the innate and the adaptive responses against infectious agents, with the induction of interferon (INF) type I (INF-α and INF-β) but also with the control of an excessive inflammatory reaction through the reduction of interleukin-1β production.\textsuperscript{9} A wide array of immune responses was shown after OM-85 exposure in vitro and animal studies: increased expression of surface molecules involved in antigen presentation to T-lymphocytes and polyclonal production of immunoglobulins, including RSV- and influenza virus-specific antibodies in mice not exposed to the viruses, reduced HRV replication in airway epithelial cells, and decreased susceptibility to Streptococcus pneumoniae and Klebsiella pneumoniae superinfection after influenza virus infection.\textsuperscript{9} These effects are also associated with immunoregulatory activities on excessive inflammatory responses and attenuation of Th2 allergic shift, hence correcting the Th1/Th2 lymphocyte imbalance through activation of T-regulatory cells in mice.

**FIGURE 1** A. Immaturity of the innate and the adaptive immune system cells at birth. B. Modulatory activities of OM-85 on immune-effector and parenchymal cells [Color figure can be viewed at wileyonlinelibrary.com]
Wheezeing and shortness of breath remain the most common symptoms presenting in pediatric practice. There is a pressing need to introduce effective management strategies for infants and toddlers with wheezing/early-life asthma for several reasons. First, preschool children have the highest rate of medical encounters, emergency department visits, and hospital admissions for wheezing and asthma symptoms, compared with other age groups. Second, episodes of wheezing and shortness of breath lead to more limitation of sport and every-day activities than older children. Third, early life wheezeing and repeated and cumulative exacerbations may be causally associated with airway remodeling and loss of respiratory function. The clinical efficacy of OM-85 reported in children with wheezing/asthma has been shown in a number of studies. Raži et al., in a 12-month study in children with acute virus-induced wheezing illness, demonstrated that 3 months on OM-85 reduced the number and duration of virus-induced wheezing episodes, with the beneficial effect carrying over for 9 months after the discontinuation of the treatment. The reductions in exacerbations appeared to be related to the reduced incidence of upper RTIs in this, as well as other studies conducted in China with wheezing as clinical endpoint. In another study of 400 children aged 3 to 6 years with a history of recurrent RTIs, the treated group received OM-85 (200 patients) for 3 months for 2 consecutive years while 200 children served as control. In the treated group, the number of patients who did not experience any new episode of RTI, as well as the number of RTIs and of wheezing episodes were significantly lower than in the group not treated with OM-85. The results were similar in the 1st and 2nd year of OM-85 administration demonstrating that a second prophylactic cycle can be useful to maintain protection. The safety profile was overall good. Other clinical studies are evaluating the effect of OM-85 on prevention of wheezing illness in young children and the respective mechanisms governing these effects (for review see Esposito et al).

7 | CONCLUSIONS

Experimental and clinical data, in particular for OM-85, support the rationale for use of OM-85 in prophylaxis against RTIs and wheezing/asthma exacerbations in children. OM-85 was well tolerated in all clinical trials with a frequency of adverse events comparable to that seen with placebo. Undesirable events are mild and transient, and the safety profile remains stable over time.

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