Proceedings

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15th International Congress on Pediatric Pulmonology, Naples, Italy, June 23–26, 2016
The International Congress of Pediatric Pulmonology (CIPP) is the main international meeting devoted to Pediatric Pulmonology. CIPP has acquired a reputable status as the forum for new information, treatment guidelines, interactions and exchange of ideas between leading specialists and practitioners in Pediatric Pulmonology from both developed and developing countries. Through a continuing partnership with Pediatric Pulmonology, the only International Journal devoted to pediatric lung diseases, the abstracts of papers that will be presented in the 15th International Congress of Pediatric Pulmonology (CIPP XV) in Naples, Italy on June 23–25, 2016 will reach a wider audience. These presentations cover areas of concern such as poorly controlled asthma, respiratory infections and its complications, neonatal lung diseases and its outcomes, cystic fibrosis, sleep disordered breathing, critical care, rare lung diseases and new treatment options. As a collection, they reflect the current developments in the field and the global perspective of the Congress.

—Alexander Tuazon, MD
President, CIPP XV
CIPP XV Postgraduate Course: Lung Function Testing in Infants and Young Children

POSTGRADUATE COURSE ON LFT

#1. INFANT PULMONARY FUNCTION TESTS

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Marked developmental changes in respiratory physiology occur during the first years of life which affect both the measurement and interpretation of lung function in infants and young children. There are also major differences in how lung function is measured in infants when compared to older subjects and these differences relate mainly to sleep state, sedation, ethical issues, posture and the need to miniaturise and adapt equipment for measurements in small subjects who are preferential nose breathers and who cannot be asked to undertake special breathing manoeuvres. Thus, when undertaking infant lung function tests (ILFT), a basic understanding of developmental physiology is essential.

Developmental changes: During infancy the thoracic cage is flaccid and less efficient, and the relative dysfunction of the diaphragm will result in reduced efficiency and lower fatigue threshold compared with older children. In young infants, the highly compliant chest wall results in minimal outward elastic recoil, such that, during passive expiration, the lungs recoil to a much lower volume in relation to total lung capacity than in older subjects. The potential difficulties imposed by the compliant chest wall, which include instability of FRC and the tendency for small airway closure during tidal breathing, are at least partially compensated by the dynamic elevation of end expiratory level, whereby infants breathe in before they reach their passively determined resting lung volume. This occurs whenever the duration of expiration is less than 3 expiratory time constants, in other words, in the presence of either a short expiratory time (rapid respiratory rate) and/or a long expiratory time constant (usually associated with an elevated respiratory rate). In addition to changes in respiratory rate, babies often use laryngeal and post inspiratory diaphragmatic activity to slow (or brake) expiratory flow. In addition, due to airway — parenchymal interdependence, airway calibre is highly dependent on the surrounding distending pressure. This is particularly true for the intra-thoracic airways which lack the cartilaginous support of the trachea and which become increasingly compliant toward the periphery of the lung. The intra-thoracic airways are subject to marked changes in distending pressure throughout the breathing cycle. At high lung volumes, elastic recoil increases thereby holding airways wide open but there is progressive decrease in airway calibre during expiration. This volume dependency of airway calibre, and hence tendency to airway closure towards end expiration is particularly marked in the presence of airway disease, low chest wall recoil (infants) or loss of lung recoil (elderly).1

Airways are large at birth in relation to lung volume. The different growth patterns of lungs and airways after birth result in a changing relationship between flows and volumes due to what has been termed dysanaptic growth and influence the rate of lung emptying in relation to lung volume with growth.1 While there is the potential for longitudinal assessments of parameters such as FEV0.5 from birth, some caution will need to be exercised when interpreting results. FEV0.5 during infancy reflects airway calibre at low lung volume (FEF85%) whereas in a preschool child, FEV0.5 may reflect more central airway function (FEF60%) due to the reduced rate of lung emptying with growth. Therefore, longitudinal measurements of FEV0.5 in the same child are unlikely to provide physiological information from the same airway generations on each occasion.

Which test when?
The choice of which test or combination of tests to undertake must be guided not only by the clinical condition or specific research question being investigated, but also by the expertise of the operators. Those less experienced with the undertaking of ILFTs will inevitably take longer, have a higher failure rate and find it more difficult to complete a complex protocol within the limited time that the infant remains in quiet sleep.

Tidal breathing
Accurate measurement of tidal breathing is fundamental to most infant ILFTs. Although superficially appearing to be one of the simplest investigations to undertake, such measurements and their interpretation are in fact highly complex. Patterns of tidal flow-volume loops can yield potentially important information about the likely site of obstruction.2 Peripheral airway narrowing generally produces a concave pattern of the expiratory flow-volume loop, with peak tidal flow occurring early in expiration. This pattern probably reflects a reduction in post-inspiratory diaphragmatic activity, or laryngeal braking in the presence of a prolonged \( \tau_e \) due to elevated airway resistance. Flattening of the expiratory limb is suggestive of a fixed extra-thoracic airway obstruction, whereas marked convexity of the volume axis may reflect physiologic braking of expiratory flow. However, considerable caution is required when interpreting such loops due to marked natural physiologic variability within and between children, particularly during early infancy.

Passive respiratory mechanics (Single occlusion technique)
Measurements of passive respiratory mechanics (compliance, resistance, and \( \tau_e \)) are potentially possible if a state of relaxation can be induced in the respiratory system.3 The occlusion technique for measuring passive respiratory mechanics is based on the ability to invoke the HBR by performing brief intermittent airway occlusions during spontaneous tidal breathing. Activation of vagally mediated pulmonary stretch receptors when the airway is occluded above FRC leads to inhibition of inspiration and prolongation of expiratory time.

Provided there is no respiratory muscle activity and rapid equilibration of pressures across the respiratory system during airway occlusion, alveolar pressure and hence elastic recoil of the respiratory system can be measured at the airway opening. By relating this recoil pressure to the volume in the lungs above the passively determined end-expiratory volume at time of airway occlusion, or to the air follow occurring on release of the occlusion, the compliance and resistance of the respiratory system can be measured. Results are usually expressed as the mean of three to five valid measurements.

With persistence, these conditions can be achieved in the majority of healthy infants during quiet sleep, but they are more difficult to satisfy in infants with severe airway disease, in whom pressure equilibration may not occur rapidly enough in the presence of severe airway obstruction or a rapid respiratory rate, and in whom the respiratory system can rarely be described by a single time constant, due to heterogeneous distribution of any airway obstruction or interstitial lung disease. It should also be remembered that results from the single-occlusion technique reflect the combined mechanics of the entire respiratory system (chest wall, lungs, and airway), which may
reduce the ability to detect subtle changes in lung and airway function in those with respiratory disease.

**Plethysmography**

Measurements of lung volume are essential for accurate interpretation of respiratory mechanics, and may be a valuable means of defining normal lung growth. However, the only lung volume that can be measured routinely in infants is the resting lung volume at end expiration, i.e., the functional residual capacity (FRC). FRC\textsubscript{pleth} measures the total volume of gas within the lungs, i.e., all compressible gas in the thorax including any trapped gas. However, as it depends on rapid equilibration of pressure at the airway opening, there may be errors in the presence of severe airway obstruction (i.e., FRC\textsubscript{pleth} may be overestimated).

The commonest abnormality of lung volume during infancy is that associated with airway obstruction, wherein both hyperinflation (due to dynamic elevation of lung volume in the presence of an elevated airway resistance and a long $t_{RV}$) and gas trapping (due to peripheral airway closure) result in elevated FRC values in wheezy infants and those with diseases such as CF.

**Forced expiratory techniques**

Partial expiratory flow volume (PEFV) curves can be produced by wrapping a jacket around the infant’s chest and abdomen, and inflating this at the end of tidal inspiration to force expiration. The resultant changes in air flow (and hence volume) are recorded through a PNT attached to a face mask, through which the infant breathes. This technique is referred to as the “squeeze”, or tidal rapid thoraco-abdominal compression (RTC) technique.\textsuperscript{4} The maximal forced expired flow at FRC ($V\textsubscript{maxFRC}$), which is a measure of forced expired flows (FEF) at low lung volumes (i.e., similar to FEF\textsubscript{50} in older children), is the most commonly reported parameter derived from this technique.

For accurate and reproducible $V\textsubscript{maxFRC}$ data, it is essential that:

- any leaks around the face mask are eliminated
- the jacket is fitted correctly
- a stable and representative EEL is established before forcing expiration
- flow limitation is achieved

**The raised volume RTC**

Despite the popularity of the tidal RTC, its value when assessing either baseline airway function or bronchial responsiveness may be limited by the dependence of reported values of $V\textsubscript{maxFRC}$ on resting lung volume, which may be unstable in infants, particularly in the presence of disease or following interventions. The RTC technique has therefore been modified to allow measurements over an extended volume range using what has become known as the raised volume rapid thoracic-abdominal compression (RVRTC) technique.\textsuperscript{5} The RVRTC allows the infant’s lungs to be inflated toward total lung capacity before rapid inflation of the jacket initiates forced expiration from this elevated lung volume, with the manoeuvre ending when the infant reaches residual volume (RV). Application of 3–5 augmented breaths, using medical air, to induce a respiratory pause before forcing expiration generally overcomes the problem of infants inspiriring before full expiration to RV has been achieved.

Several studies have indicated that RVRTC may be more discriminative than tidal RTC for distinguishing the effects of respiratory disease on airway function. Although there is insufficient evidence to produce firm guidelines, an ATS-ERS Task Force has produced a consensus statement that provides preliminary recommendations pertaining to equipment, study procedures, and reporting of data for the RVRTC, based on what is perceived to be current best practice.\textsuperscript{5}

**Advantages and Limitations of the RVRTC**

FEF\textsubscript{50} can only be reliably reported if a valid assessment of FVC is available. Underestimation of FVC (with concomitant overestimation of FEF\textsubscript{50}) will occur if the child breathes in before RV has been reached. By contrast, underestimation of FVC because of failure to deliver the specified inflation pressure,\textsuperscript{6} or because of accumulation of gas in the stomach during the lung inflations, will result in underestimation of both FEV\textsubscript{1} and FEF\textsubscript{50}. Failure to reach flow limitation by using too low a jacket pressure may have minimal effect on FVC, but will underestimate both FEV\textsubscript{1} and FEF\textsubscript{50}.\textsuperscript{7}

The raised volume technique is technically more demanding than partial flow-volume manoeuvres. Extensive training and dedicated personnel who can ensure precision with respect to timing and inflation pressures are essential to assure accurate results.

**Importance of appropriate reference data**

Like most medical observations, reliable interpretations of lung function test results rely on the availability of appropriate reference data to help distinguish between health and disease and to assess the severity and nature of any functional impairment. However, the choice of a reference equation may dramatically influence the interpretation of results and the use of inappropriate reference equation can lead to serious errors, in both under- and over-estimation of the abnormality.\textsuperscript{8} Recently, equipment-specific reference equations for interpreting infant lung function data collected using the Jaeger BabyBody device has just been published\textsuperscript{9,10} which will enhance interpretation of infant lung function results particularly during longitudinal follow-up. A detailed manual of ILFT using the Jaeger BabyBody Plethysmograph is available for download from http://discovery.ucl.ac.uk/1430460.\textsuperscript{11}

**References**


**#2. FORCED OSCILLATION TECHNIQUE IN PRESCHOOL CHILDREN**

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Although having information on lung function during the preschool age (2–5 years) would be extremely important, measuring lung function in...
preschoolers is often very difficult, mainly due to their physiological differences from older children and their short attention span (1). For instance, obtaining a reliable and reproducible forced expiratory flow-volume maneuver in a 3-year-old boy may be unfeasible, since the acceptability criteria for spirometry are often unmet at this age. During the last century, we have fortunately witnessed the implementation of several lung function techniques that can be performed during tidal breathing and are therefore very appealing for the use in preschool children. It is important to highlight that the feasibility of any lung function technique in preschool children strongly depends on the capability of the operator of keeping the child quiet and focused (1). The American Thoracic Society/European Respiratory Society (ATS/ERS) Working Group on Lung Function in Young Children has published technical recommendations for most preschool techniques (1) and their clinical applications have also been recently summarized (2). This lecture will describe the forced oscillation technique (FOT), that for which its characteristics make it one of the most used lung function techniques in preschool children, focusing on its technical aspects, interpretation, and clinical applications.

FOT is a non-invasive technique performed during tidal breathing that allows the measurement of the impedance of the respiratory system (Zrs). Low-frequency pressure oscillations generated by a loudspeaker (usually 4–48 Hz) are applied to the mouth and superimposed to spontaneous breathing (1). Forcing signals based on sinusoidal waves or impulses have been used, both as single-frequency or composite signals. The resulting changes of mouth pressure and flow are measured, allowing the calculation of the two components of Zrs, resistance (Rrs) and reactance (Xrs). Rrs reflects the frictional losses of the respiratory system, while Xrs reflects its elastic properties at low frequencies and the inertial forces of the air columns at higher frequencies. Elastic and inertial forces are equal and opposite at the resonant frequency (Fres), i.e. the frequency at which Xrs is zero. Frequencies between 5 and 10 Hz are considered to reflect the mechanical properties of the total airways, while lower frequencies also reflect the contribution of lung tissue and higher frequencies reflect the properties of central and upper airways (1).

In preschool children, FOT is performed while the child is seated with the head slightly extended. The child should wear a nose clip and breathe quietly through a mouthpiece and anti-bacterial filter and his/her cheeks should be supported by the operator’s hands to reduce upper airway compliance (1). Each measurement should cover several breathing cycles (at least 8 s), the mean of 3–5 measurements should be reported, and the coefficient of variation (CV) should be calculated for each frequency and used as a reliability index (1). Overall, the feasibility of FOT is reported to be very good in preschool children (between 79% and 95%) (2) and several commercial FOT systems are now available.

For the interpretation of a technique, it is important to know its reference values and its repeatability. Several reference equations have been published using FOT in preschool children (2–4) and its short-term inter-measurement coefficient of repeatability (CR, 2 standard deviations of the mean difference between two measurements about 15 min apart) has been shown to be between 1.1 to 2.6 hPa·L⁻¹·s for Rrs (corresponding to a relative change of about 12–30%) and 1.2 to 2.0 hPa·L⁻¹·s for Xrs (4–6). Similar repeatability values are reported after 2 weeks. The maximal bronchodilator response in healthy preschool children is also known, being about a 35% decrease for Rrs, and 65% increase for Xrs (6,7).

FOT has been used in many studies in preschool children with recurrent wheezing, children born prematurely, and those with cystic fibrosis (2). FOT has been shown to have a sensitivity of 76–90% and a specificity of 55–65% in discriminating healthy children from those with a possible diagnosis of asthma, especially with the help of the bronchodilator response (2). However, there is still no evidence for the clinical utility of FOT in preschool children (2,8) and longitudinal studies in this regard are needed.

References

#3. MULTIPLE BREATH WASHOUT IN PRESCHOOL CHILDREN

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Physiological Aspects
The importance of the peripheral airways in different lung diseases is increasingly recognized. Lung periphery is a low resistance system where means of gas transport (ventilation) are convection and diffusion dependent [1]. Transient or progressive increase of ventilation inhomogeneity, an estimate of peripheral lung function, often occurs early in prevalent chronic lung diseases. In preschool children aged 2–6 years with cystic fibrosis (CF), increased ventilation inhomogeneity may be present despite few respiratory symptoms and normal spirometry. Increased ventilation inhomogeneity has a high positive predictive value for structural pathologies such as bronchiectasis and relates to poor lung function outcomes later in life [2,3]. However, early intervention studies in CF provide evidence that, for example, 48 weeks inhalation therapy with hypertonic saline solution (7%) may improve ventilation inhomogeneity [4]. Data in older CF patients are reassuring. Interestingly, treatment responses in ventilation inhomogeneity from short-term interventions, such as bronchodilator inhalation in preschool children with severe wheeze, and hypertonic saline or intravenous antibiotics in older children with CF, seem more heterogeneous [5]. The latter may relate to complex dynamic changes in obstruction or bronchodilator response on multiple airway levels and patchily distributed airway clusters.

Technical Aspects
Ventilation inhomogeneity can be assessed by multiple-breathe washout (MBW) estimating the tidal breathing effort required to ventilate a tracer gas...
such as sulfur hexafluoride (SF₆) or nitrogen. A recent MBW consensus is available and a similar document specifically for preschool children is underway [1]. Usually, an open by-pass system is manually switched from medical or room air to SF₆ or 100% oxygen for nitrogen MBW. MBW is performed until the end-tidal inert gas concentration reaches 1/40th of its starting concentration. Commonly reported indices are functional residual capacity (FRC) and lung clearance index (LCI = cumulative expired volume/FRC), a marker of global ventilation inhomogeneity. For more detailed characterization of ventilation inhomogeneity, some setups allow calculation of the slope indices Scand and Sacin reflecting convection- and diffusion-convection-dependent ventilation inhomogeneity, respectively. The latter was recently shown to closely correlate with tracer gas diffusion in adults with asthma using magnetic resonance imaging.

**Chances and Challenges in Clinics**

Several centers apply MBW as a clinical routine test with varying success [6]. Maintenance of adequate mouthpiece/facemask seal and regular tidal breathing for several minutes can be demanding. Preliminary data from Toronto suggest that the use of facemasks does not improve success rates compared to a mouthpiece with a nose clip. In addition, greater dead space from the facemask may influence ventilation inhomogeneity indices and makes direct comparison with data obtained by mouthpiece difficult. Few MBW setups have been validated for the use in the preschool age range as recommended in the current consensus [7]. Pure oxygen for nitrogen MBW may however alter breathing patterns in infants but this does not seem to be the case in older children [8, 9].

No criteria yet exist to identify the “best” MBW attempt as compared to spirometry. Averaged indices from triplicate MBW with FRC varying ≤10% within tests are encouraged but can be problematic in young children. Short-term repeatability between tests depends on the index and the setup. The coefficient of repeatability of LCI from two tests 20 minutes apart is 9–11% and similar to adults. Variability for Scord and Sacin in preschool children is much greater compared to adults [5, 7]. The minimal clinically important difference between two tests remains unclear. Normative data are preliminary and also depend on the setup. For LCI, the upper limit of normal (mean + 1.96 × standard deviations) appears to be 8.4 for a SF₆ setup and 7.9 (lung turnover) for a nitrogen setup [6, 10].

**Conclusion**

MBW is challenging in preschool children but is nonetheless considered as a sensitive physiological outcome measure; especially in CF. More studies in other disease groups are warranted. The impact of MBW on clinical decision making is less established and hampered by scanty data from available setups. The upcoming consensus will provide guidance for validation and application of MBW in preschool children.

**References**


Janus looks back: where are we now?

Much of what we do has stagnated over the past decades, and makes depressing reading.

- We use umbrella terms such as bronchiolitis and asthma, often with no agreement about what they mean, little understanding of pathophysiology and pathways, and with no specific treatments [1].
- For many diseases we have very little in the way of evidence-based treatments, and rely on extrapolation from adult studies or other more common diseases.
- Our means of monitoring what is going on are pitiful, little beyond asking ‘how are you?’ and ‘are you taking treatment’ for many diseases and especially below school age.
- Our interactions are stuck in the same sterile model of face to face consultations, often hurried on the paediatrician’s side and preceded by a long wait by the family.
- We are stuck in silos: developed world vs. low and middle income countries (LMICs), paediatric respiratory medicine vs. adult disease, and within institutional silos in the developed world. Fragmentation has led to our children becoming second class citizens, not least in having paediatric research projects fragmented.
- As a further consequence, too much research is becoming increasingly inward looking and developed world focussed – do we really need another inhaled steroid/long acting β-2 agonist combination? Really? Especially when many children with asthma in LMICs cannot even get beclometasone regularly?

Janus looks forward: Where do we want to go?

In summary: modern concepts of disease, learning more from the diversity of disease across the globe, better monitoring and communications, and really big studies on pathway specific treatments of disease.

- The best paradigm of modern disease management is cystic fibrosis (CF): a disease which for the most part is readily diagnosed with a simple, cheap and widely available test (the sweat test); for which the gene is known, and an understanding of the different classes of genes mean we have passed to the age of designer, gene class mutation-specific therapies, such as ivacaftor, lumacaftor and ataluren. We would have never appreciated the benefits of ivacaftor if it had been given to every child with a chronic productive cough, or even every child with CF [2].

Similarly, anti-IL5 strategies were nearly lost as a therapeutic modality in asthma because they were initially trialled in the wrong sub-phenotype. We need to reach the CF stage with all other airway diseases. We must develop biomarkers of important disease pathways, and make them available across the world.

- On the attack on lung attacks. We use the flabby word ‘exacerbations’, implying that these are reversible, minor nuisances. In reality, in many airway diseases, they are markers of worse outcomes, both short and long-term. The cardiologists respond in a focussed way to ‘heart attacks’ – it should be the same for us with ‘lung attacks’.
- Do the big studies early – the dismal recommendation for hypertonic saline in bronchiolitis made on the basis of pitiful evidence has been overturned by really big studies which should have been done in the first place [3,4]. Again a lesson from CF where the evidence base is being driven relentlessly forward by a series of definitive trials. This has been facilitated by units coming together, being driven out of silos by patient advocacy and power. Another challenge in research is to do the globally important studies, not those that stuff the financial maws of developed world, big pharma. Why do we not have proper evidence-based therapy in children, particularly in the many diverse rare diseases we encounter?
- Advocacy for children must become more powerful. We know that tobacco smoke exposure, traffic pollution, and indoor pollution in LMICs are associated with worse lung growth, and that interventions to rectify these adverse exposures improve lung growth. Why do we let adults continue to harm children with tobacco and polluting vehicles both antenatally and postnatally – do we need these in residential areas? Why do we allow poverty to harm children through the medium of biomass fuels? Paediatricians across the world should unite against common pollutants, with their long term adverse effects, whether these adverse exposures are local or general across the world. If our voice is not heard for children, then whose will be?
- We can track satellites to the edge of our solar system and beyond; surely we must track whether treatment is being taken (and not merely the device activated) and whether the child is symptomatic a bit more accurately than this. As children with rapidly progressive diseases such as CF once was become fitter and fitter, will they want to keep trailing up to clinics? We will minimise these with automated monitoring, as smartphones become smaller, smarter and cheaper.
- We must bring advances to children across the world, and also learn from each other across the globe. Airway disease in LMICs, with a huge early burden of infection, is likely very different from the developed world. One of many gloomy examples is from paediatric sleep medicine – more and more measurements are routine in the developed world, but the greater the sophistication, the greater the irrelevance to LMICs. We are a global family, and must function that way.

Janus tries to predict: how will we get there?

Above all things, stop being complacent and challenge established concepts and always, always challenge dogma, especially if they are held as Gospel! Part of the route we need to go is:

- Think of the dog which did not bark in the night-time – what are the facts which do not fit? Remember the idiot who thought he saw spirochetes in duodenal ulcers? We now cure ulcers with antibiotics. The so-called sterile lung is no such thing [5] and is as impossible as a flat earth, yet both

THE FIELD OF PAEDIATRIC RESPIRATORY MEDICINE: WHERE ARE WE HEADING?

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Introduction Like the double-headed god, Janus, this talk requires me to look back to inform speculation about the future of our speciality – a dangerous occupation, in particular as (hopefully) increasing longevity will allow me to see how off target I was! The aim of this talk is to give a manifesto for paediatric pulmonology in the next ten years and beyond, and (of course!) by so doing stir up controversy.

Janus looks back: where are we now?

Like the double-headed god, Janus looks back: where are we now?
were given credibility for far too long. Indeed airway bacteria are needed for normal development [6]; what is our 21st century concept of an airway infection?

- Leading on, we need to go beyond Koch’s postulates. They have served us well, and of course in some diseases (TB the obvious example) are still applicable. But what is airway infection? The word carries bad connotations. Micro-organisms can be present as the primary adverse event and be harmful; present secondary to disruption of mucosal defences and be harmful, beneficial or neutral; present and beneficial or neutral; and many other permutations can be imagined. Bacteria are present in the airway at the time of asthma attacks; so should we treat asthma attacks with antibiotics [7]? Janus says no, not without a huge paradigm shift in the past, asthma was treated with antibiotics repetitively, with no benefit. We definitely need a new approach before going that route.

- There is strength in numbers, but not in committees. Groups coming together are the key, bringing different skills to the table, but decision making by committee never works. So we need people who are leaders, thinking clearly but also able to pull teams together across disciplinary boundaries. The STELAR initiative is a clear example of the power of this approach [8]

- Paediatrics must come out of its silo – having had our adolescent rebellion against adult medicine, we must recognise we have so many commonalities with adult physicians. Daringly, Janus predicts the decline of the stand-alone Children’s hospital, which is only relevant for those few diseases with no survival to, or sequelae in, adult life. Medicine itself must also come out of the silo – we have so much to learn from bio-engineers, physicists, mathematicians and so many others

- Above all else, answers will NOT come from big data, but from incisive thinking – we need next-generation thinkers, not next-generation sequencing

Janus sums up

This is an exciting time for our subspeciality – now is the time for the upcoming leaders to transform our approaches and bring us into the 21st century in our approaches to disease management, extending across the globe.

References
Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality worldwide and represents a significant public health concern. Prevalence varies from 5% to 22% among adults older than 50 years and represents the fourth most common cause of death worldwide. COPD has always been considered exclusively as an adult disease, characterized by an incomplete reversible and progressive obstruction, associated with inflammation. Functionally, COPD is defined as a chronic airflow obstruction with a forced expired volume in one second/forced vital capacity (FEV₁/FVC) ratio of less than 70% following bronchodilatation. However, using a fixed ratio to make a diagnosis is often not clinically accurate; in fact, the “normal” range of FEV₁/FVC ratio changes with age. Originally, COPD was considered a “lifestyle” disease caused by cigarette smoking but, in the last decade, the evidence that many nonsmokers get premature air flow obstruction led to new interesting research. Treating children and adolescents, we are used to consider diseases as a multifactorial evolution process and COPD, even if clinically apparent in adulthood, is now accepted to have its origins very early in life, therefore it is an interesting topic also for pediatricians.

As well known, a critical time for airway and alveolar development extends from the first weeks of pregnancy to school-age (some studies suggest that it might continue until the age of 21 years); therefore, significant stimuli and insults during this period could determine developmental adaptations that will generate permanent structural, physiological and epigenetic changes. For instance, lung function can already be compromised during lung development in utero in those children whose mothers smoked in pregnancy or had an inadequate nutrition. Other known risk factors, leading to impaired lung function soon after birth, are maternal atopy and hypertension. Whether some of these effects are mediated directly or indirectly through prematurity (<33 weeks or late preterms), low birth weight or rapid catch-up growth in infancy have not been completely established. Although the multiple risk factors affecting fetal lung development are described individually in the literature, continuous interactions between these factors are essential in predisposing to COPD.

After birth, several genetic factors, environmental factors and lifestyle habits might lead to different entities of chronic obstructive pulmonary disease depending on when they are encountered and in what combinations. It has been already shown that indoor and outdoor air pollution and other environmental triggers, such as parental cigarette smoking, are to be considered significant risk factors for the development of COPD. Differently, the negative impact of early viral infections on long-term lung development and function is still under debate. The most recent hypothesis is that lung development is actually already altered due to antenatal insults and predisposes the child to early respiratory illnesses and subsequent chronic airway obstruction. Moreover, high relevance for the risk of COPD could be given to early bacterial colonization and the presence of healthy lower airway flora which is closely related to a normal immunological development and regular response to airway stimuli. As known for other respiratory illnesses, COPD is a multifactorial disease in which environmental factors interact with personal genetic characteristics. Finally, dietary factors and nutritional aspects during fetal development and along all life course also play an important role in the respiratory functional status of subjects. In childhood, both malnutrition and obesity, the latter being more frequent in western countries, often track into adulthood and negatively affect lung function towards airway obstruction conditions.

In summary, COPD can no longer be considered just a “self-inflicted” adult disease of heavy smoking subjects but is definitively a more complex and heterogeneous illness. The role of all health professionals involved with the care of pregnant women and of pediatricians on preventing risk factors during and after pregnancy and subsequently on optimization of lung health in childhood is important. It is now recognized that COPD is a multifactorial disease which has part of its origins in utero and in the early years of life. More research studies are needed but both genetic factors and environmental factors need to be taken into account in our daily practice as they are already accepted to influence lung development and play important etiologic roles in chronic obstructive pulmonary disease.

Bibliography

- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy For The Diagnosis, Management, and Prevention of COPD (Updated 2016).
multicenter Canadian Oxygen Trial (COT), infants born at 23–27 wk gestational age (GA) were randomized to a lower (85–89%) or higher (91–95%) pulse oximeter saturation (SpO2) target range. SpO2 and pulse rate were continuously monitored, stored and downloaded. This allowed us to separately examine the relationships between episodes of hypoxemia (SpO2 < 80%) or bradycardia (pulse rate < 80 per minute) and protocol-specified outcomes of COT participants. Our main study question was: Among extremely preterm infants who survive to 36 weeks postmenstrual age, what are the associations between neonatal hypoxemia or bradycardia and the risks of a late death after 36 weeks postmenstrual age (PMA) or disability at 18 months corrected age? (2)

COT enrolled 1201 infants within 24 h of birth, who were randomized to the above target ranges using modified oximeters that displayed off-set SpO2 values between 84 and 96%. Averaging time was set to 16 s; data were sampled and stored every 10 s. Recordings lasted from enrollment until at least reaching 36 wk PMA. Downloaded data were screened for validity and invalid data excluded. Episodes of hypoxemia, defined as a single or consecutive values < 80% SpO2, and equivalent episodes of bradycardia, were identified; episode length was defined as the number of consecutive 10 s data entries below threshold, such that 6 consecutive entries below threshold approximated an episode duration of 1 min. An “area-under-the-curve” (AUC) was calculated for each episode as the product of its duration times the average depth below the threshold for this episode. Exposure to hypoxemia/bradycardia was calculated as the %time below threshold and as the average AUC/day.

All outcomes had been pre-specified for COT (2); only death was restricted to those occurring between 36 wk PMA and 18 months corrected age. Disability was defined as one or more of the following: motor impairment (GMCSF ≥ 2 level 2), cognitive or language delay (cognitive or language score in Bayley III < 85), severe hearing loss (prescription of hearing aids or cochlear implants) and bilateral blindness (corrected visual acuity less than 20/200 in the better eye). Secondary outcomes were motor impairment, cognitive or language delay, and severe retinopathy of prematurity (stages 4 or 5 or needing retinal/intravitreal treatment). Associations were assessed using logistic regression, adjusted for a pre-specified set of covariates (GA, gender, primary caregiver’s education, antenatal steroid use, multiple birth, study center). Data were subdivided into deciles of %time with hypoxemia/bradycardia. To check whether risk gradients changed with the duration of the hypoxic episodes, %time with hypoxemia was computed separately for episodes with <6 vs. ≥6 consecutive 10 s SpO2-values < 80%. Risk gradients were calculated from the logistic model as odds ratios contrasting the highest decile of hypoxic exposure with the lowest, based on the mean %time with hypoxemia in each of the two respective deciles.

Of the 1201 COT participants, 1035 survived to 36 wk PMA and 1019 could be included in the analysis cohort. Their mean GA at birth was 25.8 wk (SD 1.1), birth weight 855 g (189). 76% had been ventilated at enrollment, and 86% had received surfactant; 43% had the primary outcome of late death or disability, 40% cognitive or language delay, 6% developed motor impairment, and 13% severe ROP. Valid oximetry data were available for a median duration of 68.3 days (IQR 56.8–86.0). Median %time spent hypoxic was 3.3% (1.6–6.1); only 0.12% (0.09–1.17) of the time was spent with bradycardia. Hypoxic episodes lasting for ≥1 min. occurred at a median rate of 12 (5–24)/day, compared to 74 (37–113)/day for shorter episodes.

Mean %time with hypoxemia ranged from 0.4% in the lowest to 13.5% in the highest decile, with the probability of each adverse outcome investigated increasing with the %time spent hypoxic. Infants in the highest decile for hypoxic exposure had 2.6 times the odds of developing the primary outcome of late death or disability than infants in the lowest decile (95% CI 1.5–4.6). Corresponding odds ratios (OR) for the other outcomes were 5.3 (2.3–12.0) for motor impairment, 2.3 (1.3–4.0) for cognitive or language delay and 3.0 (1.4–6.2) for severe ROP. Risk gradients were much smaller for %time with bradycardia, with motor impairment showing the only statistically significant relationship. For all outcomes, stepwise modeling consistently selected exposure to hypoxemia over bradycardia on the first step, with bradycardia offering no additional prognostic information. Also for each outcome, ORs were lower and non-significant for shorter (<1 min) than for longer (≥1 min) episodes of hypoxemia. Equivalent analyses for AUC as predictor of outcome yielded similar results, but no meaningful advantage over the easier-to-calculate %time spent hypoxic. The differences in hypoxic exposure between infants who did and did not develop adverse outcomes became greater with increasing postnatal age, with the greatest risk gradients being present at 9–10 wk PMA. Also, the association between exposure to hypoxic episodes lasting ≥1 min. and the primary outcome was stronger for infants randomized to a higher SpO2 target range (91–95%) than for those randomized to a lower range (81–85%), i.e. larger fluctuations in SpO2 (reaching values < 80% from a higher baseline) seemed to have a stronger effect on death or disability than smaller ones.

In summary, this post-hoc analysis showed that in extremely immature infants, the risk of death beyond 36 wk PMA or disability increased with an increasing proportion of time spent with intermittent hypoxemia. The risks of motor impairment, cognitive or language delay, and severe retinopathy of prematurity were also increased. Intermittent bradycardia did not significantly add to the risk of adverse outcome, suggesting that bradycardia, in the absence of hypoxemia, may not be of prognostic importance. The severity of intermittent hypoxemia, expressed as the AUC, added little prognostic value to the simpler measure of the %time spent hypoxic. The duration of the hypoxic episodes, however, mattered: only those lasting for approximately one minute or more were significantly associated with an increased risk of an adverse outcome. Associations between hypoxic exposure and adverse outcomes were stronger at later postnatal ages and for infants who had been randomly assigned to a target oxygen saturation range of 91–95% compared with those assigned to a target range of 85–89%.

Associations such as those found here can never prove causality. Thus, while our data may suggest that prolonged intermittent hypoxemia may contribute to neurodevelopmental impairment, it is also possible that recurrent prolonged hypoxemia may be a consequence of previously acquired brain or lung injury. If, however, the former is true, then efforts to avoid intermittent hypoxemia should be increased. For example, neonatal caffeine therapy improves motor skills, reduces apnea and assists in the weaning from respiratory support (4), but whether this is due to a beneficial effect on intermittent hypoxemia is yet unclear. Also, other strategies currently applied to reduce intermittent hypoxemia, e.g. synchronized nasal ventilation or doxapram administration (5,6), should be further studied, perhaps with a focus on hypoxic episodes lasting for at least 1 min.

References
Pulmonary hypertension (PH) contributes significantly to high morbidity and mortality in the diverse pulmonary, cardiac, and systemic disorders in children. Despite growing awareness of the impact of PH and related pulmonary vascular disease (PVD) in children, pediatric PVD has been understudied and remains poorly understood. PH-related hospitalizations of children are increasing, which likely reflect improved recognition and awareness of the role of PH in diverse settings, or perhaps, an actual increase in the incidence of disease. Problematically, there is a limited understanding of disease-specific mechanisms and outcomes in pediatric PVD. Studies are often complicated by the marked heterogeneity of conditions and co-morbidities associated with PVD, the relatively small number of patients at each center, the dependence on anecdotal experience or adult-based studies, and other factors.

While similarities exist regarding the etiology and disease pathogenesis of some forms of pediatric and adult PH, many cardiopulmonary and systemic diseases associated with PH are unique to neonates, infants and children. First, multiple aspects of the developmental biology of the growing lung are key determinants of disease pathobiology. Vascular injury during susceptible periods of growth and adaptation can have long-standing impact on vascular growth throughout childhood and may impact growth of the distal lung airspace as well. Examples include the growing recognition of the important impact of PVD after premature birth, the contribution to poor outcomes in many developmental lung diseases, the association with genetic syndromes, especially Down syndrome, and other factors, that reflect both prenatal and postnatal influences.

In addition, there are striking maturational differences in responsiveness to PH-specific therapies, drug pharmacodynamics and pharmacokinetics, and the potential for long-lived adverse effects. In addition, little is understood regarding critical co-morbidities that impact long term outcomes in specific diseases with PH; how to best monitor disease progression or response to therapy; and whether early recognition or preventive therapeutic strategies can be applied in children to minimize disease severity during adulthood.

The definition of PH in pediatrics is nearly identical to that applied to adults but some important differences exist. Pulmonary artery pressure (PAP) exceeds 25 mmHg. However, the lack of elevated PAP does not exclude the presence of pulmonary hypertensive vascular disease (PHVD) in some settings. In particular, PVR is a new measurement of disease and management of PHVD in children with congenital heart disease (CHD). Pulmonary PH is currently categorized in similar fashion as adult PH, which is based on the World Health Organization (WHO) classification that was most recently revised at the 5th World Symposium for Pulmonary Hypertension that was held in Nice, France. Based on concerns regarding the applicability of an adult-focused system for the phenotypic heterogeneity of neonatal and childhood PH, the pediatric task force of the Pulmonary Vascular Research Institute, an international collaborative group that was created to promote global research in PH, proposed a novel system that may prove useful as a pediatric-specific system. The goals of the Panama Classification System are to highlight the phenotypic heterogeneity of PHVD from the fetus to the adolescent and the impact on diagnosis, treatment and research, but whether this system has clinical utility remains unknown.

Although the true incidence and prevalence of PH in the pediatric population remain uncertain, recent epidemiologic data from national or international registries estimated an annual incidence of 64 cases per million children. The incidence of idiopathic PAH was 0.7 cases per million and PAH associated with CHD was 2.2 cases per million. Delays in making the diagnosis of 1–2 years after the onset of disease are not uncommon in pediatric PH, which is likely due to the non-specific nature of early symptoms, such as dyspnea on exertion, fatigue and syncope. Children with PAH are often misdiagnosed with more common childhood conditions such as asthma, vasovagal syncope or seizures prior to diagnosis with PAH.

Due to disease complexity and the importance of experience with specific diagnostic procedures and therapeutic strategies, the evaluation and care for pediatric PH patients should be co-managed by specialty PH centers that include comprehensive, multidisciplinary medical subspecialists, nursing, and social work expertise. Routine follow up visits should be performed, at a minimum, every 3–6 months with more frequent visits for patients with advanced disease or after initiation of changes to therapy. Those co-managed should be seen, at a minimum biannually by or in consultation with PH specialty centers. At the time of initial PH diagnosis, a comprehensive history and physical examination in combination with diagnostic testing for assessment of PH classification, and formal assessment of cardiac function should be performed. Specifically, a chest x-ray, electrocardiogram, echocardiogram, chest CT with and without contrast, 6 minute walk test, laboratory studies including brain natriuretic peptide (BNP), and cardiac catheterization should be considered critical components of a thorough evaluation. Other tests such as a sleep study, cardiopulmonary exercise testing, additional laboratory work, magnetic resonance imaging, and lung perfusion scans may have greater value in select populations.

Survival in pediatric PH has improved dramatically since the advent of targeted PH therapies. In contrast with a 3 year survival rate of less than 50% in historic data, the Registry to Evaluate Early and Long-Term PAH (REVEAL) reported 1-, 3-, and 5-year estimated survival rates in children of 96%, 84%, and 74%, respectively, with no significant difference between IPAH and CHD-associated PAH. Additional data are needed from prospective registries and informatic studies to better understand the true prevalence, natural history and outcomes of diverse forms of pediatric PH. Recently, the American Thoracic Society and American Heart Association sponsored the development of guidelines for the care of children with PH, that may help standardize care and outlines critical knowledge gaps for future clinical studies. The establishment of multi-disciplinary clinics with specialized expertise in pediatric PH, which includes specialties such as pulmonary, cardiology, neonatology and others, will likely continue to enhance long-term outcomes.

References

Pediatric Pulmonology
HFNC has been used since some 15 years now in preterm newborns, first as an alternative to nasal CPAP in infants with apnea of prematurity, and subsequently for initial respiratory support at birth and post-extrusion. More recently, its use has been advocated for moderate to severe acute viral bronchiolitis in infants as well as various other forms of acute respiratory distress in children and even adults. Of note, most studies to date have been observational; fortunately, several randomized control trials are currently underway (2). A recent randomized clinical trial in adults with non-hypocapnic acute hypoxemic ventilatory failure showed that treatment with HFNC, oxygen delivered by mask or noninvasive ventilation did not result in significantly different intubation rates; in addition, HFNC was superior in decreasing the number of days with endotracheal intubation and 90-day mortality (3). Of note, the use of HFNC implies close monitoring to identify the need for escalation to other types of respiratory support without delay. Aside from the acute setting, the use of HFNC has been reported as an alternative to nasal CPAP in obstructive sleep-disordered breathing in infants and children. Further studies are also needed for this promising indication.

#4. NON-INVASIVE RESPIRATORY SUPPORT: SELECTED HIGHLIGHTS 2016

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Introduction

From the intensive care unit to the home setting or from the extreme preterm newborn to the frail elderly person, non-invasive respiratory support is increasingly used for the treatment or prevention of acute ventilatory failure, as well as for the treatment of chronic respiratory insufficiency. In particular, the number of available support modalities and interfaces for neonates and children, as well as the indications for non-invasive respiratory support have continuously grown over the last 10 years or so. For example, nasal CPAP or nasal intermittent positive pressure ventilation has replaced endotracheal ventilation as the mainstay of respiratory distress syndrome treatment in preterm newborns. As well, with the recognition that patient-ventilator asynchrony can lead to failure of non-invasive ventilation, synchronized modes of non-invasive ventilation, and in particular neurally-adjusted ventilatory assist, have been claimed to be superior to other ventilatory modalities in the intensive care unit. In the home setting, while long-awaited interfaces have been developed for young children, potential beneficial new modalities such as AVAPS (Average Volume Assured Pressure Support) are now available, and round-the-clock non-invasive ventilation has become a frequent occurrence. All of the developments in non-invasive respiratory support that have emerged in recent years in pediatrics cannot be comprehensively presented in the following update. My biased contribution will highlight three topics, which may be as of yet unknown and/or appear of particular clinical relevance.

1- High Flow Nasal Cannula

High Flow Nasal Cannula (HFNC) usually refers to the delivery of a humidified and warmed oxygen-air mixture (21% to 100%) at flow rates >2 L/min (or = 2L/kg/min) in infants and >6 L/min in children (up to 60 L/min in adults). Reported physiological advantages of HFNC include increased mucociliary clearance (gas humidification), decreased inspiratory resistance (humidification and warming of gas), upper airway dead space washout, airway positive pressure (inconstant, depending on the diameter of the nasal prongs relative to the nares, and on the flow delivered to the patient) and decreased work of breathing (1). Other clinical advantages are dyspnea relief, a more efficient oxygen delivery compared to facial mask, and better comfort/tolerance than non-invasive respiratory support such as nasal CPAP or non-invasive ventilation. Moreover, easiness of implementation is appealing, including in low-income countries.
laryngeal closure was never observed during neurally-adjusted ventilatory assist. In addition, it was abolished by mild hypercapnia (PaO\textsubscript{2} = 50 mmHg), but not prevented by increasing the inspiratory pressurization time (10). It remains unclear whether such laryngeal closure is beneficial, namely by protecting against a too high positive airway pressure, the latter of which may over-distend the lung. Alternatively, laryngeal closure could be deleterious, by limiting lung ventilation and diverting the gas flow either into the esophagus or externally through to the mouth.

References

#5. BEST NEW OPTIONS FOR TREATING OR PREVENTING SEVERE RSV INFECTIONS AND BRONCHIOLITIS

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RSV is the most frequent cause of bronchiolitis and pneumonia in infants and young children, and a source of significant morbidity, mortality, and financial burden worldwide (1). Transmission occurs through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infected individuals. Viral shedding persists for approximately 1 week, but can be significantly prolonged in immunocompromised individuals (2).

Infants with RSV infection typically present with upper respiratory symptoms that frequently progress to involve the lower respiratory tract with cough, wheeze, and increased work of breathing (3). Chest radiographs typically show hyperinflation, patchy infiltrates, and atelectasis. Apnea can be the presenting manifestation, especially in young infants. Supportive care is the mainstay of therapy for RSV disease and is directed at ensuring adequate oxygenation, improving respiratory toilet, and meeting fluid and nutrition requirements (4). Severe respiratory failure requires mechanical ventilatory support, and occasionally HFOV or ECMO.

Treatment
Adrenergic α- and β-agonists do not provide consistent benefit in the treatment of RSV disease, although a brief trial with objective evaluation of the response may be warranted. Neither systemic nor inhaled corticosteroids have been shown to provide clear advantages in the treatment of RSV disease, and therefore their use is not recommended. The antiviral drug ribavirin is also not recommended for routine treatment of RSV infection, but may be considered in select immunocompromised individuals (5). Recently, treatment of experimentally inoculated adult human volunteers with new oral antivirals started after the infection had become established to inhibit fusion of the RSV capsid with cell membranes has shown some promise (6). However, these studies are still at a very early stage, and substantial additional evidence is necessary to carefully evaluate their potential role in the prevention and therapy of RSV disease in clinical settings. In particular, the sample size of these studies was quite small and it is problematic to extrapolate such data to the natural target population of naturally infected infants.

Prevention
No vaccine exists today for active prophylaxis against RSV. A formalin-inactivated vaccine marketed in the United States in the 1960s had to be withdrawn because — in addition to being poorly immunogenic — it predisposed children to aberrant Th2-type immune responses and life-threatening disease upon subsequent exposure to wild-type virus. Since then, a vast array of experimental approaches, ranging from purified capsid proteins to attenuated or inactivated virus, have failed to deliver a safe and effective vaccine. Only recently, new hope has been sparked by the use of cutting-edge structural biology to engineer a stabilized and customized version of the RSV F surface protein (“immunogen”) that binds highly protective antibodies and triggers a potent RSV-specific neutralizing response when injected into animals. Perhaps the most important success in the war against RSV so far has been the development of safe and effective passive prophylaxis, first with polyclonal intravenous immunoglobulin, and later with monoclonal antibodies for intramuscular administration (7). Palivizumab is a humanized IgG1 monoclonal antibody (hMAB) developed by MedImmune, Inc. and licensed by the United States Food and Drug Administration (FDA) since 1998 for the prophylaxis of children at high risk for severe RSV disease. With this technology, murine-derived sequences complimentary to the A antigenic site of the RSV F-protein were grafted into a human IgG frame, resulting in a protein that is minimally immunogenic. Palivizumab is administered monthly during the RSV season as an intramuscular dose of 15 mg/kg, which has consistently shown an excellent safety profile. Unfortunately, its use is currently limited to infants at high risk for severe disease due to limited clinical benefits and high costs. AAP guidelines providing a better definition of “high risk for severe RSV disease” were originally published a few months after FDA approval, and have been subsequently revised 4 times to account for new evidence from post-marketing studies and to balance the limited clinical benefits with the high costs of this expensive biological agent (currently ~$3,000 per vial). The most recent AAP Policy Statement - published in 2014 to replace the recommendations found in the 2012 Red Book and in the 2006 AAP guidelines for the diagnosis and management of bronchiolitis - is significantly more restrictive than the previous revisions (8). Palivizumab prophylaxis is now recommended only in the first year of life for otherwise healthy infants born before 29 weeks gestation and for infants born before 32 weeks gestation with chronic lung disease of prematurity...
(CLD) defined as a requirement for supplemental oxygen for at least 28 days after birth. Prophylaxis is no longer recommended in the second year of life, except for infants with CLD still requiring oxygen, corticosteroids or diuretics, and should be discontinued after a breakthrough RSV hospitalization. Palivizumab may be considered also for children with hemodynamically significant congenital heart defects, profound immunodeficiency, and pulmonary or neuromuscular pathologies impairing airway clearance, but no formal recommendation was made for patients with Down syndrome or cystic fibrosis due to insufficient data.

As shown by preclinical studies in cotton rats, palivizumab provides optimal protection with blood levels above 40 μg/ml. Unfortunately, by using the recommended dosage, trough concentrations after the first monthly injection fall below the protective level in more than half of the patients. Subsequently, trough levels increase after each monthly injection because of progressive accumulation. This explains why almost half of all breakthrough RSV hospitalizations in prophylaxed infants occur after the first injection, while less than one-third occur after the first two. Furthermore, palivizumab dosage is not sufficient to reach protective levels in the nasal mucosa, and therefore does not prevent infection of the upper airways or middle ear.

To address these limitations, a second-generation IgG1 monoclonal antibody (motavizumab) was synthesized based on computer modeling, studied in a variety of preclinical models, and tested clinically up to a large multi-center phase III trial. The new monoclonal antibody had 70-fold higher affinity for the RSV F protein and was fully humanized. However, the FDA Advisory Committee voted not to recommend approval of motavizumab, justifying this decision based on questionable evidence that the new antibody provided additional benefit in comparison to palivizumab (non-superiority) and on concerns about the rare (2–3%) but statistically significant increase in serious adverse events involving the skin of infants.

Solid epidemiologic evidence suggests that early RSV bronchiolitis predisposes to recurrent wheezing and asthma during the first decade of life (9). This hypothesis has been confirmed recently by a randomized DBPC study showing that palivizumab significantly reduces the frequency of wheezing in infancy (10). However, this evidence is still limited to prematurely born infants and cannot be generalized yet to otherwise healthy children born at full term.

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#6. ENVIRONMENTAL CONTROL IN THE MANAGEMENT OF ASTHMA
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Introduction
In the recent decades, asthma and allergies incidence have increased, possibly related to changes in environmental conditions. In particular, children who live in inner cities have been reported to present with more severe asthma, requiring more important levels of medication, poorer disease control and greater healthcare costs and morbidity.

Exposure to indoor and outdoor pollutants and allergens has been speculated to be involved in asthma development and exacerbations. Consequently reducing asthma morbidity requires planning to reduce contributing factors and not only clinical aspects.

Environmental triggers are in- and outdoor allergens and irritants, including domestic pets, mould, house dust mite, environmental tobacco smoke, air pollution and aeroallergens.

Nowadays children spend a lot of time in indoor environments and preventive strategies to reduce exposure to these factors include different multifaceted interventions tailored to the specific sensitizations.

Preventive strategies in environmental control
Environmental control has been proposed to have a key role in asthma prevention and management.

Often, children are sensitized to a number of allergens and a personalized approach targeted to allergen and trigger avoidance may represent an appropriate strategy.

Nevertheless, most studies are focused on a single allergen, although a multifaceted approach is preferred. In fact, it has been reported that a single intervention intended as preventive strategy cannot significantly reduce asthma symptoms and exacerbations while the combination of multiple and combined strategies may be effective.

In 2000, and updated in 2014, the Committee on the Assessment of Asthma and Indoor Air of the IOM summarized the scientific evidence on the relationship between asthma exacerbations and indoor allergen exposure1. Different strategies of interventions have been demonstrated to be effective in reducing asthma symptoms and exacerbations.

A global program of intervention can be tailored in three main steps. First, a tailored in-home educational activity aimed to reduce asthma triggers in sensitized individuals; second, removal of mould items combined with reduction in humidity and leaks; third, implementation of preventive strategies to reduce exposure to HDN.

Dust mite exposure (HDM)

Dermatophagoides farinae and Dermatophagoides pteronyssinus allergens are concentrated in dust feces and are potent inducers of allergic disease.

House dust mite is one of the most common sources of indoor allergens, in particular at home and in the school environment, and are strongly associated with a humidity level >50%.

Exposure to high levels of HDM allergens is associated with a higher risk of allergic sensitization, asthma development and exacerbations, with a decline in lung function2. Several studies demonstrated a dose-dependent correlation between HDM exposition and allergen sensitization with greater medication use, health care utilization3. A relevant correlation was also found between exhaled nitric oxide (FeNO) measurement and HDM exposure in relation to airway inflammation. These data induced to speculate that a reduced exposure to mite allergens may improve quality of life in asthmatic patients.
Regarding this group of allergens, the best strategy to reduce HDM exposure includes washing and drying bedding weekly at high temperature, regular cleaning, use of dust-mite impermeable pillows, mattresses and box spring covers, control of indoor humidity below 50%, carpet avoidance and use of high efficiency particulate air (HEPA) vacuum cleaners. In some countries, “low-allergen schools” designs characterized by improving ventilation, use of materials with poor emission of organic volatile compounds and central heating system have also been attempted. The hypothesis that exposure to environmental factors may have a major influence on developing allergic diseases has been also studied with a number of reports showing strong beneficial effects of high-altitude stay on both severe non-astotic and astotic asthma. Some studies supported the hypothesis that exposure to environmental factors may have a major influence on developing allergic diseases and that allergen avoidance should be part of asthma treatment in allergic subjects. Routine analysis of samples from bedding and mattresses in high altitude residential houses failed to reveal the presence of mites, pollens and second hand smoking. A close correlation was demonstrated between prolonged allergen avoidance and a decrease in BHR in two childhood asthmatic populations. BHR improvement was significant after 3 months, with a further increase after 6 and 9 months, indicating a gradual improvement with allergen avoidance. In addition, a clear decrease in total and Dpt-specific serum IgE was observed.

A 3-month period of antigen avoidance in patients with asthma at high altitude can also significantly reduce eosinophils and epithelial cells in the airways. BHR improvement was significant after 3 months, with a further increase after 6 and 9 months, indicating a gradual improvement with allergen avoidance. In addition, a clear decrease in total and Dpt-specific serum IgE was observed.

Environmental Tobacco Smoke (ETS)

Tobacco smoke contains semi-volatile, volatile and solid organic particles that are toxicant, carcinogens and irritant for eyes and respiratory tract. Studies showed that more than 50% of children with asthma are exposed to ETS and more than 60% of them have a mother or a caregiver who smokes, though most of the parents and caregivers are aware of the toxic effect of ETS on children’s health and asthma exacerbation. It is also important to underline the harmful effects of the so-called “third hand smoke” (THS) in children. THS is due to smoke particles that remain in the indoor environment and on the surfaces of furniture and clothes after active smoking. Most-represented smoke pollutants are nicotine, formaldehyde, phenol, naphthalene, specific nitrosamine and 3-ethylhenpyridine which can undergo chemical and physical transformation. Most of these can persist for weeks to months on settled dust and surfaces and make children more susceptible to collateral effects. Smoke-free law programs that prohibit smoking in public places can decrease adult exposure to ETS but they may be less effective for children due to the effect of second and third hand smoke exposure. Therefore, effective strategies to control children’s ETS exposure need to mainly focus on the avoidance of second hand smoke, in particular at home, where public health measures and laws cannot be effective as in public areas. Though HEPA filters have been demonstrated to be effective for smoke control, TSH remains the most harmful exposure. The relevance of direct, indirect and undetected tobacco smoke exposure in children with chronic asthma was evaluated in patients living for prolonged periods in residential institutions at high altitude, suggesting that it could represent an additional relevant determinant in their disease control. In particular, studies on the effect of smoke exposure prevention in asthmatic children showed that cotinine level in urine, evaluated on the 1st day and after a week at the residential home, showed a rapid decrease in the level of this marker.

Outdoor allergen and air pollution

In the first year of life, exposure to air pollutants and outdoor allergens may be related to the development of wheezing and cough. Outdoor allergen control includes recognizing the peak of season allergen and how to prevent indoor contamination. The characteristic pollen size (15–50 μm) makes them more suitable to deposit in the upper and lower airways. Dry, hot and windy days increase symptoms in allergic individuals because insect and wind transport pollen more easily. Correct information to patients and families regarding the pollen season for relevant allergens can be useful for patient counseling. Several studies have shown an increased risk of severe asthma exacerbations during thunderstorms. This has been reported in particular in patients allergic to pollens and molds probably due to a sudden release of large amounts of respirable allergenic fragments, particularly fungal spores. Patients sensitive to these allergens should be informed of this phenomenon and advised in order to reduce the potential risk due to thunderstorm.

Conclusion

Environmental control measures in the management of asthma may represent a composite tool of intervention involving different determinants underlying the development of the disease and disease exacerbations. Interventional programs of environmental determinants may represent an additional strategy to integrate pharmacological approach in the management of allergic asthmatic children.

Bibliography


#7. HOW TO BEST TREAT CHILDREN WITH MILD PERSISTENT ASTHMA

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Most children with asthma have recurrent episodes of acute airway obstruction, especially during the fall and winter periods, followed by variably long symptom-free periods. As a consequence, and using the criteria proposed by the current National Heart, Lung and Blood Institute guidelines in the US in 2007(1), mild persistent asthma is the most common presentation of the disease in a general pediatric setting. Those guidelines introduced the concept that children and adults with 2 or more exacerbations during the previous year should be “considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.” In other words, it was not necessary to have any interval symptoms to be considered a patient with “persistent” disease. However, the concept of “persistent asthma” was abandoned in the most recent version (2015) of the Global Initiative for Asthma (GINA) guidelines.

The new GINA guidelines recommend assessment of severity “retrospectively from the level of treatment required to control symptoms and exacerbations”. Thus, GINA proposes to assess severity “once the patient has been on controller treatment for several months and, if appropriate, treatment step down has been attempted to find the patient’s minimum effective level of treatment”. At that time, “mild asthma is (defined as) asthma that is well controlled with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose inhaled corticosteroids (ICS), leukotriene receptor antagonists or chromones.” The GINA guidelines thus invert the equation: it does not predetermine severity based on symptoms and exacerbations and then decides what therapy to prescribe; it starts therapy (usually with ICS) adjusting it subsequently depending on response, and finally decides level of severity depending on which level of therapy is required to maintain control. A major drawback of the new classification scheme proposed in the GINA guidelines is that the true dose of controller treatment reaching the airways may vary considerably among children prescribed the same controller dose. Moreover, the factors that reduce the “airway dose” are very difficult to verify objectively. A major such factor is adherence. There is now great awareness among asthma experts (and acknowledged in all the latest Guidelines) that lack of adherence has been historically overlooked as a major factor in determining lack of asthma control. This is particularly true among patients with lower socio-economic status, who are often those most vulnerable due to increased prevalence of risk factors for asthma exacerbations. Williams and coworkers (3) showed, for example, that among the mostly African American asthma patients participating in the SAPPHIRE study (n = 298), adherence, assessed as the average proportion of prescribed ICS medication taken per patient for the time period starting 6 months before the initial visit to the time of the initial visit, was (mean ± SD) 26 ± 25%. They also showed that patients whose adherence was between 0 and <75% had similar rates of asthma exacerbation, with patients with adherence of 75% or more showing significant protection against exacerbations. They estimated that 24% of asthma exacerbations were attributable to ICS medication nonadherence (3).

Surprisingly, adherence to therapy has also been shown to decrease with time in long-term clinical trials. As part of a randomized clinical trial, Nikkander and coworkers (4) studied 115 children aged 5–10 years with mild/moderate asthma receiving twice daily budesonide. Adherence to study medication was assessed objectively for the first and last 45-day periods in the study. Mean adherence was 86% during the first 45 days and 59% during the last 45 days. The largest decline in true adherence occurred in older children (aged 9–10 years). These results suggest that, even among patients participating in a clinical trial, who are often selected among those more prone to follow the prescribed therapeutic indications, adherence to daily therapy markedly wanes with time to levels that are not sufficiently protective against asthma exacerbations.

Addressing this striking hindrance to successful asthma therapy would require the availability of efficient instruments to assess and improve adherence in everyday practice. Unfortunately, few such instruments exist. Dose counters are not yet an integral part of asthma treatment strategies (5) and only dose counters with time and date recordings could truly allow determination of daily adherence. Few practices have access to pharmacy data that would allow practitioners to assess refill rates and thus adherence. Use of exhaled nitric oxide (eNO) has been suggested as a potential tool to assess adherence, but weak correlations between daily dose usage and adherence have been reported (6). As a consequence, practitioners have to rely on questioning parents/children, and even sophisticated instruments such as the Medication Adherence Report Scale for Asthma (MARS-A) show relatively modest correlations with electronic dose counters (7).

Interventions to increase adherence have also yielded mixed results. A recent, rigorous, randomized, pragmatic clinical trial tested a speech recognition intervention to improve adherence to pediatric asthma controller medication (8). Speech recognition telephone calls to parents in the intervention group were triggered when an ICS refill was due or overdue. Usual instructions were given to the control group. Main outcome variable was adherence to pediatric asthma controller medication, measured as the medication possession ratio over 24 months. The intervention was successful in increasing adherence, which was 44.5% in the intervention group and 35.5% in the usual care group (p < 0.001). Still, as explained earlier, adherence of less than 50% is insufficient to ensure protection against exacerbations in susceptible patients. Interestingly, higher adherence in the intervention group was not accompanied by lower asthma-related care utilization. The authors attributed this apparently paradoxical finding to the rather mild asthma that was prevalent among the school age children involved in the study. This finding clearly suggests that, among children with mild asthma, demanding universal adherence to a strict program of daily ICS usage may not only be unattainable, but also unnecessary and counterproductive. Williams et al. (3) have indeed shown that ICS use increases after asthma exacerbations, whereas larger doses of ICS may be more useful shortly before exacerbations, when the first symptoms of viral infection occur.

A potential unwanted consequence of the lack of adherence to ICS is likely to be the unnecessary prescription of step up therapy for children whose symptoms are not apparently controlled with low dose ICS. Moreover, if the indications contained in the latest version of the GINA guidelines are followed, non-adherent children with mild asthma could be labeled as having more severe disease when they present with apparently uncontrolled disease. The label of moderate or severe asthma attributed to such children could often trigger parental anxiety and erroneous restriction of activities and exercise. It is thus imperative that the potential for lack of adherence be
considered by practitioners in children with uncontrolled asthma, even when patients and caregivers do not acknowledge that such lack of adherence may be a problem.

It is also necessary to carefully assess alternative approaches to daily therapy. We recently determined if, in school age children with mild persistent asthma as defined by the NHLBI guidelines, intermittent use of ICS concomitantly with albuterol whenever a reliever was needed, could provide protection against asthma exacerbations (9). We found that rates of exacerbation were similar in children using daily ICS as in those using as-needed ICS, and treatment failures (defined as the need for two courses of oral prednisone within a six month period) were significantly lower in the as-needed ICS arm as compared with the placebo arm. Of interest was the fact that daily therapy was associated with a modest reduction in height velocity as compared with placebo, whereas no reduction in height velocity was observed in the as-needed arm.

The data currently available thus suggest that, although daily ICS continues to be the treatment of choice for school age children with mild asthma, adherence to such treatment is lower than necessary to prevent potential exacerbations in a large proportion of patients. Well-conducted efforts to improve adherence to daily therapy in children with mild asthma have been successful, but have not accomplished the goal of increasing adherence up to fully acceptable levels. It is now clear that some children with mild asthma may gain sufficient asthma control with lower than recommended doses of ICS, and that a strategy that concentrates ICS administration at times when it is most needed, i.e., at times when symptoms are increasing, may prevent such exacerbations from occurring. Such a strategy could be attempted in children with mild asthma who are not likely to be adherent and who could benefit from lower doses of ICS, given at the right time during the usual course of their disease.

References

#8. THE VIRUS-BACTERIA INTERPLAY IN EARLY CHILDHOOD AND ITS IMPACT ON RECURRENT WHEEZE/ASTHMA

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Data accumulating from longitudinal birth cohorts, especially from Australia and the USA, have demonstrated the major importance of lower respiratory viral infections associated with wheeze in increasing the risk of subsequent asthma1–5. The vexed question as to whether this is primarily a “viral” or “host-response” effect has not been settled6–4. While some evidence points to an increased risk of asthma for infants who wheeze with human rhinovirus infections in early life, there is still the impression that this virus selects susceptible hosts rather than “causes” long-lasting damage to airways. In addition, there are data suggesting that asthmatics have a decreased innate immune response to respiratory viral infections, allowing easier spread to the lower airways6–4. However, the literature on this is not uniformly supportive and none has been generated in infants or young children; thus the “chicken or egg” question remains open in early life. In addition, the risk of asthma is increased by sensitization to aeroallergens in early life4–8 but the link between wheeze, allergic sensitization and subsequent asthma is unclear. Plausible mechanisms exist by which respiratory viral infections can compromise respiratory health in early life and lung function in the longer term.

There is increasing recognition that complex immunophenotypes underlie asthma4–9. The presence of allergen-specific IgE antibodies to aeroallergens is not sufficient to induce allergic diseases such as asthma, eczema and rhinoconjunctivitis. We have recently published data that suggest that the ratio between allergen-specific IgG1 and IgE may be a better determinant of the risk of expressing allergic disease4–10. There is also increasing recognition that both the presence of microbes in the upper airway and the way that the immune system responds to these is likely to impact on respiratory health9. Early life colonization of the upper airway with bacteria, including H. influenzae and S. pneumoniae has been associated with subsequent asthma in childhood11 whereas their presence in later life may be innocuous, suggesting that the age when specific microorganisms are first encountered may influence disease risk. Data from a cohort of high-risk infants12 suggest that the nasal microbiota during the first year of life is simple with one or two genera, such as Corynebacterium, Staphylococcus, Alliococcus, Streptococcus, Moraxella or Haemophilus, being dominant on a given occasion but that it is highly dynamic with profiles changing over time and with viral infections13–12.

The presence of potential bacterial pathogens is not necessarily associated with disease risk, suggesting that an effective mechanism must normally operate to protect against trans-epithelial invasion in situations, such as viral infections, where local homeostasis is disturbed and barrier function compromised. Immune recognition of invading bacteria has the potential to play such a role. We have demonstrated a potential mechanism whereby the development of IgG1 (Th-1 immunity) and IgE (Th-2 immunity) antibodies against bacterial antigens may play important roles in limiting tissue-damaging inflammatory responses to bacterial invasion across respiratory epithelium especially in the upper airway8. Data from a high-risk birth cohort indicate that a delayed postnatal rise in serum titres of IgG1 against H. influenzae and S. pneumoniae in children with a family history of atopy is associated with increased risk for sensitization to perennial aeroallergens and of persistent asthma at 5 years of age13–14. The likely role of specific IgG1 antibody is to accelerate phagocytic clearance of organisms that breach the mucosal barrier and thus limit the potential for tissue damage15. However, bacterial pathogens that spread to and invade the lower airway epithelium are likely to induce an excessive Th-1-induced immune response accompanied by tissue-destructive inflammation. This may be more likely to occur at times when viral infections escape the normally-efficient upper airway immune surveillance, spread to the lower airways and enable potentially pathogenic
bacteria to reach the lower airways. The presence of such bacteria in the lower airways is likely to generate a vigorous inflammatory response and significant lower respiratory symptoms, which may result in exaggerated and unbalanced Th-1 immunity and increased disease risk.

We have also recently demonstrated in another community-based cohort that Th2 immunity against respiratory mucosal dwelling bacteria (e.g. H. influenzae and S. pneumoniae), detectable as bacterial specific serum IgE, is present in almost all teenagers regardless of atopic status and that the strength of this immunity is inversely associated with risk for asthma.10 This IgE is likely to be a surrogate marker for underlying populations of bacterial-specific Th-2 memory cells secreting IL-4 and IL-13; pluripotent cytokines that are likely to play a role in down-regulating bacterial-induced macrophage activation and preventing the secretion of pro-inflammatory cytokines (IL-1, IL-6, TNFα) that are likely to induce local tissue damage8,9. Exaggerated and unbalanced Th-2 immunity is likely to be associated with eosinophilic inflammation and tissue damage, as seen in chronic asthma, thus achieving a balanced immune response is critical to normal airway function and respiratory health. Deficiencies in the normal immune recognition of bacterial incursion across the respiratory epithelium, especially at times of respiratory viral infection that spreads to the lower airways, is likely to result in an unbalanced immune response and translate into increased respiratory symptoms; repeated episodes are likely to compromise lung function and respiratory health.

References

#9. RADIATION SAFETY CONSIDERATIONS FOR PEDIATRIC LUNG IMAGING

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The goal of lung imaging is to provide clinically relevant information not readily obtainable by other means. Challenges of imaging the lungs of infants and children include the rapid respiratory rate, the small size of the anatomic structures, the inability to breath-hold, the risks of sedation, and the risks of ionizing radiation and radiation-induced cancer from chest radiography (CXR) and computed tomography (CT). As with any medical procedure, the benefits and risks must be weighed appropriately. Cohort and case-control epidemiologic studies of atomic bomb, accidental, occupational, and therapeutic irradiation have generally shown a linear dose-response for solid tumors with greater risk at younger age of exposure. Recent studies have shown an increased incidence of certain cancers in cohorts exposed to CT scans in childhood and adolescence, although these studies were potentially confounded by cancer predisposition and reverse causation. Assuming a linear no-threshold (LNT) dose-response model and the preferred estimates from the Biological Effects of Ionizing Radiation (BEIR) VII report, the lifetime attributable risk of cancer mortality from a chest CT scan with an effective dose of 2 milliSievert (mSv) averaged over a population of 10-year-old girls is approximately 1/4500, which is similar to the likelihood that a coin toss will come up heads 12 times in a row. However, it should be noted that such estimates are subject to considerable imprecision and uncertainty for individual patients due to errors in extrapolating risks from statistical models and variability in susceptibility. Some experts contend that the radiation doses associated with diagnostic imaging fall under a threshold safe dose or are even beneficial, a concept known as hormesis. Making assumptions about individuals based on aggregate group statistics represent a fallacy of inference and undermine the objective of personalized medicine.

Due to the high baseline rate of cancer and confounding factors, epidemiologic studies may never be able to conclusively establish the precise risk of cancer from diagnostic irradiation. A promising alternative approach to personalized risk assessment is the use of cellular and molecular biomarkers of radiation exposure and susceptibility, such as assays of radiation-induced DNA double-strand break (DSB) repair. Unrepaired DNA DSBs in tissue stem cells are thought to be a mechanism of carcinogenesis, and an individual’s capacity for DNA DSB repair may be more important than the radiation dose as a determinant of radiation risk. Iodinated contrast agents amplify the DNA damage from radiation, underscoring the principle that chest CT should be performed with contrast only when indicated. For the evaluation of diffuse lung disease, bronchiectasis or pulmonary nodules, chest CT does not require contrast, while contrast-enhanced CT is preferred to assess complicated pneumo-nia, mediastinal lymphadenopathy or vascular abnormalities. While magnetic resonance imaging (MRI) is being investigated as an alternative to CT for imaging the lungs that does not involve ionizing radiation exposure, pediatric MRI requires sedation much more often than CT and MRI may also induce DNA DSBs, bringing into question the purported safety of MRI compared to CT.

Personalized risk assessment must also take into consideration inherent disease-related mortality and the latency of radiation-induced cancer, since patients with shortened life expectancies may not live long enough for radiation-induced cancers to develop. For example, mathematical modeling shows that the loss of life expectancy from cystic fibrosis is more than 500x

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the predicted loss of life expectancy related to radiation-induced cancer from a monitoring protocol entailing biennial chest CT beginning in infancy and extending through childhood and adolescence. Misperception of risk impedes informed medical decision-making. Risks tend to be overweighted when they are unknown or low, sensationalized by the media, delayed in effect, invisible, and not under control by the exposed, all of which are operative in the setting of radiation. Diagnostic radiation is viewed more rationally when framed in a positive manner (very high likelihood of no adverse effect), and put into proper perspective. Assuming a global average annual natural background radiation dose of 2.4 mSv, chest CT dose of 2 mSv, and CXR dose of 0.02 mSv, the background equivalent radiation time is 10 months for a CT and 2 days for a CXR. In terms of iatrogenic medical risks, the estimated population-averaged radiation-induced cancer mortality risk of 0.02% associated with a 2 mSv chest CT in a 10-year-old girl compares to the 0.5–1% rate of a preventable adverse event per pediatric hematologic, many of which are related to misdiagnosis. Justification of a radiologic exam should be on the basis of the expected diagnostic value, and the small hypothetical risks should not be discussed without also acknowledging the large well-documented benefits. The focus should be on patient care, not patient scare, and decisions made on the basis of fact, not fear.

References
10. McCollough CH. To scan or not to scan: Consideration of medical benefit in the justification of CT scanning. Health Phys 2016;110:287-290

#10. EARLY-LIFE ORIGINS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES

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Chronic obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), have a high prevalence and are a major public health concern. It seems clear that the early stages of life play a key part in the onset of chronic obstructive respiratory diseases, although they may become clinically apparent only later on. Gene-environment interactions and early-life risk factors can lead to permanent developmental adaptations that result in impaired lung structure and metabolism. Consequently, altered immunological responses and abnormal levels of inflammation can trigger a maladaptive response to harmful agents in adulthood, accelerating the age-related decline in respiratory function.

Lung repair processes involved in the pathogenesis of respiratory diseases reiterate many mechanisms and pathways implicated in the lung’s original development. Lung morphogenesis begins at 5 weeks of gestation and includes five different stages, the last of which — alveolarization — may continue throughout childhood and adolescence, and even into adulthood. Perinatal insults can alter both gene expression and epigenetic determinants, thereby influencing the lung’s capacity for growth and repair. For instance, extensive epithelial damage with exposure of the basal lamina causes inflammation and cell apoptosis. If the subsequent regeneration process is ineffective, then remodeling occurs, and the resulting aberrant tissue features (e.g. fibrosis and emphysema) can predispose to COPD. Perinatal insults may also induce the release of excessive levels of growth factors and cytokines common to lung development and repair processes, such as transforming growth factor beta (TGF-β) and vascular endothelial growth factor. Appropriate levels of these mediators are crucial to lung development, but excessive amounts promote fibrosis and abnormal microvascular endothelial regeneration and repair.

Another crucial aspect in the genesis of chronic obstructive lung diseases is an altered immunological response. Innate immune defense mechanisms are the mainstay of the newborn’s immune system, whereas an adaptive immune response is almost completely lacking. Infants are born with a limited capacity to produce Th1 cytokines, and neonates’ antigen-presenting cells generally show weaker responses to innate stimuli than those of adults. Experimental and human observational studies have shown that the degree of innate mucosal immune stimulation determines whether innate responses prevent or enhance the onset of allergic reactions.

New data are emerging on the relationship between the airway microbiome and the immune system. Newborns colonized by S. pneumoniae, H. influenzae, or M. catarrhalis in the hypopharyngeal region are at higher risk of developing an inflammatory/immune response of their airway mucosa that can lead to recurrent wheezing and toddler asthma. Potentially pathogenic bacteria (H. influenzae, S. pneumoniae, M. catarrhalis and P. aeruginosa) are reportedly found in the distal airways of almost one in three COPD patients. Bacterial colonization of the lower airways is associated with higher neutrophil counts and higher concentrations of inflammatory biomarkers, and affected individuals experience a more severe decline in lung function and more exacerbations.

Recent studies have identified microorganisms in the lungs of healthy individuals as well. The lung microbiome is already complex in health, and disrupted in asthma and COPD. Interaction between the epithelial cells and the microbiome is considered crucial for maintaining an adequate barrier function and for lung homeostasis, hence changes in the microorganisms colonizing the lower airways may interfere with the protective action of epithelial cells.

Alongside anomalous lung development and repair processes, and altered immune responses, early environmental factors are important in the onset of respiratory diseases. They may take effect in utero (e.g. amniotic fluid composition, exposure to smoke and maternal micronutrient intake), perinatally (e.g. factors relating to premature birth and the onset of bronchopulmonary dysplasia [BPD]), and/or postnatally (e.g. exposure to nicotine and environmental pollutants, diet, growth patterns, respiratory infections and early allergic sensitization).

Fetal airway development is definitely linked to the amniotic fluid, which induces lung growth and maturation via mechanical and cytokine-induced mechanisms. The amniotic fluid contains high concentrations of proinflammatory cytokines, which peak at the time of delivery. These proinflammatory mediators are thought to be involved in fetal lung maturation, and this could explain why preterm birth and caesarean section are risk factors for asthma. As the composition of the amniotic fluid changes during pregnancy, preterm infants are exposed to suboptimal

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proinflammatory cytokine levels and patterns, and this may impair normal airway development. Infants born by scheduled caesarean section are similarly exposed to lower concentrations of inflammatory mediators in the amniotic fluid; furthermore vaginal delivery may protect against the onset of allergic asthma thanks to the newborn’s acquisition of bacteria such as Clostridium difficile at birth.

Lung maturation is particularly impaired by premature birth before the 32nd week of gestation, when the lungs are still in the saccular stage of development. The newborn’s airways are more compliant, smaller, and have fewer alveolar attachments. Intrauterine inflammation (often associated with premature birth) can further interfere with lung development and have a role in BPD, although evidence of this issue is conflicting. A number of early postnatal therapeutic interventions that cause hyperoxia and volutrauma may also exacerbate lung injury in the premature newborn.

The association between preterm birth and a higher risk of wheezing disorders is particularly strong for children born under 32 weeks of gestation, but even late-preterm children have a significantly higher than normal respiratory morbidity. The impaired lung function of preterm children persists throughout childhood, adolescence and early adulthood. Maternal smoking during pregnancy and postnatal exposure to tobacco smoke are major risk factors for lung function impairment and a higher risk of wheezing and asthma, and the harmful effects of pre- and postnatal exposure to smoke persist into adulthood. Preclinical and clinical studies suggest that the mechanisms underlying the harmful effects of smoke on fetal lung development involve an interaction with asthma susceptibility genes and a dysregulated cytokine production.

Environmental agents such as airborne pollutants and industrial chemicals involved in plastics manufacturing are also recognized risk factors for chronic obstructive airway diseases. Exposure to traffic-related pollutants in utero and during the first year of life has been related to a higher risk of asthma and lung growth impairment; these adverse effects regress when children move to areas with cleaner air. Contradictory results have emerged on the association between exposure to indoor biomass fuel use for cooking and/or heating and the risk of asthma. Although some studies have correlated exposure to plastics manufacturing with the onset of childhood respiratory problems, it is not clear which specific plastic components might be responsible.

Diet in pregnancy and childhood is known to influence lung development, but a detailed understanding of the underlying mechanisms is still lacking. Prenatally, poor maternal nutrition during pregnancy has been recognized as a risk factor for obstructive airway disease in adulthood. On the other hand, different dietary patterns during pregnancy (Mediterranean, vegetarian or “processed” diets) do not influence the risk of developing respiratory diseases in childhood and later on. Specific micronutrient intake (e.g. folate, homocysteine, vitamin B12, vitamin E, vitamin D, probiotic supplementation) during pregnancy has been extensively investigated, but most studies found no association with the risk of asthma and COPD. Postnatally, breastfeeding is associated with a lower risk of respiratory diseases. Exposure to a greater variety of foods in the first year of life appears to protect against the risk of childhood asthma and food allergies. The role of vitamin D supplementation in promoting healthy lung development is still unclear. Recent studies suggest that catch-up growth in infants born preterm is associated with a decline in lung function and a higher risk of childhood asthma: this may relate to a direct mechanical effect on lung function, and to active immunological factors released by adipose tissue, such as leptin.

A link has been suggested between exposure to allergens in early life and the onset of asthma and reduced lung function over time, but findings are inconsistent. Neither allergen avoidance nor allergen exposure seemed effective in preventing the inception of allergic airway disease, although there is evidence to suggest that early exposure to food allergens prevents allergic sensitization. Viral and bacterial respiratory infections during infancy are associated with the onset of childhood asthma and a risk factor for COPD. Whether these associations reflect causal mechanisms or a common underlying factor, such as susceptible lung, is not known.

The mechanism correlating viral respiratory infections — among which respiratory syncytial virus (RSV) and human rhinovirus (HRV) have been the most studied — with recurrent wheezing is not completely understood. Neutrophilic infiltration of the airways caused by RSV infection may damage airway architecture, resulting in wheezing when any subsequent viral infection occurs. A significant association exists between infant hospitalization for RSV and long-term recurrent wheezing and asthma. A nonrandomized trial among late-preterm infants showed that RSV prophylaxis in non-atopic children reduced the relative risk of recurrent wheezing by 80%. Cohort studies have also shown that up to 50% of children who experienced a severe RSV infection during infancy were diagnosed with asthma at school age. If the association between RSV infection and recurrent wheezing and asthma is causal, then developing effective vaccines against RSV could contain the burden of asthma. HRV-associated wheezing during infancy correlates strongly with asthma at school age. It is also worth bearing in mind that virus-mediated asthma and the pathogenesis of COPD may involve a genetic predisposition.

Chronic respiratory diseases such as asthma and COPD are extremely complex syndromes that originate early in life. Their pathogenesis has yet to be fully understood and warrants further investigation, including using novel approaches such as the “-omic” technologies. Among the “-omics”, metabolomics is considered the best for phenotyping purposes, since it studies the metabolic profiles resulting from genetic information and environmental factors. Metabolomics has allowed characterizing patients who already have asthma or COPD. The next challenge is to apply this novel approach very early in life to identify individuals likely to develop a chronic respiratory disease. This could have a profound impact on the management of these conditions by supporting the adoption of effective prevention strategies and/or targeted early treatments.

References

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ILL-25 and allergic inflammation

Asthma is recognised to be a heterogeneous disease and there is much interest in the identification of biomarkers that distinguish particular subsets of patients, particularly if the biomarker predicts response to therapy. IL-25 has been shown to identify a subset of asthmatics that were phenotypically different from the main population examined. This IL-25hi subset of patients had greater airway hyperresponsiveness (AHR), enhanced eosinophils in the airways and peripheral circulation, higher serum IgE levels and increased remodelling as measured by basement membrane thickening. In addition, QPCR analysis of bronchial brushings determined greater expression of a key Th2 gene signature (transcripts for perioestin CLCA1 and serpin B2) in patients in the IL-25hi subset compared to those with lower IL-25 levels. Interestingly, the IL-25hi group showed improved lung function following treatment with inhaled corticosteroids. Importantly, plasma IL-25 levels correlated with the pulmonary allergic inflammation and lung IL-25 levels as well as the positive response to ICS, suggesting the potential of IL-25 as a biomarker for this subgroup of patients.

IL-33 and allergic asthma

The importance of IL-33 in the pathogenesis of pulmonary allergic disease, specifically asthma, has been highlighted by the repeated identification of the IL-33 and ST2/IL1RL1 genes as major susceptibility loci in GWAS studies. Murine studies have revealed that IL-33 is a key initiator of acute and chronic allergic airways disease, with some suggestion that it may be more important than IL-25. The proposed mechanism of action is via release of IL-33 from the pulmonary epithelium following exposure to allergen and subsequent induction of both type 2 innate lymphoid cells and adaptive T helper 2 (Th2) cells which release Th2 cytokines resulting in the pathophysiological features of asthma. In addition, the magnitude of its role is influenced by allergen type, with fungal allergens showing significantly greater epithelial IL-33 release compared to house dust mite. Despite the data from experimental models, evidence of increased pulmonary epithelial expression or release of IL-33 in human asthma is lacking. Expression studies have failed to show increased epithelial IL-33 in bronchial biopsies from adults or children with asthma. However, expression in submucosal inflammatory cells was increased in paediatric severe asthma. In contrast to other cytokines, expression of IL-33 is apparent in both the nucleus and cytoplasm of pulmonary cells, but the mechanism by which it is released remains unknown.

In favour of IL-33 as a therapeutic target for established asthma, is the evidence from human studies of its increased expression in more severe disease. It is relatively steroid resistant and promotes airway remodelling thus favouring its role as a steroid sparing agent and potentially as one of the first therapeutic targets for structural airway changes in asthma. However, since systemic levels have not been shown to be increased in asthma, it is likely that only increased pulmonary levels are pathological. This suggests tissue-specific blocking of IL-33, rather than systemic ablation, is more likely to be beneficial clinically.

TSLP and allergic disease

Despite conflicting data from murine models for the role of TSLP in allergic airways disease, and limited data relating to its function in humans, this is the only epithelial cytokine that has been tested as a therapeutic target. An antibody directed at the TSLP receptor was used in a cynomolgus monkey model of asthma demonstrating reduced eosinophilic inflammation, allergen-induced AHR and IL-13 levels. Furthermore, an antibody designed to neutralise TSLP function has been tested in asthmatic patients for its ability to modulate disease. Although the preliminary data are encouraging, and show treatment with an anti-TSLP antibody reduced allergen-induced broncho-constriction and inflammation, a significant limitation was that all patients were steroid naïve and had only mild disease, thus not reflective of patients for whom these reagents would be considered in clinical practice. As a result, the utility of an anti-TSLP antibody in asthmatics remains uncertain.

Summary

Although the triad of innate epithelial cytokines (IL-25, IL-33 and TSLP) are expressed in human lung tissue and immune cells, their involvement in mediating allergic pulmonary responses in patients is much less clear than in murine models of disease. A lot more data is required from studies in humans to confirm the function of these cytokines in mediating allergic pulmonary disease before they can be confirmed as therapeutic targets.

References

II. TOPIC SESSIONS

PART 1

1. POORLY CONTROLLED ASTHMA

#1 - HOW TO MANAGE A CHILD WITH DIFFICULT ASTHMA?

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Diagnosis and management

Although the majority of children with asthma achieve symptom control on low or moderate doses of maintenance inhaled steroids, there is a small proportion that remain uncontrolled despite high doses of prescribed maintenance therapy. These children are prescribed treatments equivalent to stage 4/5 of the British Thoracic Society (BTS) guidelines for asthma management, and either need at least this amount of therapy to achieve control, or have persistent symptoms and frequent exacerbations despite maximal treatment. Children with poor control despite maximal prescribed therapy have Problematic Severe Asthma1. However, the reasons for poor control may be very varied and can broadly be divided into two sub-categories. The first, “Difficult Asthma” is the term used to describe patients whose asthma is difficult to control because of a failure to address the basics of asthma management, an incorrect diagnosis has been made, or there has been a failure to address associated comorbidities. Underlying reversible and modifiable factors that can result in poor control include poor adherence, unfavourable environmental exposures such as tobacco smoke and aero-allergens to which the patient is sensitised, poor inhaler technique and psychosocial issues2. If modifiable factors are successfully identified and addressed, then control can be achieved in children with Difficult Asthma without the need for escalating therapy or additional invasive investigations. A multi-disciplinary team (MDT) is critical to enable modifiable factors to be identified and addressed in children with Difficult Asthma. The team must include specialist respiratory nurses, a psychologist, pharmacist, physiotherapist and medical staff. Significant resources are therefore required to manage paediatric Difficult Asthma optimally and only specialist centres should be tasked with the assessment of these patients. Although this may have an impact on healthcare resources, long term benefits for lung health are significant. The second sub-category of children that have poor asthma control despite maximal therapy are those with true Severe Asthma. These patients remain with persistent symptoms, or can only be controlled on maximal doses of maintenance therapy, often including oral steroids. AFTER underlying reversible or modifiable factors have been identified and addressed3. Importantly, more than half of all children with Problematic Severe Asthma have Difficult Asthma because of underlying modifiable or reversible factors preventing asthma control4. Therefore, the overall approach to managing a child with Problematic Severe Asthma includes an initial step to identify and treat Difficult Asthma, and if symptoms persist after this, true Severe Asthma can be confirmed, which requires additional investigation and management5.

Very clear criteria and definitions that allow distinctions between Difficult and Severe Asthma have been specified for both adults and children aged six years and above by the European Respiratory Society and American Thoracic Society6. An important point to consider when faced with a child that has poor asthma control despite maximal doses of prescribed maintenance therapy is that one above a threshold of treatment (>800mcg/day or equivalent of budesonide), the child should be referred to a specialist for further management. The National Review of Asthma Deaths in the UK identified 20% of asthma deaths occurred in patients who should have been referred to a specialist for management of problematic asthma7.

References


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Regular follow-up and longitudinal assessment of outcomes

The modifiable factors that result in a child having Difficult Asthma may be identified extremely efficiently if the MDT approach described is adopted. However, what remains equally important is the continuing assessment and follow-up of patients with difficult asthma in order to ensure:

1. Maintenance therapy is reduced to the minimal amount needed to achieve control
2. Symptoms do improve after all modifiable factors have been addressed, and there is no progression to true severe asthma — either after short term follow-up or in the longer term
3. The basics of inhaler technique / device / adherence / allergen exposure are all being maintained

A retrospective analysis of follow-up of children with difficult asthma for up to six years revealed that those in whom underlying modifiable factors were identified and addressed had an improvement in lung function and reduction in exacerbations over time, while being able to reduce maintenance dose of inhaled steroids such that the majority fell below the threshold for problematic severe asthma8. However, there was a large drop out in the number of patients that could be traced for the full six years, highlighting the need for better prospective longitudinal data of outcomes for children with difficult asthma. These missing data are essential in light of recent cohort studies that have followed children with severe asthma to adulthood and shown the irreversible reduction in lung function and prevalence of COPD9.

Key issues in the management of childhood Difficult Asthma

- Confirm the diagnosis
- Treat associated diagnoses, especially allergic rhinitis
- Identify and address the obvious basics of asthma management: inhaler dose, technique, device, asthma plan, asthma education, adherence check by performing prescription uptake check, objective evidence of smoke exposure
- Identify and address more complex modifiable factors: confirm adherence using electronic monitoring; home visit for allergen exposure, availability of medication, smoke exposure, psychosocial factors; school visit
- Physiotherapy assessment for dysfunctional breathing
- Address adherence in an individualised manner – tailoring the intervention to the reasons for non-adherence
- Regular follow-up with annual review of all basics

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Asthma is one of the most common chronic diseases in children, with a high prevalence in many developed and developing countries. Worldwide prevalence of asthma in children varies from 1.6–36.8% according to the International Study of Asthma and Allergies in Childhood (ISSAC) study. (1) Despite its high prevalence, information about the prevalence of severe asthma in children is unknown, particularly in countries in transition. Some estimates come from different studies that have shown that the prevalence of severe asthma in a general population is approximately 0.5–5% among children with asthma, however its true prevalence in a low-income country is unknown. (2–4) According to ISSAC phase III, the centers with the highest prevalence of severe asthma symptoms were mostly from English language countries, Latin America, Africa, the Indian subcontinent and the Eastern Mediterranean. (5) Lack of control of the disease has been attributed to various factors such as low accessibility to basic medications, weak healthcare services, poor compliance with prescribed therapy, lack of asthma education, and social and cultural factors. In general, asthma in both children and adults represents a significant problem in public health given the reduced quality of life, school or work absenteeism and increased healthcare costs, especially in countries in transition. In addition, asthma severity and control in childhood are of particular importance as they have been shown to translate into asthma morbidity in adulthood. (6) Practical guidelines addressing the management of severe asthma in children have pointed out various aspects important in the development of this condition: medication issues, the environment, asthma education, co-morbidity, and psychological problems. Worldwide, but particularly in countries in transition, both intrinsic (race, ethnicity, weight) and extrinsic (exposure to allergens, indoor or outdoor pollutants) factors may overlap in a single child to enhance or diminish asthma control and severity. Different to many developing countries from other continents, asthma is highly prevalent in Latin America. Moreover, ISSAC phase III showed that asthma prevalence in this region is still on the rise. Furthermore, evidence suggests that poorly controlled asthma in some areas of Latin America leads to significant economic costs attributed to emergency and unscheduled visits, and high mortality rates from asthma. (7) Similar to other regions, asthma control is not obtained in most patients, despite available management guidelines and evidence of ICS as controllers. Several surveys have shown that close to 2.4% of all patients met all the GINA criteria for total asthma control, proposing under-recognition of uncontrolled asthma, underuse of appropriate controller treatment, inadequate patient education, and patient denial as possible explanations. (8) Also, several risk factors such as poverty, environmental factors, diet, genetics, vitamin D deficiency and tobacco smoking have detrimental effects on asthma control. Cross-sectional data from 616 children with asthma in Costa Rica suggested that low serum vitamin D detected in children with mild to moderate asthma is associated with asthma severity. (9) Since the development of worldwide guidelines on the diagnosis and management of asthma, special attention on achieving and maintaining asthma control as the key goal in asthma treatment has been a priority. In clinical studies of children with asthma, satisfactory asthma control can be achieved and maintained in most patients by regular treatment with ICS. Nevertheless, large population-based surveys consistently show that poor asthma control is common in many children with asthma, despite ICS treatment. (10) Other studies have shown a reduction in the number of hospitalizations caused by asthma in various countries in transition when effective preventive and controller measures are implemented. (11) Mainly avoidance of risk factors, importance on the use of basic medications and patient education. Patients should be educated about the cause of asthma, what triggers the condition, how it should be monitored and managed and, importantly, the outcomes that can be expected and when to recognize lack of asthma control. Moreover, health professionals should also be educated regarding under-recognition and under-treatment of asthma, as patients or parents tend to deny the severity of symptoms.

In a recent study performed in Costa Rica (12), we aimed to examine trends in hospitalization and mortality due to asthma over a 15-year period (1997–2011), in particular following a National Asthma Plan (NAP). This NAP consisted of education meetings at all major public health care centers, emphasizing early diagnosis, early treatment using ICS as first-line therapy for asthma control, early use of reliever medication to treat exacerbations, appropriate referral to specialists for asthma care, and avoidance of common allergen sources (e.g. dust-mite and cockroaches) or tobacco smoke. Concurrent with this program, general practitioners, pediatricians and internists were first allowed to prescribe ICS for asthma (only pulmonologists or allergists could prescribe ICS before 2003). As a result of the implementation of the NAP, the total number of asthma hospitalizations in Costa Rica in both children and adults decreased by approximately 53% over this period. In children younger than 10 years, hospitalizations for asthma were reduced by 57% in boys and 54% in girls between 1997 and 2011. In addition, the number of deaths due to asthma decreased by 80% over the 12-year period, with a more marked reduction occurring after implementation of the NAP. In parallel with the decrement in asthma hospitalization and mortality, the number of prescriptions for ICS (beclometasone) increased by 129%.

In summary, asthma prevalence in deprived regions is high and shows increased severity. Reasons for inadequate asthma control in poor populations include low accessibility to effective controller medications, weak infrastructure of health services for the management of chronic disease, poor adherence to therapy, lack of educational approaches, and social, cultural and language barriers. However, recent studies have shown several alternatives to control its burden and improve outcomes. There is urgent need for more research into severe asthma, in particular in children in countries in transition.

References


2. TEAM SCIENCE TO SOLVE ASTHMA AND ALLERGIES

#1 - MACHINE LEARNING TO UNDERSTAND SUBTYPES OF CHILDHOOD WHEEZING

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Introduction
It has now become a much used adage that asthma is not a single disease but rather multiple diseases which present with common symptoms[1, 2]. This paradigm has been fundamental in shaping the way we think about asthma and possible approaches to treatment and management strategies. If one is not treating a single disease when we talk about what is commonly known as the syndrome of asthma, then we need a more personalised medication strategy to treat these different syndromes. Alongside this acknowledgment of moving medicine towards more personalised treatment and management strategies, statistics and machine learning have been instrumental in helping us to shape the face of medicine by fostering engagement between clinicians, basic scientists, statisticians and mathematical modellers in order to attain a more unbiased approach to classifying different subgroups of patients using probabilistic models. The proliferation of genetic, molecular, clinical and biological data has made it necessary to use a cross-disciplinary approach to understanding the underlying mechanisms which precipitate distinct profiles of asthma and allergic disease during childhood.

Statistical analysis to understand subtypes of childhood wheezing
The seminal paper by Martinez et al.[3] was the first to propose the existence of different subgroups of childhood wheezing. Based on visual assessment of patterns of wheeze during childhood using data from the Tuscan Children's Respiratory Study, they identified four groups of wheezers: “No Wheeze”, “Transient Early Wheeze”, “Late-onset Wheeze” and “Persistent Wheeze”. This classification has been used as a classical basis for subsequent definitions of distinct subgroups of wheeze and has provided the building block for statistical pattern recognition methods to identify heterogeneous groups of children based on probabilistic modelling of the longitudinal profiles of asthma and wheeze over time. One such statistical technique is latent class analysis. Latent class analysis assumes that the longitudinal fluctuation observed in data is measured with uncertainty. Some of this uncertainty is due to random error, but another element of this uncertainty may be due to the existence of a subgroup or latent class which explains some of the heterogeneity in clinical measures which is not directly observed. Henderson et al. were the first to apply such models using a data-driven approach based on wheeze observations from the Avon Longitudinal Study of Parents and Children[4]. Using latent class analysis based on parental reporting of wheeze, this group identified two additional phenotypes to those identified by Martinez et al.: “Prolonged Early” and “Intermediate-onset” wheeze. This classification has been replicated in other studies.[5]

One of the caveats of basing these modelling strategies on parental reporting of wheeze is that parents may not be able to correctly ascertain a clinical diagnosis of wheeze[6]. In light of this, Belgrave et al. extended these methods by jointly modelling data from both parental questionnaires and general practitioner records which provided complementary data to give a more accurate measure of wheeze[7]. This model identified two classes of persistent wheeze: a “Persistent Controlled Wheeze” group and a “Persistent Troublesome Wheeze” group who had poorer lung function and more reactive airways compared to the other wheeze groups, including the “Persistent Controlled Wheeze” group.

Where Machine Learning begins and statistical modelling ends
Identifying consistently defined and optimal numbers of subgroups of wheeze across different cohorts is challenging. Within the era of “big data” rather than focusing on traditional statistical methodology, the medical field is looking towards data science as a means to extract knowledge and meaning from the vast quantity of information provided by clinical data. To achieve this, both traditional statistical inference methods based on robust assumptions and machine learning models which are more amenable to data complexity, breadth and depth. Although there is overlap between the functionality of machine learning and statistics, the flexibility of machine learning is driven towards learning from data and integrating new information in order to update models and create more accurate models with better model performance. The programmatic focus of machine learning which incorporates vast amounts of computational power provides an excellent framework where tools traditionally used for statistical modelling would be unable to accommodate large, multi-scale datasets.

The road ahead
In the near future, the capability of machine learning to be able to learn from data interactively may facilitate computer-assisted reasoning in identifying subgroups of patients. Identifying such subgroups may be crucial in proposing effective personalised treatment strategies. Such an approach will also allow us to capitalise on the existent data. As data-transparency and data-sharing become more widespread in the global community, we will have a better understanding of the evolution of asthma and allergic diseases.

Summary
Research into identifying heterogeneous subgroups of asthma and allergic disease has reached crucial milestones. We have moved from a subjective approach to classifying subgroups of wheezers, whereby the clinician gives a clinical assessment or diagnosis of the most likely subgroup based on observed clinical history, and we are moving towards computer-assisted reasoning, whereby we can use new information to predict the most likely class assignment based on models derived from prospective data. Such reasoning would also allow us to model the evolution of asthma and allergic diseases in the future.

References
Populations of microbes (such as bacteria and yeasts) inhabit the skin and all mucosal surfaces. Healthy individuals host thousands of different types of bacteria, which are coexistent communities with metabolic functions, such as fermenting unused energy substrates, educating the immune system, and producing hormones to influence host metabolism such as directing the host to store fats. In particular, specific microbe-host interactions are thought to be critical for inducing mucosal tolerance and immune regulatory cells such as Tregs. Why do we develop “tolerance” to the microbes living in us and on us? Perhaps we should consider tolerance as an alternative defense strategy. The continuous effort involved in destroying the microbes that surround us would impair organ function and require vast amounts of energy, which is not compatible with life. For this reason, it makes much more sense to have robust tolerance mechanisms that work in tune with potent effector responses, to ensure optimal host fitness. An intriguing question is that posed by the concept of the hygiene hypothesis in that altered exposure to microbes may influence the induction of tolerogenic immune responses, thereby making individuals more susceptible to react aggressively to non-dangerous encounters with antigens such as allergens. The balance between immune tolerance and inflammation is regulated through the crosstalk between epithelial and immune cells with the microbiome involving many signaling pathways and molecules. Direct contact with bacterial-associated structures can activate receptors (e.g., TLRs) on host cells, which induce signaling cascades resulting in both innate and adaptive polarized immune responses. The microbiome is also metabolically active and microbial metabolites have been shown to exert significant effects on host immune signaling networks (e.g., SCFAs and biogenic amines). The biogenic amine histamine can promote either pro- or anti-inflammatory effects depending on which of its four receptors are activated (2). Some, but not all, commensal bacteria express histidine decarboxylase (the enzyme needed to convert histidine to histamine). Lactobacillus saerimneri 30a produces high levels of biologically active histamine and feeding this strain to mice resulted in a deterioration in health, particularly in histamine receptor 2 knock-out mice (3). Significant efforts are underway to determine the positive and negative health effects associated with production of histamine by the microbiota (4).

Abnormalities in microbiome composition and metabolic activity have been shown in a wide range of disease states including type-2 diabetes, obesity, inflammatory bowel disease, colorectal cancer and allergies. Efforts to use microbiome-associated therapeutics (e.g., probiotics) have clearly shown beneficial effects in animal models, with inconsistent findings in humans probably due to differences in the bacterial strains used. One probiotic bacterium that has shown consistent immunoregulatory effects in murine models and humans is B. longum subsp. longum 35624. Murine models have demonstrated that oral consumption of this strain results in the induction of Treg cells and these Treg cells dampen NFκB activation, preventing excessive inflammation induced by Salmonella infection (5, 6). Similarly, in humans, oral consumption induces Treg cells, which is associated with increased secretion of IL-10 by peripheral blood cells (7). Interestingly, this strain reduces systemic pro-inflammatory biomarkers in patients with psoriasis, IBS patients with chronic fatigue syndrome and patients with ulcerative colitis (8). The mechanism involved includes the recognition of this bacterium via TLR-2/6 and DC-SIGN by myeloid dendritic cells, resulting in changes in dendritic cell cytokine secretion and the production of metabolites such as retinoic acid (9). However, these effects and mechanisms are not seen even with closely related bacterial strains, suggesting that careful selection of microbes is essential for the future clinical development of immunotherapeutic microbes for allergy and asthma. Overall, it can be concluded that the vast majority of microbes, which interact continuously with the host, are not bad. Certain specific microbes can positively influence the host, while there is a minority that can have negative effects on the host.

References


#3 - GENETICS OF CHILDHOOD WHEEZING DISORDERS (SESSION: TEAM SCIENCE TO SOLVE ASTHMA AND ALLERGY)

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Summary

Asthma and other childhood wheezing disorders are highly heritable diseases with twin studies suggesting the heritability to be 50–80%. Nevertheless, elucidating the genetic background has proven difficult. The first era of genetic studies, mainly candidate gene studies, were largely disappointing with many reported genetic associations that subsequently did not replicate. The identification of susceptibility genes was accelerated by new methodologies in terms of microarrays allowing determination of hundreds of thousands of genetic variants, typically Single Nucleotide Polymorphisms (SNPs). This allowed for conduction of so-called Genome-Wide Association Studies (GWAS) searching for susceptibility loci across the genome without a priori hypotheses about disease mechanisms. The downside of the large number of variants tested is the high level of statistical evidence needed to avoid spurious (false positive) associations. Typically,
GWAS findings are based upon association p-values below $5 \times 10^{-8}$, so-called “genome-wide significance”, as well as replication in independent populations. This generally requires very large sample sizes and in order to obtain these, a ‘Team Science’ approach has been used where several studies have combined their data in meta-GWAS. The largest GWAS on asthma to date combined data from 23 different studies involving more than 26,000 individuals from the GABRIEL consortium and identified 6 genome-wide significant asthma loci.(1) Similar meta-GWAS have been conducted, for example by the EAGLE consortium, revealing a number of susceptibility loci for asthma-related traits, including FeNO,(2) eczema,(3) and allergic sensitization.(4)

It could be expected that the large heterogeneity in disease phenotypes introduced by combining many different studies in meta-GWAS would preclude valid discoveries. Nevertheless, GWAS on asthma and the related traits have resulted in identification of relatively few, but robust, loci with more consistency between studies compared to previous candidate gene studies. One example of this is the first large-scale GWAS on allergic sensitization.(4) By meta-analysis of data from 16 different studies, it included a discovery phase of approximately 5,800 cases and 10,000 controls and a similar-sized replication phase. Allergic sensitization was assessed objectively and defined by elevated levels of allergen-specific IgE and/or a positive skin prick test. This study identified 10 loci associated with allergic sensitization at the genome-wide significant level and with robust replication. Simultaneously, another large GWAS was performed on allergic symptoms including approximately 54,000 individuals.(5) In spite of the large phenotype differences between the two studies, there was a high agreement in results with all of the 10 genome-wide significant loci from the sensitization study also showing strong association in the study on allergic symptoms, and previous GWAS findings were confirmed.

There has been some disappointment with the results from GWAS. The identified loci only explain a minor part of the heritability, and the susceptibility variants identified in GWAS are mainly common variants with relatively small effect sizes (often with odds ratios around 1.1 per risk allele) with no clinical relevance on the individual level.(1-4) On the other hand, GWAS have identified novel and robust susceptibility loci, with the potential to provide important understanding of disease mechanisms. Also, comparison of results from GWAS on different diseases and traits have increased the understanding of the mechanistic relationship between these, for example the relationship between allergic sensitization and asthma,(4) between allergen-specific IgE and total IgE levels,(4,5) and between atopy and autoimmune.(3-5) Larger, consortium-based studies on asthma and the related phenotypes are ongoing and are expected to identify many novel susceptibility loci. Novel loci discovered from these larger studies are likely to have even smaller effect sizes than the ones previously found but, from the perspective of understanding disease pathology, each novel locus may potentially pinpoint a novel mechanism and a potential treatment target. Furthermore, the era of genome-wide nucleotide sequencing applied on gene expression- and epigenome-profiling has brought new possibilities of combining GWAS data with data from large public ‘omics reservoirs. These data will increase the usefulness of GWAS data by providing understanding of functional effects related to susceptibility loci, and future GWAS on asthma and related diseases will be a part of integrated approaches to discover how different molecular layers modulate the genetic effect on disease, and will thereby be a central component in the attempt to tailor and improve medical treatment.

Asthma is a highly heterogeneous disease probably consisting of several subtypes of disease associated with different functional mechanisms. Genetic loci may be involved in specific disease mechanisms and thereby help understanding this heterogeneity. For example, the strongest asthma locus identified in GWAS, the 17q12-21 locus, seems strongly associated with an asthma phenotype characterized by onset in early childhood (1) and recurrent, severe exacerbations (6) and was stronger associated with asthma than allergic rhinitis.(5) In contrast, another locus at chromosome 11q13 has been associated with multiple allergy-related phenotypes, including allergic sensitization,(4) allergic symptoms,(5) eczema,(3) and asthma, suggesting a different, allergy-related, disease mechanism. The heterogeneous nature of asthma suggests that an alternative to increasing sample size in genetic studies is to focus on more specific phenotypes. Such phenotypes are likely closer associated to specific mechanisms and the genetic substrates and might therefore increase study power. This was demonstrated by a GWAS focusing on a specific asthma phenotype characterized by onset in early childhood and recurrent, severe exacerbations.(6) In spite of the relatively small sample size, this study resulted in association results of the same magnitude as previous much larger GWAS (1) and with much larger effect sizes, particularly for the children with the highest number of exacerbations. One novel asthma gene, CDHR3, was identified, and it was confirmed, in a collaborative effort involving several birth cohort studies, that the CDHR3 locus was strongly associated with asthma exacerbations in the first years of life, both in individuals of European and non-European ancestry. These results highlight the potential of future genetic studies focusing on more homogenous phenotypes.

One important future step is the translation of genetic associations to disease mechanisms. A major limitation of GWAS is that they often merely identify a susceptibility locus without any clear relationship to a specific gene or biological function. Two examples of this are the 17q12-21 and 11q13 loci mentioned above, where the underlying mechanisms are still poorly understood several years after their discovery, even though these loci are strong and probably central to the pathogenesis of asthma and allergy. One example of a GWAS discovery where the functional mechanism might have been identified is CDHR3. In the discovery study (6), it was suggested that the association to asthma was caused by a specific functional variant affecting surface expression of CDHR3. A later study reported that CDHR3 functions as a rhinovirus C receptor and showed that the functional variant associated with asthma exacerbations increases rhinovirus C binding and replication.(7) This potentially explains the underlying mechanism of this locus and identifies a target for future asthma and virology research.

Another major future challenge is to understand how genetic susceptibility interacts with environmental factors. Gene-environment interactions are not accounted for in normal GWAS and that might be one reason for the large heritability not explained by GWAS findings. One important environmental risk factor for childhood asthma and other wheezing disorders is viral infections, and focusing on this environmental factor might be a tool to understanding mechanisms of asthma genes.(8) As an example, children with 17q12-21 risk variants seem more susceptible to rhinovirus infections, (9) and the finding that CDHR3 seems to be a rhinovirus C receptor (7) indicates that children carrying CDHR3 risk variants will have a specific susceptibility to rhinovirus C infections, a hypothesis that is currently being tested. Only a few genome-wide gene-environment interaction studies have been performed, and the results of these have generally been disappointing without convincing findings. There are many inherent challenges in such studies. First, they might require even larger sample sizes than normal GWAS, and exact information on environmental exposures is difficult to obtain in such large-scale studies. Furthermore, the effect of a specific environmental exposure can be difficult to disentangle from that of other related environmental factors. An alternative approach is to perform cell or animal models where specific exposures can be controlled.(8) A recent study investigated the potentially protective effect of endotoxin and farm dust exposure in a mouse model of house dust mite-sensitized asthma.(10) It was found that A20 was an important mediator of the protective effects of endotoxin exposure, and this was validated in human bronchial epithelial cells. Furthermore, a potential modifying effect of A20 was supported by ‘look up’ of SNPs located near the human TNAIP3 gene using data from an earlier genome-wide interaction study. This potential gene-environment interaction needs to be replicated, but this study exemplifies how mechanistic studies targeting specific environmental exposures and the use of experimental models can facilitate identification of genes involved in gene-environment interactions.

In conclusion, improved understanding of the genetic architecture of asthma and other childhood wheezing disorders will require a combination of GWAS focusing on more homogeneous subtypes of disease, gene-environment interaction studies in birth cohorts and in cell models, and integration with other types of omics data. This challenge can only be
overcome by a ‘Team Science’ approach bringing together many studies to provide sufficient statistical power and bringing together researchers from many disciplines to translate clinical associations to mechanistic understanding. Such studies present great challenges but also the opportunity to understand asthma pathogenesis and heterogeneity, and ultimately to improve prevention and treatment of disease.

References
10. Schuijs MJ, Willart MA, Vergote K, Geras D, Deswarte K, Ege MJ, et al. Identification of colonizing from pathogenic organisms may not be possible on respiratory specimens and co-infections are common. Improvement in specimen collection and improved molecular techniques for detection of organisms have enabled more accurate detection of organisms, particularly for identifying children who need antibiotics. [2] Radiological diagnosis of pneumonia has relied largely on chest X-ray, principally consolidation or interstitial infiltrates. [3] However, chest X-rays are subject to variable interpretation, expose a child to ionizing radiation and require infrastructure and skill to do. Recently, chest ultrasound has been suggested as a feasible imaging modality for diagnosis of childhood pneumonia. Ultrasound has several advantages including that it may be used as a point-of-care test, can be taught to non-radiologists, is quick to perform and does not involve exposure to radiation. Initial studies suggest that it has high sensitivity and specificity for pneumonia compared to chest X-rays. [4, 5] Diagnosis of the etiology of pneumonia remains challenging as bacteremia is rare, distinguishing colonizing from pathogenic organisms may not be possible on respiratory specimens and co-infections are common. Improvement in specimen collection and improved molecular techniques for detection of organisms have enabled more accurate detection of organisms, however ascribing etiology may be difficult unless the organism is invariably pathogenic. Advances in specimen collection include the use of induced sputum in infants and young children, which provides a better specimen for detection of specific pathogens such as B. pertussis or M. tuberculosis. [6] Urine antigen detection has not proven to be useful for pneumococcal pneumonia or for pulmonary tuberculosis in children.[7, 8] For induced sputum, testing of sequential, repeat specimens provides a point of care test for diagnosing pneumonia. It is more accurate for diagnosing pleural effusion, alveolar consolidation and alveolar interstitial syndrome than auscultation or chest radiography, and can also be used to diagnose pneumothorax. The addition of mediastinal ultrasound is also useful for identification of lymphadenopathy in children with suspected TB, through the suprasternal approach. Non-radiologists with limited training have shown a high success rate for diagnosing pneumonia using chest ultrasound. This presentation will therefore focus on demonstrating a simplified technique for performing POCUS of the chest for pneumonia, that is appropriate for clinicians. Normal imaging findings in healthy lungs, i.e. ‘lung sliding’, A-lines and B-lines as well as examples of common pathologies including consolidation, B+ lines of interstitial syndrome, effusions and pneumothorax will be demonstrated. The role of POCUS in developing countries and other remote settings with limited resources will be discussed through examples.

#2 - ADVANCES IN THE DIAGNOSIS OF CHILDHOOD PNEUMONIA

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Effective treatment of pneumonia and prevention of associated mortality and morbidity requires timely and accurate diagnosis, with appropriate use of antibiotics. Diagnosis of pneumonia has relied predominantly on clinical and radiological features. The World Health Organization (WHO) case management guidelines, relying predominantly on age-specific tachypnea or lower chest indrawing, have served as a cornerstone for diagnosis in primary care settings providing pneumonia definitions with high sensitivity. Recently, WHO definitions have changed to classify children with lower chest indrawing as having pneumonia rather than severe pneumonia and recommending treatment with oral antibiotics as ambulatory cases. [1] However, a recent meta-analysis reported that no single clinical feature is sufficient to accurately diagnose radiological pneumonia and that the WHO recommended diagnostic signs alone lack sufficient sensitivity or specificity, particularly for identifying children who need antibiotics. [2] Radiological diagnosis of pneumonia has relied largely on changes in chest X-ray, principally consolidation or interstitial infiltrates. [3] However, chest X-rays are subject to variable interpretation, expose a child to ionizing radiation and require infrastructure and skill to do. Recently, chest ultrasound has been suggested as a feasible imaging modality for diagnosis of childhood pneumonia. Ultrasound has several advantages including that it can be used as a point-of-care test, can be taught to non-radiologists, is quick to perform and does not involve exposure to radiation. Initial studies suggest that it has high sensitivity and specificity for pneumonia compared to chest X-rays. [4, 5] Diagnosis of the etiology of pneumonia remains challenging as bacteremia is rare, distinguishing colonizing from pathogenic organisms may not be possible on respiratory specimens and co-infections are common. Improvement in specimen collection and improved molecular techniques for detection of organisms have enabled more accurate detection of organisms, however ascribing etiology may be difficult unless the organism is invariably pathogenic. Advances in specimen collection include the use of induced sputum in infants and young children, which provides a better specimen for detection of specific pathogens such as B. pertussis or M. tuberculosis. [6] Urine antigen detection has not proven to be useful for pneumococcal pneumonia or for pulmonary tuberculosis in children.[7, 8] For induced sputum, testing of sequential, repeat specimens provides a point of care test for diagnosing pneumonia. It is more accurate for diagnosing pleural effusion, alveolar consolidation and alveolar interstitial syndrome than auscultation or chest radiography, and can also be used to diagnose pneumothorax. The addition of mediastinal ultrasound is also useful for identification of lymphadenopathy in children with suspected TB, through the suprasternal approach. Non-radiologists with limited training have shown a high success rate for diagnosing pneumonia using chest ultrasound. This presentation will therefore focus on demonstrating a simplified technique for performing POCUS of the chest for pneumonia, that is appropriate for clinicians. Normal imaging findings in healthy lungs, i.e. ‘lung sliding’, A-lines and B-lines as well as examples of common pathologies including consolidation, B+ lines of interstitial syndrome, effusions and pneumothorax will be demonstrated. The role of POCUS in developing countries and other remote settings with limited resources will be discussed through examples.

#1 - POINT OF CARE ULTRASOUND IN CHILDREN

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Affordable high-quality portable ultrasound machines have allowed for point-of-care ultrasound (POCUS) to develop in medical disciplines outside of radiology departments. POCUS refers predominantly to physician-performed ultrasound at the patient’s bedside, in the emergency room or in clinic settings. This reduces diagnostic times, facilitates rapid clinical decision-making and reduces the burden on radiology departments. The main advantage of ultrasound over other diagnostic imaging tests is that it carries no radiation burden and is virtually risk free, making it ideal for use in children. Other advantages are its relatively low cost, mobility, ease of use and its digital nature, allowing for tele-reading when necessary. Chest ultrasound is a useful point of care test for diagnosing pneumonia. It is more accurate for diagnosing pleural effusion, alveolar consolidation and alveolar interstitial syndrome than auscultation or chest radiography, and can also be used to diagnose pneumothorax. The addition of mediastinal ultrasound is also useful for identification of lymphadenopathy in children with suspected TB, through the suprasternal approach. Non-radiologists with limited training have shown a high success rate for diagnosing pneumonia using chest ultrasound. This presentation will therefore focus on demonstrating a simplified technique for performing POCUS of the chest for pneumonia, that is appropriate for clinicians. Normal imaging findings in healthy lungs, i.e. ‘lung sliding’, A-lines and B-lines as well as examples of common pathologies including consolidation, B+ lines of interstitial syndrome, effusions and pneumothorax will be demonstrated. The role of POCUS in developing countries and other remote settings with limited resources will be discussed through examples.
higher yield for pathogens such as *M. tuberculosis*. [9] Careful attention to specimen collection methods and use of different specimens may maximize the yield, especially in the context of new sensitive molecular detection techniques.[10]

With the availability of improved tools for etiological diagnosis, and with better vaccine coverage for conjugate vaccines, including pneumococcal conjugate vaccine, viral pathogens especially RSV and other bacteria, such as *S. aureus* or pertussis, are emerging as prominent causes of childhood pneumonia.[11–13] In areas of high TB prevalence, *M. tuberculosis* has been reported to be associated with acute pneumonia in children, with culture confirmed disease occurring in approximately 8% of cases.[14] However, better tools for detection of potential pathogens have also provided data on the complexity of etiology, with several potentially pathogenic organisms frequently identified in a single pneumonia episode. Further delineation of the interactions between different organisms and pneumonia pathogenesis is needed.

References


#1 - LUNG FUNCTION TESTING IN CHILDREN: IMPORTANCE OF ETHNIC SPECIFIC REFERENCE EQUATIONS

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Asthma affects as many as 334 million people of all ages in all parts of the world and is the commonest long-term respiratory condition affecting children in developed countries, the prevalence and morbidity varying by ethnic group. Accurate diagnosis and effective management of respiratory diseases such as asthma requires objective measures of lung function, but reliable use of such measures is only possible if appropriate normative ranges are available to distinguish the effects of disease and treatment from those of growth and development.

Evidence for ethnic differences in lung function

Ethnic differences in lung function have been well documented. In the past, attempts to interpret observed ethnic differences in lung function were often confounded by selection bias related to use of small population samples that were not necessarily representative or generalizable, use of different methods, equipment and quality control (QC) criteria, failure to adjust for other important determinants of lung function, including socio-economic circumstances and/or inappropriate statistical analyses. In recent years, many of these problems have been addressed by applying standard methodology, inclusion criteria and QC to large, ethnically homogeneous groups. Current research shows that after adjusting for age, sex and standing height, forced expiratory volume in 1 sec (FEV1; a measure of airway calibre) and forced vital capacity (FVC; a measure of lung size) are both reduced by approximately 14% in individuals of African ancestry (Black) across the entire life span when compared with those of European ancestry (White). Similar though smaller reductions have been observed among South Asian (from Indian subcontinent) and South-East Asian (e.g., China, Thailand, Malaysia, etc) subjects. Since these “ethnic” reductions in FEV1 and FVC are generally proportional, the FEV1/FVC ratio, which is the most commonly used outcome to assess airways obstruction, is usually independent of ethnic background, suggesting that there are no structural or functional ethnic differences in lung design. Thus the observed ethnic differences in lung function appear to be primarily limited to lung size rather than airway or dynamic respiratory characteristics. However, the same adjustment factor cannot be used for all lung volume outcomes. For example, there is evidence that the lower FVC found among Black children can be attributed at least in part to a relatively high residual volume, suggesting that factors such as anatomic differences in diaphragmatic position or respiratory muscle strength might contribute to some of the observed differences. Furthermore, lung function indices that are internally adjusted for the size of the individual’s resting lung volume, such as the Lung Clearance Index (LCI: a measure of gas mixing efficiency) or specific airways resistance (sRaw: a measure of airway calibre adjusted for lung volume), do not appear to be influenced by ethnic background. Nevertheless, since larger sample sizes will be required to confirm these findings, data interpretation of LCI and sRaw from non-White subjects should currently be undertaken with caution.

GLI-2012 equations

Recently, the Global Lung function Initiative (GLI) collated results from >74,000 healthy non-smokers aged 3–95 years to create the first all-age, multi-ethnic reference equations for spirometry with appropriate age dependent lower limits of normal. Prediction equations were derived using the LMS method, which allows simultaneous modelling of the mean (mu), the coefficient of variation (sigma) and skewness (lambda) of the...
distribution, and reference equations were derived for Caucasians (White); African-Americans (Black), North- and South-East Asians. These equations enable assessments to be evaluated over the entire age range using a single reference data set, thereby avoiding the errors that can occur when switching between equations, particularly during the transition between paediatric and adult care.  

Defining ethnicity
Ethnicity is extremely difficult to define. Self-assigned ethnicity may differ from observer-assigned ethnicity and in certain countries it is against the law to record ethnic origin for any purpose. Furthermore, in recent censuses in both the UK (2011) and US (2010), mixed-race populations have been shown to be the fastest-growing ethnic group. Thus, classifying ethnicity may become an increasingly complex task!  

Could differences in body proportions explain the ethnic differences in lung function?
Standing height is a major determinant of lung volumes, reflecting the fact that lung size is adapted to our metabolic needs. However this is not ideal since the size of the lungs is more closely related to thoracic size than leg length and differences in body proportions may underpin much of the observed ethnic variation in lung function. The Size and Lung Function In Children (SLIC) study was designed to improve normative reference ranges for lung function by taking differences in body physique into account to facilitate early diagnosis and treatment of lung disease in all children, irrespective of ethnic background. However, of the numerous additional anthropometric measurements undertaken to quantify body physique, only sitting height and chest width significantly contributed to the prediction of spirometric lung function. Chest dimensions and lean mass also significantly predicted FEV₁ and FVC within each ethnic group, but did not affect differences between groups. The persistence of ethnic differences after adjustment for sitting height, chest dimensions, body composition and socio-economic factors may reflect the fact that some factors affecting chest size such as diaphragmatic position or muscle strength cannot be assessed by anthropometry, and emphasises the importance of taking ethnicity into account when interpreting spirometry data.  

Impact of socio-economic factors on ethnic differences in lung function
While some studies have shown an association between socio-economic conditions (SEC) and lung function and suggested that this is a key factor in explaining ethnic differences in lung function, there is increasing evidence that the contribution of SEC to variability of lung function is very small except under the most adverse of conditions. A recent study in India, using identical equipment and techniques as those used in the SLIC study found that while average FEV₁ and FVC in urban Indian children were similar to those in Indian children residing in the UK, they were significantly higher than in semi-urban and rural Indian children (by 6% and 11% respectively). These results probably reflect the marked differences in the degree of social deprivation between the UK and India and suggest that there may be a threshold effect of poverty on lung function. Adjusting for sitting height has been shown to reduce the contribution of SEC to ethnic variability.  

Data interpretation and ethnic adjustments
The use of inappropriate reference equations and misinterpretation can lead to serious errors with respect to both under- and over-diagnosis. In the past, attempts to correct for ethnic differences, if made at all, tended to apply the same fixed adjustment factor across all ages, all ethnic groups, both sexes and all spirometric outcome measures, an approach now shown to be over-simplistic. In addition to errors relating to ethnic differences in lung function, misdiagnosis may also occur when fixed cut-offs, such as 80% predicted FEV₁ or 0.7 FEV₁/FVC are used, particularly in young children and elderly adults. While %predicted has historically been used to interpret lung function results, z-scores are more appropriate as they take into account the between-subject variability of measurements for any given outcome at any given age, as well as the predicted value. Similarly, use of <0.7 as a fixed threshold for abnormal FEV₁/FVC can lead to gross under-diagnosis of airway obstruction in the young and over-estimation in the elderly.  

Conclusions and recommendations
With exception of extreme deprivation, ethnic differences in lung function cannot be explained by socio-economic factors. After adjusting for confounders, genetic factors do contribute to ethnic differences in body physique and lung function. Given the marked ethnic differences in lung function, the magnitude of which are similar across the entire life span, it is essential that lung function results in children are interpreted using ethnic specific equations whether in clinical practice or epidemiological research. Although GLI-2012 do not and never will cover all ethnic groups, appropriate use of age, height and sex adjusted values of FEV₁/FVC ratio derived from these equations (which is consistent across all ethnic groups) will facilitate better identification of airway obstruction in children irrespective of ethnic background. Failure to adjust lung function for ethnic differences will result in overestimation of both the severity of airway obstruction and the severity and prevalence of restrictive lung disease.

References
5. NEW TREATMENTS AND BIOMARKERS FOR ASTHMA

#1 - "PERSONALIZED MEDICINE" AND NEW DESIGNER DRUGS FOR CHILDREN WITH ASTHMA

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Introduction
It is now recognised that asthma is a complex, heterogeneous disease. Therefore, we need to move away from offering a single approach to management for all children and consider the identification of individual phenotypes for each child to enable optimal treatment and control.

The specific facets of the disease that need to be considered and defined in each child include: i. An accurate description of symptom pattern (exacerbations alone, or persistent symptoms with and without exacerbations), ii. The nature of airway inflammation (eosinophilic, neutrophilic or non-inflamed), iii. The type and degree of structural airway changes (remodelling). Although asthma control can be achieved in most children with low-moderate doses of inhaled steroids, we remain unclear about the choice of optimal maintenance therapy for each child. How should a decision between regular inhaled steroids, or leukotriene receptor antagonists be made? When additional therapies are required to achieve control, a scientific rationale for add-on therapies also is unavailable. The majority of decisions about therapies are made using a “trial of treatment” approach. If one approach is not successful, then another is adopted without a clear thought process dictating choice of treatments. It is apparent that we need to change our current one size fits all approach to the management of asthma in children. Although perhaps less important for children with mild or moderate disease, this becomes extremely important when we consider those with more severe disease.

Personalised medicine for severe asthma
Although atopy, airway hyperresponsiveness, eosinophilic inflammation and remodelling are the cardinal pathophysiological features of paediatric asthma, we now know that each of these features can be present to very different degrees in the individual child. Pathology has been most studied in children with severe disease, and although features such as eosinophilic inflammation and increased airway smooth muscle represent the patients as a group, there is huge overlap between children with and without asthma, and a huge spread of severity of these features within the group of children with severe asthma. This within-group variability means assessments need to be made in the individual before deciding on the most appropriate add-on therapy. A proposed approach to identifying the “individual phenotype” in children with severe asthma is to split response to steroids into different domains (Bossley C et al. J Allergy Clin Immunol 2016, In Press). Not all children with asthma have abnormal lung function, not all have inflammation or remodelling, the response to a trial of systemic steroids can therefore be split into the following: i. Lung function response, ii. Inflammation response (exhaled nitric oxide and sputum eosinophils) and iii. Symptom response. We have analysed this approach in 54 patients with severe therapy resistant asthma and shown a similar proportion of children (approx. 40%) responded to systemic corticosteroids in each domain, but there were no reliable predictors of a response pattern. Furthermore, only 13% were complete responders (response in all domains), 15% were non-responders (no response in any domain) and the majority (72%) were partial responders (response in > 1 domain). These data highlight that childhood severe asthma is heterogeneous and a complete response in symptoms, inflammatory and physiological parameters is rare (Bossley C et al. J Allergy Clin Immunol 2016, In press). Individual response patterns to systemic steroids need to be applied in the future to guide the choice of add-on therapies in each child as a step towards achieving personalised medicine. Subsequently, this multi-domain approach was applied clinically to identify characteristics of responders to the add-on therapy Omalizumab. It became apparent that only those with a positive response in the inflammation domain (a significant reduction in exhaled nitric oxide after a trial of systemic steroids) had a beneficial response from Omalizumab. As increasing numbers of add-on therapies become available for use, specifically in the context of severe asthma, we need to better define pathophysiological phenotypes in individual patients and we need to understand the mechanisms mediating disease in children. In addition, we now need to incorporate individual genotypes into our definition of phenotypes to more accurately define treatment responses, as has been successfully done for response to montelukast in preschool wheeze. Not only will this individualised approach allow us to discover novel molecular targets that will be effective specifically in the paediatric population, but it will also enable us to objectively choose the best therapy tailored to the individual child.

References

#2 - CD147 AND SEVERE ASTHMA IN CHILDHOOD (SESSION: NEW TREATMENTS AND BIOMARKERS FOR ASTHMA: PROGRESS AT LAST)

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Summary:
Acute asthma exacerbations are among the most frequent causes of hospitalization in childhood and responsible for large health care expenditures. It is a main goal in international guidelines of asthma management to avoid exacerbations. Still, exacerbations are less well controlled than the daily asthma symptoms, and studies from the U.S. and
Europe consistently report that 20–40% of children with a recognized asthma diagnosis require acute medical care yearly. This is a reflection of the inadequacy of the available treatment options for prevention and treatment of exacerbations, suggesting that asthma with severe exacerbations may represent a distinct subtype of disease and demonstrating a need for improved understanding of its pathogenesis.

Asthma heritability is estimated at 50–80%. A number of genes have been verified in genome-wide association studies (GWAS), but still the genetic background of asthma remains poorly understood. Larger GWAS may reveal new susceptibility loci with smaller effects, but due to the large heterogeneity of asthma, an alternative strategy may be to increase phenotype specificity. A specific phenotype is likely to be closer related to a specific pathogenetic mechanism and may therefore markedly increase the power of genetic studies. This was the background for a GWAS focusing on a particular asthma phenotype defined by repeated, severe exacerbations in early childhood.(2)

A sufficient number of cases were obtained by identification of children with recurrent acute hospitalizations for asthma between 2 and 6 years of age in the Danish National Patient Register, and extraction of DNA from dried blood spots from the Danish Newborn Screening Biobank. The case phenotype was rare with only 1/10000 of children born in Denmark between 1982 and 1995 fulfilling the inclusion criteria. The final study comprised 1,173 children with repeated hospitalization and 2,511 healthy controls.

Five loci were identified with genome-wide significant association (P-value < 5×10⁻8): GSDMB, IL33, RAD50, IL1RL1, and CDHR3. Even though the sample size of this GWAS was less than one fifth of the largest published GWAS on asthma from the GABRIEL consortium,(3) it identified a similar number of genome-wide significant loci with similar statistical significance. The effect estimates were remarkably high with odds ratios between 1.4 and 2.3 per risk allele, compared to the odds ratios around 1.1–1.2 usually found in GWAS on complex traits. Further increasing phenotype specificity by stratified analysis in the 358 children with the highest number of exacerbations resulted in a further increase in effect estimates, with odds ratios between 1.6 and 2.7 per risk allele, and strong statistical significance.

These strong results demonstrate the value of focusing on a more specific phenotype in asthma genetics. Furthermore, it indicates that studies on this severe and early-onset phenotype is a “cost-effective” approach whereby methodologies requiring large resources and/or strong statistical power can be applied in a limited number of individuals and still provide powerful results. The top-locus in this study, at chromosome 17q12-21 near GSDMB, has consistently been associated with childhood onset asthma. (3–5) The effect size in the present study was remarkable with an OR of 2.3 (P-value = 1.3×10⁻⁶⁸) and increasing to 2.7 for the children with highest number of exacerbations. This suggests an important role for this locus in severe exacerbations in early childhood in line with a previous report from the COPSAC2000 birth cohort study.(5)

CDHR3 had not previously been associated with asthma or any other disease. The association with asthma was replicated in the publically available GABRIEL results (3) and additionally in 3 birth cohort studies (COPSAC2000, MAAS and Generation R). Phenotype-specific replication was possible in the COPSAC2000 and MAAS birth cohorts with prospective registration of acute asthma hospitalizations and exacerbations from birth to 6 years of age, showing strong association with development of exacerbations in the first years of life.(2) Replication in Generation R suggested association also in children of non-European ancestry. The top-SNP at the CDHR3 locus (rs6967330) was a non-synonymous coding SNP where the risk allele (A) results in an amino-acid change from cysteine to tyrosine. Experimental introduction of the risk allele in cell cultures showed altered cell surface expression of CDHR3, suggesting identification of the causal variant at this locus. CDHR3 is a trans-membrane protein with six extracellular cadherin domains. Protein structure modeling showed that the risk-associated variant is located at the interface between two domains where it could be involved in disulide rearrangement and interfere with inter-domain stabilization, overall protein stability or conformation, in agreement with the observation in experimental studies of altered cell surface expression.(2)

The biological function of CDHR3 is unknown but it seems to be a highly plausible asthma gene. It belongs to the cadherin gene family of transmembrane proteins involved in several cellular processes including epithelial polarity, cell-cell interaction, and differentiation (6) and is highly expressed in the lungs. Also, other members of the cadherin family have been associated with asthma and related traits, including E-cadherin.(7) Recently, it was reported that CDHR3 functions as a receptor for rhinovirus C. (8) CDHR3 was differentially expressed in epithelial cells susceptible to rhinovirus C infection compared to susceptible cells, and its expression on epithelial cells enabled rhinovirus C binding and replication. Importantly, introduction of the risk variant at rs6967330 by transfection resulted in 10-fold increased RV-C binding and progeny yield compared to the non-risk variant. These data provide strong evidence that CDHR3 is a rhinovirus C receptor and that the association signal in the CDHR3 gene might result from increased susceptibility to RV-C infections. This finding is in line with the exacerbation-related phenotype from the discovery GWAS, since rhinovirus C has been reported to be the most common viral trigger of severe asthma exacerbations in children and associated with more severe disease and higher rates of hospital readmissions compared to other respiratory viral infections.(9,10) If correct, this would indicate that children with the CDHR3 risk variants are specifically susceptible to rhinovirus C infections compared to illnesses triggered by other viruses, a hypothesis that is currently being tested.

In conclusion, the strong results found in this GWAS on childhood asthma with severe exacerbations demonstrate the value of specific phenotyping in the search for asthma genes. Focusing on this extreme subtype of disease might reveal mechanisms that would not be revealed in studies of milder disease, but might also increase the understanding of general asthma mechanisms. Identification of CDHR3 as a risk gene might be one of the first examples where the underlying mechanism of an asthma GWAS finding is understood. Future studies of this gene may improve understanding and treatment of asthma exacerbations in childhood.

References


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The timing of bacterial colonization early in life is thought to be important for appropriate immune education and the transmission from mother to the fetus during pregnancy and birth is being better described. Cultures of meconium have shown diverse groups of Gram-positive and Gram-negative bacteria, possibly not all derived post-delivery. The development of the gut microbiome is a dynamic process and early colonization with *Bacteroides* and *Bifidobacterium* species might play a crucial role in the development of immune regulation (1). Factors that can influence early life colonization include antibiotic treatment, method of delivery, maternal and infant diet and biodiversity in the home, surrounding environment and in family members. The gut microbiome increases in diversity during the first years of life. Germ-free mice, which are not exposed to live bacteria, display exaggerated TH2 and IgE responses, associated with diminished polarization of Treg cells. Monoclonization of the mice with specific microbes, but not all microbes, suppresses the IgE response and promotes Treg differentiation (2). However, certain immunological changes, such as increased INKT numbers in the mucosa, cannot be reversed following colonization of mice later in life (3). Interestingly, more severe allergic responses and anaphylaxis were observed in mice who received a microbiome transplant from allergic animals, suggesting that certain microbial species can actually promote allergic responses (4).

The immune system at birth is dominated by TH2 cells. However, the human fetus has a functional immune system at a relative early status of development comprising CD4+ and CD8+ T cells but also FOXP3+ Treg cells. One concept gaining support is that the developing fetus may become educated by whole bacteria or their genetic material that is provided via maternal serum. DNA from *Bifidobacteria* and *Lactobacilli*, two genera typically used as probiotics, are found in human placenta. In contrast, *in utero* exposure to potentially pathogenic bacteria such as *Ureaplasma* species leads to immune dysregulation commonly ending in fatal complications. Maternal consumption of probiotic-containing food components may reduce the risk for childhood allergic diseases and mouse models demonstrate a reduced risk of inflammatory bowel diseases. Epigenetic mechanisms may be critical since application of *Acinetobacter lwoffii* to pregnant mice reduced the airway hypersensitivity response of the offspring. The promoter region of IFN-γ in CD4+ T cells of the offspring had high levels of histone-4 acetylation, associated with enhanced transcription, while the IL-4 promoter region had lower levels of histone-4 acetylation (5). Moreover, exposure of pregnant mothers to the farm environment, which have high levels of *Acinetobacter lwoffii*, was associated with DNA demethylation of the Foxp3 locus and methylation of the TH2-associated genes RAD50 and IL-13. Since gut microbiota composition during the first months of life seems to be important for development of appropriate immune regulatory networks and thereby influence later life disease risk, intervention with probiotics, prebiotics or synbiotics might be most effective at this age or even during pregnancy. Prebiotics can be defined as live micro-organisms which, when educated by whole bacteria or their genetic material that is provided via transmatermal asthma protection induced by microbes. J Allergy Clin Immunol. 2011 Sep;128(3):618–25.


**PART II**

#1 - LONG TERM BENEFITS OF NEWBORN SCREENING IN CYSTIC FIBROSIS: LESSONS LEARNED

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People with cystic fibrosis (CF) are living longer lives than ever in the past. The median predicted survival in developed countries is now above 40 years of age and adults with CF are outnumbering pediatric patients in several
regions. Various reasons may explain such improvement in life expectancy, including the establishment of CF-dedicated and multidisciplinary centers; greater attention to nutritional issues and use of pancreatic enzymes replacement therapy; airflow clearance techniques tailored to individual needs and attitudes; infection control measures; use of antibiotics both chronically by inhalation and aggressively to treat pulmonary exacerbations; macolyclic and airway hydration therapies; and liver and lung transplantation (1, 2). On account of the overwhelming evidence that organ impairment begins very early, even in asymptomatic CF infants, there is now general consensus that at least some of these strategies of care should be implemented as soon as possible in order to prevent or delay irreversible structural lung damage. Indeed, this has possibly been the main argument in favor of CF NBS (3).

The strength of such argument has been tested by several studies and considering different approaches. Randomized studies – Only two randomized trials on newborn screening for CF have been completed (5, 6, 7). These evaluations need many years of follow-up and, given the high degree of evidence in favor of CF newborn screening presently available, further implementation of similar studies seems improbable and possibly non ethical.

Observational studies – Although most of these studies confirm clinical benefits from early diagnosis of CF, their results are hampered by several biases inherent to the methodological approach. The constant improvement in treatment and the consequent longer survival has an influence on the comparison of screened individuals and unscreened historical controls. On the other hand, examining the clinical evolution of screened infants and unscreened controls from different geographical areas but born in the same years may be affected by different care practices. Finally, ascertainment biases may also have an impact on the assessment of outcomes, as patients presenting clinically are likely to have more severe CF than those identified through screening or unscreened patients with very critical disease may have died before being diagnosed.

Health economics studies – These studies use surrogate end-points, such as the quantity of treatment needed to remain healthy, and are based on the assumption that the optimal management offered to CF patients makes it harder to detect evidence of better clinical outcome in those diagnosed by screening. Late-diagnosed patients may show clinical pictures similar to those diagnosed early, but at the expense of a considerably heavier burden of care (8).

Most of these studies have focused on respiratory and nutritional outcomes and on HTA assessments. Their overall results clearly point in the direction of a positive effect on height and weight, of longer survival and of health service savings in populations screened at birth for CF. Positive effects may also be obtained in several other domains, namely:

- The prevention of salt loss syndrome thanks to early beginning of salt supplementation
- The opportunity of surveying from birth the natural history of CF
- A better understanding of the early stages of CF
- The possibility of testing presumptomatic therapeutic strategies, both conventional and patient targeted.
- In already symptomatic infants, the limitation of a distressing and often prolonged delay before diagnosis.
- Early offer of genetic analysis and counseling to parents and relatives.
- Programs with good sensitivity allow a precise determination of the local birth prevalence of CF and indirectly of carrier frequency and mutation distribution.

References

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#2 - CLINICAL APPROACH TO THE DIAGNOSIS AND TREATMENT OF ATYPICAL CYSTIC FIBROSIS

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Cystic Fibrosis (CF) is associated with the presence of two CF-causing mutations, one in each parental CFTR gene, resulting in the absence or abnormality of the CFTR protein and defect in electrolyte transport across epithelial membranes, the most well known being sweat chloride >60 mmol/L. Even in 2016, CF remains by essence a clinical diagnosis. The wide range and severity of symptoms/ organs involved between and within individuals makes it a clinical decision as to whether or not a person should be managed as a CF patient. This is especially the case in a small number of ambiguous or atypical cases.

Clinical Frame of atypical Cystic Fibrosis

In 1998, a first diagnosis consensus listed criteria for CF diagnosis: (i) one or more of the phenotypic features of the disease or (ii) CF in a sibling or (iii) a positive immunoreactive trypsin (IRT), in association with at least one other feature, including a positive sweat test result on two occasions, a CF-causing mutation in each CFTR gene or an abnormal nasal potential difference (NPD) (1). This consensus statement of the US Cystic Fibrosis Foundation was later modified in Europe based on the concept of CFTR dysfunction included in the diagnosis algorithm (2).

Most atypical CF patients are diagnosed based on sweat tests and/or genetic analysis. These “mild CF” individuals usually present later in their lives with pancreatic sufficiency and milder respiratory disease. They frequently carry wide clinical spectrum mutations.

The difficulty occurs when patients present with clinical symptoms suggestive of CF and a sweat chloride value in the intermediate range (30–59 mmol/l). Among these subjects, those with abnormalities in NPD measurement or 2 identified CFTR mutations have, on average, more severe lung disease than the remaining subjects, although their disease symptoms are milder than those in subjects with a sweat chloride concentration above 60 mmol/L. Therefore, from a physician’s and also from a patient’s perspective, these individuals must be differentiated from subjects with the classical life-shortening form of CF. The remaining cases, termed “possible” or “borderline”, are difficult to classify because there is poor agreement between sweat test results and prognosis on the one hand and the frequent presence of at least one CFTR mutation of uncertain clinical relevance on the other.

The term “CFTR-related disorders” (CFTR-RDs) designates these varied conditions, which include multi-system disease and monosymptomatic disorders associated with CFTR dysfunction but which do not fulfill the diagnostic criteria for CF (3).

This encompasses 3 main clinical entities with CFTR dysfunction: CBAVD (congenital bilateral absence of the vas deferens), acute recurrent or chronic pancreatitis and disseminated bronchiectasis.

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Diagnosis of CBAVD is based on palpable vas deferens on scrotal examination. Even if in a proportion of men scrotal palpable vas deferens are present, surgical exploration reveals a fibrous cord or a non-permeable duct. CBAVD males have either a severe and a mild/variable (88%) or two mild/variable (12%) CFTR mutations (4). Approximately 34% of men with CBAVD have a CFTR mutation in one gene and the splicing variant IVS8-5T on the other allele, often in association with a longer polymorphic dinucleotide repeat, a combination that does not result in CF, but reduces levels of functional CFTR protein in Wolfian tissues, which constitutively produce less full-length CFTR mRNAs than other tissues (5).

About 30% of patients with idiopathic chronic pancreatitis or recurrent acute pancreatitis are found to carry CFTR mutations. No specific CFTR mutations have been reported, but rare class 4 or class 5 mutations are often found (6).

An increased incidence of CFTR gene mutations has been found in bronchiectasis. According to the studies, at least 1 CFTR mutation is found in 10–50%, and 2 mutations in 5–20% of cases. Mutations found are mostly uncommon and likely to result in residual CFTR function (7). No specific CFTR mutation is associated directly with bronchiectasis.

### Diagnostic workup for the diagnosis of atypical CF

Individuals with sweat chloride values in the intermediate range between 30 to 99 mmol/L should undergo extensive CFTR mutation analysis, if only 1 or no mutation has been found on genetic test screening. If the patient carries 2 CF-causing mutations, the diagnosis of CF is made. In the other cases, ancillary tests may help establish a diagnosis of CF by revealing a second organ disease phenotype, such as pancreatic insufficiency (fetal pancreatic elastase), CBAVD in males, lung or sinus involvement with positive sputum cultures for a CF-associated pathogen (especially *P. aeruginosa*). Sweat chloride testing should be repeated. Careful attention should be paid to exclude other known etiologies. These patients should be followed in a CF center.

A sweat chloride value ≤29 mmol/L makes the diagnosis of CF unlikely. However, as some mutations with typical CF may be associated with negative sweat test (3849 T0B, D1152H, etc.), these individuals should have extensive genetic testing.

Many mutations or variations in the *CFTR* gene are associated with a wide spectrum of clinical phenotypes or even no disease at all (mutations of unclear significance) (8). This is because of the limited number of mutations clinically and specifically annotated to date.

As CFTR-RDs occur within a continuous gradient of CFTR dysfunction, CFTR function may serve as a surrogate marker for CF diagnosis (9). Therefore, CFTR bioassay tests (nasal potential difference (NPD); intestinal ion channel measurements from rectal biopsies in Ussing chamber) may clarify the diagnostic status if they clearly indicate CFTR dysfunction. However, those tests are available in only a few centers. The lack of clear reference values and validation studies make them difficult to use in routine assessment.

### Treatment

Treatment for patients with symptoms suggestive of CF and intermediate sweat test must be individualized, according to the symptoms of the patients, i.e. single organ disease such as congenital bilateral absence of the vas deferens (CBAVD), sinusitis, nasal polyps, diffuse bronchiectasis, acute and recurrent chronic pancreatitis (2). These patients must be monitored carefully for development of any complications and appropriate therapy implementation.

It should be pointed out, however, that labeling patients with mild or unclear manifestations with a CF diagnosis may have negative implications such as psychological, reproductive, social, employment, and insurance issues. Therefore the explanation of the diagnostic challenge, including also prognosis, must be fully and honestly explained to the patient and or his family.

### Bibliography


### #3 - CF AND PCD: SIMILARITIES AND DIFFERENCES

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Effective mucociliary clearance (MCC) in the respiratory system requires proper mucus production and functioning airway surface fluid layer as well as competent and coordinated ciliary beating. The vital role of these systems is best demonstrated in patients with genetic defects such as primary ciliary dyskinesia (PCD) and cystic fibrosis (CF), both of which are characterized by impaired MCC leading to acute and chronic sino-pulmonary infections. PCD is caused by defects in genes that encode the structure or regulate the movement or function of the respiratory cilia. CF is caused by mutations in the CFTR gene causing abnormality in the airway surface fluid layer, with production of thickened and viscous mucus leading to impaired MCC. In both diseases, recurrent and chronic respiratory infections and persistent inflammation cause progressive lung damage.

Most patients with CF suffer from pancreatic insufficiency (CF-PI); however, approximately 15% have sufficient pancreatic enzyme production to maintain normal fat absorption (CF-PS). Patients with PCD are similar to patients with CF-PS in that they have normal pancreatic function, and are usually without the nutritional deficiencies that are typically associated with more severe pulmonary disease in CF. In addition, PCD and CF-PS are often diagnosed at a later age and have better survival compared to CF-PI (1,2).

Therefore when comparing CF and PCD, one should differentiate between patients with CF-PI and CF-PS. Santamaria et al. compared chest HRCT scan scores for patients with PCD and a group of age- and gender-matched CF patients and showed that patients with PCD had significantly less structural damage than CF patients (3). A recent study comparing between PCD and CF-PS and CF-PI revealed that patients with PCD had disease severity in terms of pulmonary function and structural abnormality similar to patients with CF-PS, which was significantly less severe when compared to patients with CF-PI (4). Furthermore, when comparing structural abnormalities by HRCT, there was a significant disparity in the distribution of the structural changes in the lungs between the three groups of patients: in PCD, the upper lung zones were relatively preserved and most changes were localized to the middle and lower lobes, whereas in CF-PI, the upper lobes were remarkably involved. In CF-PS, there was no characteristic distribution of the structural damage (4). Other studies showed that In PCD, contrary to CF groups, there was no correlation between FEV₁ and CT Score and between FEV₁ and age (3–8), which provides further support to
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the understanding that, in PCD, lung function is not a strong indicator of severity of lung disease and therefore, follow-up by low radiation chest HRCT scans should be considered. It is important to note that, in general, patients with PCD receive less intensive therapy (9). They are not always followed regularly in specialized centers, and many are not adherent to routine treatments.

The most common bacterial infection in PCD patients is H. influenzae, which is significantly less common in older CF patients (4,10). In CF, chronic infection with P. aeruginosa is associated with a more severe lung disease (11). However, among patients with PCD, there was no correlation between P. aeruginosa infection and pulmonary function or HRCT severity score, suggesting a different role for this microorganism in the pathogenesis of pulmonary disease in PCD (4).

Bush et al. compared the mucous properties in both diseases and demonstrated that inflammation, measured by IL-8 concentration, was greater in PCD sputa, and that there were no significant differences in biophysical or transport properties of sputum between the two groups; however, survival in patients with PCD was generally better (12). Ratjen et al. (13) assessed the inflammatory response in the airways of CF and PCD patients during pulmonary exacerbation. In stable PCD patients, no significant differences were found in sputum inflammatory markers between individuals colonized with different bacterial pathogens. However, higher bacterial density for S. aureus and H. influenzae was found in patients with CF versus PCD, and the absolute neutrophil counts were higher in PCD patients. While sputum elastase activity was similar in PCD and CF at the time of exacerbation, it decreased with antibiotic therapy in PCD but not CF patients. Thus, PCD patients differ from those with CF in their responses to treatment of pulmonary exacerbations, with higher neutrophil elastase activity persisting in the CF airways at the end of treatment. Joenesen et al. (14) measured the difference in breath profiles of patients with PCD and CF, with and without distinct chronic lung infections, using an electronic nose. No significant difference was found between the breath profiles of PCD patients with a chronic PA infection and PCD patients without a chronic infection. However, there was a significant difference between the breath profiles of CF patients with a chronic PA infection and CF patients without a chronic PA infection, suggesting a different response to infection between PCD and CF.

In conclusion, although PCD and CF are both characterized by impaired MCC and respiratory infections, patients with PCD have a different lung infection and pulmonary function or HRCT severity score, suggesting a different role for this microorganism in the pathogenesis of pulmonary disease in PCD (4).

Bacterial infection and pulmonary function or HRCT severity score, suggesting a different role for this microorganism in the pathogenesis of pulmonary disease in PCD (4).

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Hospital, Taichung; and National Taiwan University Hospital, Taipei (Taiwan) to compare intra-tracheal administration of surfactant/budesonide with that of surfactant alone on the incidence of death or BPD. The results of this study were recently published in AJRCM (9). Between April 1, 2009 and March 1, 2013, all infants with respiratory distress shortly after birth were assessed for eligibility for the study. The inclusion criteria were determined within 4 hours after birth and included: 1) birth weight less than 1,500 g, 2) radiographic evidence of severe respiratory distress syndrome (RDS) (grades III–IV), 3) on mechanical ventilation, 4) fraction of inspired oxygen (FiO2) at least [271] 0.5, and 5) absence of severe congenital anomalies or lethal cardiopulmonary disorder. These infants were considered to be at high risk for developing BPD.

Two hundred and sixty-five infants with severe RDS were randomly assigned into two groups: 131 intervention (surfactant and budesonide), 134 control (surfactant only). The intervention infants received surfactant (100 mg/kg) (Abbott Laboratories, Abbott Park, IL) and budesonide (0.25 mg/kg), (Pulmicort nebulizing suspension; Astra Zeneca, London, UK) and the control infants received surfactant only (100 mg/kg). In the intervention group, this dose provided a concentration ratio of surfactant to budesonide greater than 50:1; this mixture was demonstrated in vitro, using a surfacometer and high-performance liquid chromatography, not to affect the biophysical and chemical properties of the surfactant. Repeated administrations of surfactant/ budesonide or surfactant only were given every 8 hours to infants in the intervention or control group, respectively, until they required a FiO2 less than 0.3, or were extubated or received a maximum of 6 doses. During the study, a respiratory care protocol was followed by the participating hospitals.

BPD was diagnosed at 36 postmenstrual weeks if the infant continuously required supplemental oxygen. Tracheal aspirates were assayed for interleukin (IL-1, IL-6, IL-8) levels. A follow up study on neuromotor function and cognitive function was performed at 2–3 years of corrected age. The intervention group had a significantly lower incidence of BPD or death than the control infant group [55/131 (42.0%) vs. 89/134 (66%); risk ratio 0.58, 95% CI: 0.44 to 0.77, p < 0.001; three doses: 85/131 (64.9%) vs. 49/134 (36.6%;) p = 0.09; three doses: 3/131 (2.3%) vs. 23/134 (17.2%), p < 0.001; four doses 0/131 (0%) vs. 1/134 (0.7%); six doses: 0/131 (0%) vs. 3/134 (2.2%). The intervention group required significantly fewer doses of surfactant than the control group [one dose: 85/131 (64.9%) vs. 49/134 (36.6%;) p < 0.001; two doses: 43/131 (32.8%) vs. 58/134 (43.3%) p = 0.09; three doses: 3/131 (2.3%) vs. 23/134 (17.2%), p < 0.001; four doses 0/131 (0%) vs. 1/134 (0.7%); six doses: 0/131 (0%) vs. 3/134 (2.2%).] The intervention group had significantly lower interleukin levels (IL-1, IL-6, IL-8) in tracheal aspirates at 12 hours and lower IL-8 at 3–5 and 7–8 days.

There was no significant difference between the groups during the study in serum electrolytes, glucose, BUN and in blood pressure, and in physical growth. There was no significant difference between the groups in neuromotor function, and in MDI, PDI and in neurodevelopmental impairment (NDI) score when examined at 2–3 years of corrected age. We concluded that in very low birth weight infants with severe respiratory distress syndrome, intra-tracheal administration of surfactant/budesonide compared with surfactant alone significantly decreased the incidence of BPD or death without apparent short term or long term adverse effect. Further large-sample, double-blind trials are warranted.

### References

2. Watterberg KL; American Academy of Pediatrics; Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent bronchopulmonary dysplasia. Pediatrics 2010;126:800–808.

#2 - PULMONARY FUNCTION TESTING IN INFANTS AND YOUNG CHILDREN

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## Introduction

Measuring lung function in “non-collaborating” children has always been one of most difficult tasks for pediatric pulmonologists. This is because young children are not able to perform the voluntary forced expiratory maneuvers generally used in adults and schoolchildren. In infants and children up to 2 years, this problem has been generally overcome by the use of sedation, although this contributes to make lung function measurements less suitable for routine clinical use in this age group. Preschool children (2–5 years) are too old to be sedated and yet too young to properly perform the forced expiratory maneuvers required for spirometry. For this age group, several techniques that just require tidal breathing have been implemented during the past decades. The American Thoracic Society/European Respiratory Society (ATS/ERS) Working Group on Lung Function in Young Children has published technical recommendations for most infant (1,2) and preschool techniques (3) and their clinical applications have also been recently summarized (4). This lecture will focus on the most used pulmonary function tests (PFTs) in infants and preschool children.

## Infants

Chloral hydrate (80–100 mg/kg, maximum 1 g) is commonly used to sedate infants and young children up to 2 years for performing lung function testing. However, chloral hydrate is no longer available in the U.S.A. and the use of other sedatives might lead to different results (4). The most commonly used PFTs in infants are the raised volume rapid thoracoabdominal compression (RVRTC) and infant plethysmography. Other PFTs that are performed during tidal breathing (e.g.: tidal breathing measurements, multiple breath washout, forced oscillation technique) are more suitable to be used without sedation, especially in younger infants.

The **raised volume rapid thoracoabdominal compression (RVRTC)** allows for the measurement of forced expiratory flow and volume in sedated infants (2). Repeated inflations using a pressure of 30 cmH2O are applied through a facemask and an inflatable jacket is then activated to rapidly compress the infant’s chest and abdomen to obtain forced vital capacity (FVC), forced expiratory volume in 0.5 seconds (FEV0.5) and forced expiratory flow (FEF) at defined proportions of FVC. To ensure that flow limitation has been reached, the inflation pressure of the jacket is increased at each maneuver until no further increase in flow is noticed. Recently published reference equations using a current commercially available device (5) will improve the interpretation of the results. RVRTC has been successfully used in children with all kinds of respiratory diseases, including children with cystic fibrosis (CF), children born prematurely, and those with recurrent wheezing (4), showing its capability to distinguish disease...
populations from healthy control subjects and to detect lung function changes in clinical intervention trials. However, its long-term clinical utility still remains to be established. Moreover, the need for sedation along with the time and resource intensity required are other important limitations for its use in routine clinical practice (4).

Infant plethysmography is used to measure functional residual capacity (FRCpleth) in sedated infants (1). Specific airway resistance (sRaw) can also be measured, provided that a proper electronic thermal compensation is applied to the system to account for thermal artifacts. This technique is based on the same principle (Boyle’s law) as plethysmography for older subjects and uses an infant whole body plethysmograph where the infant lies supine breathing through a facemask sealed with silicon putty (1). Infant plethysmography has been successfully applied to children with lung disease, especially CF and bronchopulmonary dysplasia (BPD) (4). However, as for RVRTC, its long-term clinical utility remains to be ascertained and its role in routine clinical practice is hence very limited.

Preschool children

Preschool children (2–5 years) are too old to be sedated, but also too young to properly perform the forced expiratory maneuvers required for spirometry. For this age group, several techniques that just require tidal breathing have been implemented during the past decades, allowing for lung function to be measured in awake children (3). Also, modified acceptability criteria for spirometry have been proposed for the use in preschool children (3). It is important to highlight that the feasibility of any lung function technique in preschool children strongly depends on the capability of the operator of keeping the child quiet and focused (3).

Spirometry has been proposed for preschool children using modified acceptability criteria (3). Since the forced expiratory volume in 1 second (FEV1) often cannot be obtained in preschoolers due to their different lung physiology, the use of FEV in 0.5 (FEV0.5) or 0.75 seconds (FEV0.75) is recommended in this age group. Also, FVC should not be reported if flow stops at more than 10% of peak flow (early termination), but FEV may still be reported. Less stringent repeatability criteria have also been proposed in preschool children: at least two acceptable maneuvers should be obtained with the two FVC and FEV within 100 mL or 10%, but in case of a single acceptable maneuver, this should be recorded nevertheless (3). Spirometry is reported to be feasible in 55–85% of 4–5 year old children, but its feasibility tends to be much lower in younger children (4). Global multi-ethnic reference equations including preschool children have recently been published (6). Spirometry has been reported to discriminate healthy controls from preschool children with CF and with recurrent wheezing, although substantial overlap between groups may occur and bronchodilator response appears to be more sensitive than baseline values (4). However, a careful and rigorous approach to the use of spirometry must be taken in preschool children and several gaps in our knowledge still limit the application of this technique to clinical practice in this age group (4).

The interrupter technique is based on the principle that a sudden flow interruption at the mouth during tidal breathing would make alveolar pressure rapidly equilibrate with mouth pressure, thus allowing an estimation of alveolar pressure by measuring mouth pressure. The interrupter resistance (Rint) is then calculated dividing the change in mouth pressure by the flow measured immediately before the interruption (“classical” technique) or immediately after the interruption (“opening” technique). Measuring Rint has been proved to be particularly suitable for preschool children, its feasibility being generally higher than 80% in this age group (4). Proper reference values have been published (7) and cut-off values for the bronchodilator response have also been reported. Rint is able to detect changes in the airflow caliber and has been successfully used in preschool children with recurrent wheezing (4). However, its utility in clinical care remains to be established, especially by longitudinal studies (4).

The forced oscillation technique (FOT) is used to measure the impedance of the respiratory system (Zrs) during tidal breathing by applying, through a mouthpiece and a filter, low-frequency pressure oscillations generated by a loudspeaker (usually 4–48 Hz) (3). Changes in flow and pressure measured at the mouth are used to calculate Zrs and its two components, resistance (Rrs, reflecting frictional losses) and reactance (Xrs, reflecting elastic properties at low frequencies and inertial forces at higher frequencies). Forcing signals based on sinusoidal waves or impulses have been used, both as single-frequency or composite signals. Frequencies between 5 and 10 Hz are considered to reflect the mechanical properties of the total airways. FOT has a good feasibility in preschool children (>80%) and several reference equations have been published (8). FOT has been used in many studies on children with recurrent wheezing, showing a good capability in discriminating health from disease, especially when bronchodilator response is used (4). However, for this technique as well, longitudinal studies on its clinical utility in young children are still needed (4).

The multiple breath washout (MBW) is based on the washout of an inert gas (typically N2 washout using 100% O2) to measure ventilation inhomogeneity and FRC during tidal breathing (3). Non-resident inert gases have also been used. The lung clearance index (LCI, the number of lung volumes expressed as FRCs required to washout the inert gas) is the most commonly used MBW index. The general standard operating procedure for this technique has been recently reported (9). LCI has a good feasibility in preschool children (nearly 80%). LCI has been successfully used in preschool children with CF (4), proving to be more sensitive than spirometry and plethysmography in detecting abnormal lung function. However, longitudinal studies on the clinical utility of MBW in preschool children are lacking (4) and more data are needed before LCI or other MBW indices can be recommended in the routine clinical management of patients with CF (10).

Specific airway resistance (sRaw) can be measured at tidal breathing in preschool children using a whole body plethysmograph. Since sRaw is the product of airway resistance by the thoracic gas volume, it can be calculated without the need to breathe against a closed valve (11), provided that a proper electronic thermal compensation is applied to obviate the need for the panting maneuver. The measurement of sRaw has a good feasibility in young children and reference values are also available (11). However, the lack of consensus on measurement methods and outcome measures makes it difficult to compare results among centers and methodological techniques are urgently needed for this technique.

Conclusions

An accurate assessment of pulmonary function is now possible in infants and preschool children using a number of techniques. Although these techniques have proven to be powerful research tools, further studies are needed to ascertain their utility in the clinical care of infants and young children with lung disease.

References

the developing endothelial cell plays a key role in the regulation and coordination of epithelial growth and distal airspace structure through the production of critical “angiocrines,” such as nitric oxide (NO), hepatocyte growth factor, vitamin A, insulin growth factor-1 and others. Thus, since angiogenesis is necessary for normal alveolarization, it has been suggested that protecting the developing pulmonary vasculature from early injury may not only lower PVR and improve gas exchange, but may enhance distal lung growth and improve long term outcomes.

Abnormalities of the pulmonary circulation in severe BPD include altered tone and reactivity, structure and growth, which can cause right heart failure, impaired gas exchange, pulmonary edema, decreased exercise capacity and other clinical problems. Physiologic abnormalities of the pulmonary circulation in BPD include elevated pulmonary vascular resistance (PVR) and abnormal vasoactivity, as evidenced by the marked vasconstrictor response to acute hypoxia and by impaired gas exchange due to abnormal distribution of lung blood flow. Abnormal pulmonary vascular structure also contributes to high PVR due to increased smooth muscle cell hyperplasia and altered vascular compliance caused by increased production of an abnormal extracellular matrix. Growth of the distal lung circulation is abnormal in infants with severe BPD, and decreased arterial growth (angiogenesis) reduces vascular surface area that further impairs gas exchange and increases the risk for the development of PH and impaired exercise capacity in older children.

Prominent bronchial or other systemic-to-pulmonary collateral vessels were noted in early morphometric studies of infants with BPD, and can be readily identified in many infants during cardiac catheterization. Although these collateral vessels are generally small, large collaterals may contribute to significant shunting of blood flow to the lung, causing edema and need for higher FiO2. In addition, recent autopsy studies suggest the presence of striking intrapulmonary anastomotic, or “shunt,” vessels that link the distal pulmonary and bronchial vessels, and may contribute to poor oxygenation. Past clinical studies have further shown that metabolic function of the pulmonary vasculature is impaired in BPD, as reflected by the lack of pulmonary clearance of circulating norepinephrine during passage through the lung, which may contribute to left ventricular dysfunction and systemic hypotension.

Clinical studies have recently shown that early echocardiographic findings of PVD after preterm birth are strongly associated with the development and severity of BPD and PH at 36 weeks corrected age. Interestingly, these findings were not only associated with a worse respiratory course during the initial hospitalization, but also late respiratory outcomes, including respiratory exacerbations, hospitalizations and the need for asthma medications. Ongoing studies are exploring the impact of PH-specific drug therapies, such as sildenafil and other agents, on PH and related complications. Thus, PVD in preterm infants with BPD is characterized by altered lung vascular development, growth, structure, and function, which precede the onset of measureable PH. PVD due to disruption of normal pulmonary vascular development in association with preterm birth is an important determinant of the pathobiology of BPD and contributes significantly to morbidity and mortality. Exposure to adverse stimuli during the antenatal and/or early postnatal periods impairs normal pulmonary vascular development and creates an imbalance between risk and resiliency factors. Recent studies have revealed the magnitude of PH in preterm infants, but many aspects of PVD remain understudied, and ongoing investigations continue to explore risk factors, mechanisms of disease, and long-term outcomes. Prospective
Studies are needed to definitively establish standardized clinical criteria for PVD and PH in BPD, and to determine the best methods for early diagnosis, risk stratification and disease monitoring. Larger collaborative studies and improved clinical infrastructure to conduct these important investigations will provide answers to these critical questions.

References

3. CF AND NON-CF BRONCHIECTASIS
#1 - CAUSES AND TREATMENTS FOR INFLAMMATION

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Recent evidence suggests that CFTR does not act as a pure ion channel but as a platform for multiple cellular signaling pathways. Importantly, the protein interactomes of WT- and F508del-CFTR are rather different, and there is growing consensus that indirect measures that avoid the enhanced degradation of F508del-CFTR may restore its function. Recently, we discovered that CFTR orchestrates a proteostatic network that influences multiple cellular functions by acting as a hub protein. This hub-dysfunction model proposes that the proteostasis network is widely deranged, both in transgenic CF mice and in primary nasal epithelial cells freshly collected from CF patients bearing F508del-CFTR either in homozygous or compound heterozygous form, at two levels. Firstly, autophagy, the major mechanism determining cytoplasmic protein turnover, is blocked due to accumulation of the autophagic substrate SQSTM1/p62. Secondly, peptide fragments released from proteolytically-cleaved F508del-CFTR provoke an over-activation of a pleiotropic protein kinase (protein kinase CK2), which in turn contributes to F508del-CFTR degradation. Combined inhibition of TG2 by cysteamine, which is FDA-approved for the treatment of cystinosis, and over-active CK2 by the over-the-counter green-tea flavonoid epigallocatechin-gallate (EGCG) respectively rescue and stabilize a functional F508del-CFTR protein at the PM, both in mice and in primary nasal cells from CF patients bearing F508del-CFTR or other class II-CFTR mutations. Pre-clinical evidence on transgenic mice has provided the mechanistic proof-of-concept for using this combination of proteostasis regulators as an alternative CFTR-repairing therapy. Moreover the combination treatment reduces lung inflammation and this beneficial effect persists up to 2 weeks following cysteamine withdrawal provided that EGCG was administered during washout. This prompted an open-label phase-2 trial to assess the individual response to the synergistic combination of cysteamine and EGCG in CF patients bearing different CFTR mutations. The combination treatment was well tolerated and decreased sweat chloride from baseline while increasing the abundance and function of CFTR protein and restored autophagy in nasal cells. Notably, the treatment decreased CXCL8 and TNF-a in the sputum and improved respiratory function. These positive effects were particularly strong in patients carrying F508del-CFTR (or other class II) mutations in homozygosity or heterozygosity, whereas patients with class I CFTR mutation failed to respond to therapy. Altogether, these results suggest that the combination treatment acts “on target”, according to the hypothesis underpinning our drug design. Discordance in therapeutic response rate complicates mutation-specific approaches, thus entailing the need of patient-centered (personalized) approaches to assess drug efficacy. Testing the putative individual responsiveness to treatment by appropriate biomarkers before in vivo therapy should support the decision to treat. We show that restoring CFTR function in vitro in nasal cells in response to cysteamine plus EGCG, is highly predictive of whether the combination treatment will restore CFTR function in vivo. Hence, this in-vitro assay may constitute a tool to guide the clinical development of CF treatments, allowing to select patients for new therapeutic options.

#2 - MANAGEMENT OF THE CHILD WITH CYSTIC FIBROSIS DIAGNOSIS BY NEWBORN SCREENING

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The successful expansion of newborn screening for cystic fibrosis (CF) has highlighted the need for clear guidance on the management of screen-positive infants. A harmonized therapeutic strategy in infants newly diagnosed will improve clinical status at later ages. Several guidelines have been published aiming to harmonize the care of infants diagnosed with a typical form of CF at neonatal screening, including in the US, Europe and France (1,2,3).

**General frame for care**  

Infants with CF must receive care in an accredited CF care center. They must be reviewed in clinic frequently after diagnosis, for example once a month during the first 6 months of age, every 2 months until 1 year of age, and every 3 months thereafter (3). After initial diagnosis, the CF center should contact the primary care professionals for regular ambulatory follow-up to implement therapeutic strategy. Parents of infants with CF should be offered access to genetic advice and counseling.

The standard childhood immunization schedule must be applied in accordance with national guidelines. Anti-influenza vaccination is recommended for the infant from the 6th month of life and for all household
Nutritional care

Growth targets should reflect genetic potential, sibling height and local population demographics (1). French guidelines recommend to catch-up birth weight percentile at 6 months (3). At 2 years, weight-for-height should be at the 50th percentile and height at the target height percentile (target height: average of the height of the 2 parents plus 6.5 cm for boys and minus 6.5 cm for girls) (3).

Energy intake evaluation should be performed by a dietician on a regular basis and adapted to achieve the objectives of weight-for-height growth. Energy intake could be as much as 150% of the daily recommended calorie intake for the same age in the general population (4).

Breast feeding is encouraged, all the more that recent data acknowledge its protective effect against Pseudomonas aeruginosa infection (4, 5). Formula with hydrolyzed cow’s milk protein is recommended in infants with risks of malabsorption, or severe undernourishment. Sodium chloride supplementation is systematic, particularly in the case of breast feeding and should be adapted to natriuresis (6). It should be increased during periods of hot weather and all other causes of high salt loss (diarrhea, fever, ileostomy, etc.).

At initial diagnosis, infants must have pancreatic function assessed by stool fecal elastase. If elastase is normal, repeat assessment is recommended. Pancreatic enzyme replacement therapy should be started at diagnosis in case of clinical symptoms of exocrine pancreatic insufficiency even before obtaining the results of the elastase assay. The starting dose could be 2,000 IU lipase per 100ml of milk. In case of persistence of symptoms of pancreatic insufficiency despite a maximum dose of 10,000 UI/kg/day of lipase, it may be necessary to evaluate the patient’s compliance and the methods of conservation and administration of the pancreatic extracts. In case of poor weight-for-height growth despite an adapted substitutive therapy, bronchial sampling by bronchoalveolar lavage should be considered and non-infectious causes should be searched.

Respiratory care

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

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

Systematic respiratory physiotherapy is recommended from the time of diagnosis. The frequency of sessions of physiotherapy depends on the clinical status of the infant. Regular therapy might be recommended even in the asymptomatic infant (3).

Any evidence of respiratory infection justifies performing a respiratory culture and adapted antibiotic treatment of the isolated pathogens. Infection by Staphylococcus aureus sensitive to Meticillin should be treated by adapted antibioticotherapy. In case of isolation of S. aureus resistant to Meticillin, a treatment aiming eradication is recommended. Evidence of P. aeruginosa justifies systematic antibiotic treatment, even in the asymptomatic infant. Although there is still no consensus, treatment might begin with an inhaled antibiotic, eventually associated with oral Ciprofloxacin. In case of persistence of P. aeruginosa after initial therapy, or if the infant presents with severe clinical signs, intravenous antibiotics should be considered (1,2,3). For other pathogens, there is less clear agreement and treatment should be guided by local policies. In the absence of clinical improvement despite an adapted antibioticotherapy, bronchial sampling by bronchoalveolar lavage should be considered and non-infectious causes should be searched for, including gastroesophageal reflux, asthma and an ENT cause.

Respiratory syncytial virus (RSV) may have adverse effects on respiratory status in patients with CF (9). There is insufficient evidence to support systematic recommendation of Palivizumab in the CF infant even if some small studies suggest that there could be benefit from the use of RSV prophylaxis in infants with CF (10). US and French guidelines state that Palivizumab could be discussed, namely for the infant of less than 6 months of age during an epidemic period (2,3). Finally, dornase alfa, 7% hypertonic saline might be used in symptomatic infants (2).

Conclusion

With increasing numbers of infants with CF being diagnosed by newborn screening across most of Europe and in North America, we will have the opportunity for large cohort follow-up and randomized controlled trials. This will help to establish still lacking best available evidence to harmonize therapeutic strategy in infants newly diagnosed with the final aim of improving clinical status at later ages.

References


#3 - NON-CF BRONCHIECTASIS

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Bronchiectasis is the distraction of the normal anatomy of conducting airways that results in impaired mucociliary clearance leading to chronic cough, sputum production, and recurrent infections and inflammation that cause further damage to the bronchial and bronchiolar walls leading to a vicious cycle of airway injury. The prevalence of non-CF bronchiectasis (NCFB) in children differs between developed and poor countries. In the developed world, the most common cause of bronchiectasis in children is cystic fibrosis (CF), followed by primary ciliary dyskinesia and immune deficiencies. However, up to half of cases remain without a known etiology. In developing countries, a systematic review of 989 children (1) demonstrated that an etiology was identified in 63% of children, with a
previous severe pneumonia of bacterial or viral etiology and B-cell defects as the most common identified disorders.

Bronchiectasis should be suspected in patients who present with chronic productive cough of mucopurulent sputum. Physical findings in bronchiectasis patients are nonspecific but may include crackles and wheezes on lung examination and clubbing of the digits. Pulmonary function testing results generally show airflow obstruction. The diagnosis of bronchiectasis is confirmed by HRCT scan which is now the gold standard for diagnosis. These include bronchial dilatation (an internal bronchial diameter greater than the diameter of the accompanying bronchial artery [i.e., the “signet ring” formation]) and a lack of bronchial tapering on sequential slices (2). Patients in whom bronchiectasis has been diagnosed should be evaluated for potential underlying causes. They need to undergo chest CT scan to define the extent of their disease. Patients with focal disease require bronchoscopy to evaluate for a localized airway obstruction as the cause of the bronchiectasis. Patients with diffuse bronchiectasis should be assessed for underlying systemic abnormalities including congenital disorders, chronic aspiration, impaired mucociliary clearance and systemic or local innate immune dysfunction. All patients with bronchiectasis should have a regular routine microbiological examination of their sputum for routine bacterial and NTM organisms.

Pulmonary exacerbations of NCFB are known to be associated with poor outcomes, and infections are common causes. Gram-negative bacteria are isolated more frequently in patients with NCFB, with H. influenzae and P. aeruginosa representing the majority of identified species. However, up to 40% of sputum samples fail to grow any pathogenic bacteria (3). Patients with sputum samples dominated by P. aeruginosa (PA) had a higher frequency of exacerbation and poorer lung function compared to patients whose samples were dominated by other organisms (4). Nontuberculous mycobacteria (NTM) are opportunistic pathogens that afflict patients with preexisting lung disease; in particular those with NCFB, shown in a meta-analysis by Chu et al. to be prevalent in nearly 10% of the patients (5). Respiratory viruses were found in nearly 50% of exacerbations.

The goals of bronchiectasis treatment are to reduce the number of exacerbations and to improve quality of life. If an underlying systemic etiology such as immune deficiency is identified, it should be addressed. Pharmacologic agents and the mechanical mobilization of secretions have been evaluated to a limited degree in patients with non-CF bronchiectasis. Short-acting or long-acting bronchodilator adrenergic and anticholinergic agents are commonly prescribed, but there have been no randomized controlled trials to support their use. Pulmozyme had adverse effects when studied in patients with non-CF bronchiectasis. Inhaled mannitol showed improved time to first exacerbation and quality of life. Nebulized hypertonic saline solution (7%) have shown promise in the treatment of patients with both CF and non-CF bronchiectasis, but long-term prospective trials are needed. The role of the use of maintenance antibiotic therapy is uncertain in patients with non-CF bronchiectasis. Rotating oral antibiotic strategies have been commonly used. For exacerbations, antibiotic therapy should be tailored to their sputum microbiology results. Severe exacerbations, particularly in patients who are infected with organisms that are resistant to therapy with oral quinolones, require IV antibiotic therapy.

Azithromycin has been shown to attenuate MUC5AC and MUC2 gene expression, thereby suppressing the synthesis of mucin on human airway epithelial cells. Clinically, this was demonstrated in a study that found that mean 24-hour sputum volume and QOL were significantly lower in patients with bronchiectasis after 12 weeks of azithromycin compared with control subjects (6). A recent randomized, double-blind, placebo-controlled trial in adults assigning patients to receive 500 mg azithromycin or placebo three times a week for 6 months, showed that azithromycin significantly reduced the exacerbation rate with no significant effect on FEV1 (7). Based on the above and other studies, it is recommended that all patients with NCFB be treated with azithromycin. Long-term inhaled antibiotics are used for patients with uncontrolled NCFB, but until more recently, data on their efficacy have been lacking.

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The use of mechanical aids, including chest physical therapy with postural drainage, active cycle of breathing, oscillatory positive expiratory pressure devices, and high frequency assisted airway clearance, also constitute potential adjunct therapies for patients with bronchiectasis. Though these modalities are considered to be standard therapy for patients with CF bronchiectasis, their utility is less well proven in patients with non-CF bronchiectasis.

It was shown that comprehensive medical care in children with NCFB was associated with a decrease in exacerbation rates (8). These findings further exemplify the importance not only of identifying NCFB in pediatric patients, but also of ensuring that they receive close surveillance. Treatment burden with lack of immediate apparent outcomes cause patients to avoid daily therapy and seek therapy only for exacerbations.

Resectional surgery and lung transplantation are rarely required. Surgical treatment has classically been an option for patients who have localized bronchiectasis with persistent symptoms despite maximal therapy, or recurrent infections with resistant pathogens (9).

The prognosis for patients with bronchiectasis is variable given the heterogeneous nature of the disease. Because there are so few randomized controlled trials of therapies for non-CF bronchiectasis, patients must be evaluated and treated on an individual basis in a tailored, patient-focused approach in a specialized center to optimally evaluate and treat individuals with bronchiectasis.

References

4. ANTICHOLINERGICS AGENTS IN OBSTRUCTIVE AIRWAY DISEASES IN CHILDHOOD

#1 - RATIONALE FOR THE USE OF ANTICHOLINERGIC DRUGS IN OBSTRUCTIVE AIRWAY DISEASES

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Pediatrics, Istituto Giannina Gaslini, Genoa, Italy. Pulmonology and Allergy Unit and Cystic Fibrosis Center, Department of airway smooth muscle proliferation, increasing the responses to epidermal the regulation of airway smooth muscle contraction and of mucus secretion airway remodeling [2,4]. M3 receptors are the dominant receptor subtype in stimulate cell proliferation and modulate cellular responses associated with effects that require concomitant M3 receptor-mediated release of calcium muscles, they modulate different ion channels involved in cell contraction, ionic nerves and from parasympathetic nerve terminals. In airway smooth autoreceptors inhibiting the release of acetylcholine from both pregangli- airways. M2 receptors are expressed by neurons, where they function as sion. M2 and M3 receptors represent the major populations in the large and by the ganglia, where they facilitate parasympathetic neurotransmis- and water secretion, by goblet cells, where they regulate mucus production, are expressed by airway epithelial cells, where they modulate electrolyte and differentiation and electrolyte transport [3].

Nicotinic receptor structure and functions Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels, formed by five homologous or identical subunits, arranged to form a central ion channel [3,4]. Depending on the subunit composition, nAChRs show different kinetics and pharmacological properties. In lung tissues, the “muscle” nAChRs are localized at the neuromuscular junctions of the smooth muscle cells, whilst the “neuronal” nAChRs are expressed by autonomic ganglia, but also by almost every cell type, including bronchial and alveolar epithelial cells, endothelial cells, pulmonary neuroendocrine cells, submucosal glands, airway and vascular smooth muscles, fibroblasts and alveolar macrophages [4]. Although nAChRs are classically linked to the depolarization of the plasma membrane required for neurotransmission, non-neuronal nAChRs in the lung act most frequently as calcium channels and have been linked to regulatory proteins controlling cell proliferation [2–4]. The functional role of nAChRs is particularly complex and depends on subunit composition, dose response, and duration of ligand stimulation. Although nAChR activation often leads to a positive feedback loop that induces receptor expression, chronic stimulation of nAChRs can produce channel desensitization and decreased activity. The majority of studies of nAChR function in the lung are related to the effects of nicotine, i.e. to tobacco-induced mutagenesis and lung carcinogenesis, whilst little is known on the physiological functions in regulating lung growth and repair, airway epithelial cell proliferation and differentiation and electrolyte transport [3].

Muscarinic receptor structure and functions Muscarinic receptors belong to the large family of G protein-coupled receptors, characterized by seven transmembrane domains. Out of the five subtypes identified, only M1, M2 and M3 receptors have been detected in the airway and lung tissues of most mammals, including humans. Almost all airway and lung cell types express muscarinic receptors. M1 receptors are present mainly in the peripheral lung tissue and in the alveolar walls: they are expressed by airway epithelial cells, where they modulate electrolyte and water secretion, by goblet cells, where they regulate mucus production, and by the ganglia, where they facilitate parasympathetic neurotransmission. M2 and M3 receptors represent the major populations in the large airways. M2 receptors are expressed by neurons, where they function as autoreceptors inhibiting the release of acetylcholine from both pregangli- onic nerves and from parasympathetic nerve terminals. In airway smooth muscles, they modulate different ion channels involved in cell contraction, effects that require concomitant M3 receptor-mediated release of calcium from intracellular stores. In fibroblasts and smooth muscles, M2 receptors stimulate cell proliferation and modulate cellular responses associated with airway remodeling [2,4]. M3 receptors are the dominant receptor subtype in the regulation of airway smooth muscle contraction and of mucus secretion from submucosal glands and goblet cells [3]. M3 receptors can also favor airway smooth muscle proliferation, increasing the responses to epidermal growth factor and platelet-derived growth factor [3].

Non-neuronal acetylcholine production and functions Acetylcholine, in addition to the parasympathetic nerve, is also synthesized and released by a large number of non-neuronal cells, including neuroendo- crine, ciliated, basal and secretory epithelial cells where it can act as an autocrine or paracrine signaling molecule. Secretory and ciliated cells release acetylcholine into the luminal periciliary fluid, whereas endocrine and basal cells secrete acetylcholine basally [3]. Current knowledge suggests that the local auto/paracrine production of acetylcholine by epithelial cells may play a role in regulating various aspects on the innate mucosal defense mechanisms, including mucociliary clearance. Acetylcholine is known to increase ciliary beat frequency in the airways and to modulate the release of inflammatory mediators by these cells through M3 receptors and to affect inflammatory cells involved in the pathogenesis of obstructive airway diseases [3]. Expression of muscarinic receptors has also been shown to be involved in cell proliferation and release of pro-inflammatory mediators [2,3]. Arteries, veins and bronchopulmonary anastomoses also express muscarinic receptors (M3) and dilate in response to acetylcholine released by vagal nerve stimulation.

Regulation of acetylcholine release from the parasympathetic nerve terminals The postganglionic nerve fibers do not form defined synapses to their target cells but a terminal meshwork called ‘autonomic plexus’ with numerous varicosities, called sites of transmitter release, in variable and only rarely close contact to cells, such as airway smooth muscle [4]. Release of acetylcholine from the parasympathetic nerve terminals in the airways appears to be under complex prejunctional regulatory mechanisms. The available data indicate that acetylcholine release can be enhanced by a variety of pro-inflammatory mediators (histamine, bradykinin, neuro- peptides) and by β1-adrenergic agents, whilst it is under the inhibitory control of muscarinic autoreceptors and downregulated by eicosanoids, such as PGE2, opioids, nitric oxide and α2-adrenergic agents [5].

Muscarinic receptor functions and dysfunctions in airway disorders The activity of M3 receptors in smooth muscle appears to be spared or even increased in asthmatics, possibly because of a greater affinity of the acetylcholine binding site. There is also no evidence that muscarinic receptors are overexpressed or upregulated in airway smooth muscle in disorders characterized by bronchial obstruction or hyperresponsiveness although an acquired loss or impairment of neuronal M2 receptor function may be involved in their pathogenesis [15]. These functional changes occur after exposure to allergens, infectious agents (viruses) or pollutants (ozone) and result in increased acetylcholine release from parasympathetic nerves [6]. M2 autoreceptors dysfunction in allergic asthma is caused by the eosinophil basic protein released by activated eosinophils that, upon binding to M2 autoreceptor sialic acids, acts as an allostERIC antagonist [3]. With the same mechanism, an early recruitment and activation of eosinophils is thought to cause the airway hyperreactivity that follows environmental ozone exposure [3]. In contrast, viral respiratory infections are purported to induce bronchial hyperresponsiveness through different mechanisms, including: a) the inhibition of M2 receptor synthesis, mediated by the release of interferon-γ by activated CD8+ T-lymphocytes; b) the production of neumaminidase, that determines functional impairment of M2 receptor activity by cleaving their sialic acid; c) M2 receptor dysfunction, caused by the activation of the substance P (NK1) receptor overexpressed by influenza, parainfluenza and respiratory syncytial virus [3]. Interestingly, increased substance P production has been reported in patients with asthma and gastroesophageal reflux, a disorder that recognizes vagus-mediated oesophageal-tracheobronchial reflexes in its pathogenesis. Experiments performed in humans have corroborated the relevance of pathogenesis of M2 autoreceptors in generating airflow limitation showing that M2 receptor selective agonists inhibit cholinergic-induced bronchoconstriction in normal individuals but not in asthmatic patients [3]. Defects in M2 autoreceptor activity may also explain bronchoconstriction induced
by β-blockers in asthma. These drugs can increase cholinergic tone downregulating the action of endogenous catecholamines on β2-adrenoceptors present on cholinergic nerves [3].

**Anti-cholinergic agent pharmacology and clinical applications**

Thus, in extreme synthesis, the three muscarinic receptor subtypes expressed in the airways have different, somehow conflicting functions: M1 and M3 receptors facilitate cholinergic-induced events, including bronchoconstriction and mucus gland secretory activities, whilst M2 receptors have a feedback inhibitory function, regulating the release of acetylcholine from cholinergic nerve endings. This information is of great importance to understand the activity of the three anti-cholinergic agents that can be used to treat patients with reversible airway obstruction. Two of these, ipratropium and oxitropium bromide, are short-acting and non-selective muscarinic antagonists. Because of the lack in selectivity, they also block M2 receptors, increasing acetylcholine release, and therefore reducing the degree of their “useful” action on M1 and M3 receptors [3]. In contrast, the more recent long-acting anticholinergic drug tiotropium bromide is characterized by a kinetic selectivity for M1 and M3 receptors over M2 receptors: it dissociates rapidly from M2 receptors and very slowly from M1 and M3 receptors [3,7]. To date, the anti-cholinergic agents most commonly used to treat respiratory disorder in childhood is the “non-selective” ipratropium bromide which, alone or associated with inhaled β2-adrenoceptors agonists, has been demonstrated to significantly improve pulmonary function and clinical outcomes in acute asthma, in preschool wheezing, although no long-term assessments have been included [3,8]. Interestingly, preliminary data show that inhaled tiotropium bromide, once daily, is well tolerated and also improves lung function in pediatric patients with cystic fibrosis [9] and in asthmatic adolescents, symptomatic despite inhaled corticosteroids [10]. Evidence from experimental models also suggest that tiotropium bromide may also modulate the acetylcholine-induced inflammatory and remodeling changes induced in the airways by a variety of stimuli, leading to hopes of having favorable clinical responses in other respiratory disorders.

**Conclusion**

A relevant role in the pathogenesis of obstructive airway disorders is thought to be played by an increased acetylcholine release, at least in part due to M2 receptor dysfunction. The most commonly prescribed short-acting anticholinergic drug, ipratropium bromide, is not selective for muscarinic receptor subtypes. Despite some efficacy in the most common pediatric airway diseases such as asthma and pre-school wheeze and cystic fibrosis, ipratropium bromide is not commonly prescribed as a standalone medication. The more recently introduced anticholinergic drug, tiotropium bromide, has advanced pharmacologic properties such as long duration of action and a functional selectivity for M1 and M3 receptors over M2 receptors, and has shown a good efficacy and safety profile in adult respiratory disorders, such as asthma, cystic fibrosis and chronic obstructive pulmonary disease. Ongoing studies are now under way to define its therapeutic role for pediatric airway diseases.

**References**


**#2 - ANTICHOLINERGIC THERAPY FOR CHILDHOOD ASTHMA**

**Bruce K Rubin** MEngr, MD, MBA, FRPC<br><br>\<br>Inhalation of smoke from *Datura stramonium*, a member of the deadly nightshade family, was recommended for the treatment of asthma in 17th century Ayurvedic literature. General Gent, himself an asthmatic, on return from India in the early 19th century, was reported to have brought this therapy to England. Stramonium and belladonna cigarettes were widely used to treat respiratory disease until the middle of the 20th century. However there were frequent side effects, including tachycardia, hallucinations, and even addiction. With the introduction of synthetic atropine derivatives with fewer side effects, there has been a renewed interest in anticholinergic therapy for asthma.

Bronchial smooth muscle tone is predominantly set by cholinergic activation. Patients with asthma have increased bronchial smooth muscle tone and mucus hypersecretion, likely as a result of cholinergic activity. Anticholinergic medications can relax smooth muscle in children with acute asthma. These drugs also appear to have anti-inflammatory properties, and may reduce goblet cell hyperplasia driven by neutrophil elastase – a feature of severe asthma known to be resistant to steroid therapy.

The short-acting anticholinergic agents, ipratropium bromide and oxitropium bromide, have been used in asthma for many years, primarily for acute asthma in the emergency department. Paradoxically, although the addition of an anticholinergic medication to a beta agonist can decrease acute asthma severity and hospital admission, studies suggest that continuing the anticholinergic while the patient is in hospital does not hasten recovery or decrease length of hospital stay. However these studies have been small and potentially underpowered. Until the past decade, these results have dampened enthusiasm for studying anticholinergic medications as maintenance asthma therapy.

This has changed with long-acting anticholinergic (LAMA) bronchodilators under investigation or are available for treating lung disease. These include tiotropium, aclidinium, glycopyronium, glycopyrolate and umeclidinium. The once-daily LAMA, tiotropium bromide, is demonstrated to improve lung function and decrease the risk of exacerbation in adolescents and adults with moderate to severe asthma, despite the use of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABAs). In September 2015, the FDA in the United States approved tiotropium for the long-term, maintenance treatment of asthma in patients 12 years of age and older. Tiotropium by Respimat soft-mist inhaler is now included in the Global Initiative for Asthma report (GINA) 2015 Global Strategy for Asthma Management and Prevention. In Phase 3 studies, tiotropium improved asthma symptoms in 68% of enrolled subjects and decreased exacerbations by 21% whilst having a safety profile similar to that of placebo.

Studies also show that tiotropium was effective in improving pulmonary function (FEV1) and decreasing asthma attacks in children age 6–11 with poor asthma control despite use of a medium dose of ICS with or without a leukotriene modifier. There was no difference in effectiveness when comparing the FDA-approved dose or 2.5 mcg (2 × 1.25 mcg) once daily
tiotropium to a higher dose of 5 mcg. Initial studies in children younger than 6 years did not appear to show benefit. With increasing knowledge about the diverse actions of the cholinergic system in asthma and the role of muscarinic receptors in the airway, we are gaining an increased appreciation of how anticholinergic medication can play an important role in treating children and adults with chronic and poorly-controlled asthma.

**#3 - BEYOND ASTHMA: IS THERE A ROLE FOR ANTICHOLINERGIC AGENTS IN OTHER PEDIATRIC OBSTRUCTIVE AIRWAY DISEASE?**

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This short review addresses potential uses of anticholinergic medication in pediatrics beyond asthma. The last segment touches on asthma in the context of the hitherto little used drug: Tiotropium bromide. This text borrows heavily from our previous publication on the role of anticholinergic in childhood.(1)

**Pre School Wheezing**

The 2008 ERS Task Force opted to not use the term asthma to describe preschool wheezing illness since there was insufficient evidence showing that the pathophysiology of preschool wheezing illness is similar to that of asthma in older ages. The Task Force referred to Pre School Wheezing and described episodic (viral wheeze) for children who wheeze intermittently and are well between episodes versus multiple-trigger wheeze for children who wheeze both during and outside discrete episodes.(2) We will therefore in our current discussion refer to this young age morbidity as an entity that should be discussed separately from asthma, acknowledging that much has yet to be learned on the nature of this entity.

Amongst the many mechanism of virus-induced airway hyperreactivity; a common phenomenon in pediatric practice related to this young age group, studies have shown that cholinergic overactivity such as through the modulation of Substance P may mediate virus-induced airway hyperreactivity. Virus-specific CD8+ T lymphocytes may induce cholinergic activation through M2 receptor dysfunction.(3) Hence anticholinergic medications may have a role in viral-induced wheeze with compounds that display selectivity for M1 and M3 muscarinic receptors over M2 receptors having advantages over nonselective compounds. A number of small studies addressed the role of anticholinergics in acute bronchiolitis but failed to show a role for this acute intervention. A study on 69 infants who were randomly assigned to receive nebulized salbutamol, ipratropium bromide or placebo resulted in faster improved clinical scores and oxygen saturation levels in the bronchodilator groups than in the placebo, but no effect to change the natural course of the disease.(4)

In studies on this topic from 1981, inhaled ipratropium bromide administered to wheezy children (3 - 32 months of age) improved lung function when measured by total body plethysmography and forced oscillation technique.(5) The authors were unable to differentiate between responders and non-responders by clinical or by physiological parameters, but submitted that the differential distribution of obstruction between small and large airways may underlie response or lack thereof; and that subjects with a predominance of large airways obstruction were the responders to inhaled ipratropium. A logical if unproven additional speculation was that anticholinergics decrease airway secretions and with it reduce large airway resistance. A Cochrane review examining the effect of adding ipratropium bromide to B2-agonists in wheezy infants (6) suggested that the combined therapy improved symptom scores after 24 hours compared to the use of B2-agonist alone. The ERS Task Force cited above(2) offered evidence-based recommendations on the definition, assessment and treatment of wheezing disorders in preschool children. Addition of ipratropium bromide to short acting B2-agonists was suggested for patients with severe wheeze. In the 2014 review of the Task Force recommendations no reference was made to the use of anticholinergic medications.(7)

**Tracheobronchomalacia**

It is widely believed amongst pediatric pulmonologists that administration of B2-agonists in infants with airway structural instability, predominantly tracheobronchomalacia is detrimental, while the use of anticholinergics for bronchodilatation is safe. This notion derives from a study of only 3 infants with intrathoracic tracheomalacia, using infant pulmonary function testing and demonstrating that flows improved significantly after administration of metacholine but worsened after administration of albuterol.(8) These results suggest that in patients with abnormally collapsible tracheas or large bronchi, stimulation of the smooth muscle can improve airway stability, thereby increasing forced expiratory flows, while relaxation of airway smooth muscle by bronchodilators can exacerbate obstruction. The sole support for this observation comes from a review of a series of patients with tracheobronchomalacia from Chile, in whom beta-agonist medications were discontinued while the anticholinergics were not.(9) The effect of anticholinergic medication has not been assessed directly in any study, and thus whether this class of medications may have a different effect compared to beta2-agonists in such pathology has not been established. Further studies on the effect of the various bronchodilators for such pathologies using newer technologies to assess airway resistance (e.g., forced oscillation) should be undertaken. While more invasive and challenging, a technique of direct quantitative assessment of tracheal collapsibility in infants with tracheomalacia has been described, and may be the most adequate technique to answer this important clinical question.(10)

**Tiotropium bromide in pediatric use - asthma and the Asthma-COPD Overlap Syndrome**

Tiotropium bromide has a limited role in childhood asthma, largely due to lack of selectivity. The more recently introduced long-acting muscarinic antagonists/anticholinergic (LAMA), tiotropium bromide, presents advanced pharmacologic properties such as selectivity for M3 muscarinic receptors over M2 receptors and long duration of action. A high safety profile and increasing evidence of efficacy have rendered it a mainstay medication for COPD with an emerging role in adult asthma. Few studies have emerged on its role in the treatment of childhood asthma and defining its therapeutic niche for pediatric airway diseases. In a recent 1-year randomized controlled trial, tiotropium add-on therapy in adolescents with moderate asthma,(11) significantly improved lung function and was safe and well tolerated when added to at least ICS maintenance therapy. A study of 71 pediatric patients with asthma and chronic cough from an asthma center(12) concluded that tiotropium can be beneficial in 3 distinct patient populations: add-on therapy to asthmatics on maximal maintenance medication, an alternative to high-dose inhaled steroids in patients who are experiencing significant side effects, and patients with bronchomega as their predominant symptom manifested by a chronic productive cough, the latter population is most likely explained by its drying effect on airway secretions. A recent editorial(13) states “Approximately 1 in 12 people worldwide are affected by asthma or chronic obstructive pulmonary disease (COPD); once regarded as two distinct disease entities, these two conditions are now recognized as heterogeneous and often overlapping conditions. The term “asthma–COPD overlap syndrome” (ACOS) has been applied to the condition in which a person has clinical features of both asthma and COPD”. In recent years multiple reports describing this interface between asthma and COPD have been published recognizing that the demarcation line between these two entities is difficult to define. While the precise definition in various populations is still being worked out, and it is obvious that the majority of such patients are adults, there is early recognition that some pediatric populations, who are viewed as asthmatic, yet have no airway reversibility, may constitute an early presentation of the Overlap Syndrome. The mainstay therapies for COPD are long-acting inhaled bronchodilators, including long-acting B2-agonists (LABAs) and LAMAs, with its characteristic member

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being tiotropium bromide. In patients with COPD they are recognized as being equally effective because they reduce air trapping by relaxing airway smooth muscle as a result of reducing the effects of intrinsic cholinergic tone. It is therefore intriguing to speculate that once a better definition of the Overlap Syndrome emerges in pediatrics, an important role for tiotropium is likely to emerge particularly as a potential steroid sparing medication.

References

5. PEARLS

#1 - THE GLOBAL LUNG INITIATIVE

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The measurement of lung function is of major importance in clinical practice or respiratory medicine and in respiratory research. Much has been learned about the risk factors underlying respiratory disease by measuring lung function in patients and comparing it with that in healthy controls. However, for managing an individual patient or assessing risk of disease onset or progression, it is necessary to know whether an individual’s lung function is “normal” or “abnormal”. Over the years, a number of sets of normative equations have been produced by individual research groups in different parts of the world. These have been incorporated into commercially-available spirometers and used in populations other than those in which the data were collected. This situation was far from ideal, especially as some of the normative equations were many decades old.

What does the GLI mean for clinicians?

To address this situation, the Global Lung Initiative (GLI) was established in 2008 and achieved ERS Task Force status in 2010. The GLI has subsequently been endorsed by the ATS, ANZRS, APSR and TSANZ. As stated in the original publication1, the objectives were to establish improved international spirometry reference equations that

- are based on individual lung function data collected under standardized measurement conditions
- are modeled using modern statistical techniques
- allow flexible and appropriate methods of interpretation using limits of normality
- are clinically useful and can be incorporated into commercially-available equipment
- are reported in such a manner as to give a clear indication of the “normality” of an individual subjects’ lung function.

Data were obtained from 73 centers in 33 countries (n = 160,330) however not all could be used due to lack of data on ethnicity (which is illegal in France!), small numbers, missing data, lack of quality control and other factors. Data were also pooled by region with data from Europe, Israel, Australia, USA, Canada, Mexican Americans, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria, and Tunisia grouped as Caucasians; African Americans grouped separately; data from Thailand, Taiwan, China and Hong Kong grouped as South East Asians; and data from Korea and Northern China grouped as North Asia. Reference equations for healthy individuals, aged 3 to 95 years, to be compiled for Caucasians (n = 57,395), African Americans (n = 3,545) and North (n = 4,992) and South East Asians (n = 8,255). The spirometric variables reported were: FEV1, VC, FEV1/FVC (for all data sets); FEV1/VC, FEV1/FVC and FEF25 (for Caucasian children aged 3-7y); and FEF25,75 for (21 data sets only). While FEV1 and FVC varied between ethnic groups, they did so proportionally, meaning that FEV1/FVC was independent of ethnicity. The lower limit of normality for FEV1 and FVC showed age dependence that differed between males and females, reaching 90% by mid-childhood and falling progressively below 80% from approximately 40 years of age. The rate of fall in the lower limit of normal for FEV1 and FVC was identical for women but FVC declined more slowly in males. A ratio of FEV1/FVC >0.7 is taken to indicate pathological airflow limitation; however, the proportion of the healthy non-smoking population with FEV1/FVC >0.7 rises steadily to 20–25% at 80 years of age.

How well do the GLI reference equations predict lung function in people in individual countries?

Given that the GLI reference equations were compiled by pooling data from a variety of sources, one might expect that the equations would provide good estimates of lung function for populations that were well represented in the pooled data whereas they may not for populations either not included or underrepresented in the pooled data. Indeed this appears to be the case, with the GLI equations adequately representing lung function in Australasian Caucasians, but not performing as well for adults in Brazil, North Africa, Madagascar and children in Poland and peri-urban and rural India. Further study is required to ascertain how widely the GLI reference equations can and should be applied.

What constitutes “normal” data?

An important consideration when creating reference equations is what characterizes a “normal” population and who should be excluded? The dataset used to construct the GLI reference equations excluded ever smokers, but is this reasonable? If 20–30% of an adult population smoke, should they be excluded from equations designed to the lung function of that population? Maternal smoking during pregnancy results in long-term reduction in lung function but is not generally taken into consideration when defining a healthy population. “Healthy” children are often defined as those with no prior asthma or hospitalization for respiratory problems, born full term with birth weight ≥ 2.5 kg and asymptomatic at the time of testing. However, Lunn et al. recently demonstrated that with the exception of clear-cut factors such as current and chronic respiratory disease, including children born prematurely or with low birth weight, prior asthma and mildly symptomatic made little
difference to the reference equations but increased the generalizability to the target population. This debate continues!

**What is the clinical impact of switching to GLI equations?**

The implications of switching to the GLI equations will depend on how well the GLI equations represent lung function of the local population. In Poland, a switch from the 1998 Polish reference values to the 2012 GLI would see an increase in diagnosis of obstructive lung disease from 17.5% to 20.3% and an increase in diagnosis of restrictive lung disease from 3.8% to 7.6%. Whether this represents an over-diagnosis with GLI or an under-diagnosis with the old equations is a matter of clinical judgment. The impact on parents and children with cystic fibrosis is likely to be substantial as families tend to focus on lung function, especially FEV₁ expressed as a percent of predicted as evidence of the state of the child’s lung disease. A change in number for a technical reason must be balanced against the likelihood of creating anxiety in the clinic population.

**References**


**#2 - LUNG FUNCTION, AIRWAY REMODELING AND INFLAMMATION IN INFANTS, LONG-TERM OUTCOME**

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Respiratory symptoms are very frequent in infants and young children. Special emphasis has been put on symptoms signaling bronchial obstruction and bronchial hyperresponsiveness as these may be associated with early onset of asthma. Since the early 1980’s, several research groups have been focusing on early events in the development of asthma, especially seeking potential risk factors for predicting persistent symptoms. Structural changes in the bronchial mucosa and lung function impairment in children with early obstructive symptoms have also been studied. It was documented that eosinophilic inflammation and remodeling (particularly epithelial basement membrane thickening and increased airway smooth muscle mass) are consistently present in patients with persistent asthma. Interestingly, some markers of inflammation and even those of initial remodeling have already been described in children before the clinical diagnosis of asthma could be confirmed. This finding supports the hypothesis of remodeling not being a late consequence of a long lasting eosinophilic inflammation but that it may run in parallel with the development of asthma, if not even precede or initiate inflammation in the bronchial mucosa. This hypothesis was later supported by further research based on bronchial biopsies in infants. Eosinophilic inflammation and some markers of remodeling have been documented in the bronchial mucosa of symptomatic children as early as in the second year of life. In a recent study, we were able to show that basement membrane thickening could be found even in young children at risk of developing asthma even without a history of recurrent wheezing. However, the significance of these findings in terms of long term prognosis still remains less documented. It is known that airway hyperresponsiveness in infancy is associated with persistent symptoms later in childhood. Also, reduced airway patency at birth was shown to be linked to an increased risk of developing asthma and severe bronchial hyperresponsiveness by the age of 10 years.

Long-term follow up of children investigated in infancy and reassessed in later childhood have so far showed that reduced baseline lung function in symptomatic infants was significantly associated with subsequent respiratory morbidity as well as with the need of anti-asthma medication at the age of 3 years. In addition, the usage of inhaled corticosteroids at the age of 3 years also seems to be in positive correlation with basement membrane thickening and increased number of mast cells in bronchial mucosa in biotic samples taken earlier in infancy. This study has thus suggested that early morphological changes in the airway wall might indeed play a role in determining subsequent respiratory morbidity. On the other hand, at the next follow-up of these children at the age of eight years, the positive correlation between current respiratory symptoms and markers of inflammation and remodeling described in infancy was no longer found. This finding is consistent with the results of the follow-up of our group of children where we did not find a significant correlation between lung function (both FEV₁ and FVC) measured in preschool age and basement membrane thickness measured earlier in infancy and toddler’s age both in the risk group and control group of children (unpublished data). More recently, airway smooth muscle mass has come into the center of interest of many researchers in respiratory medicine. Smooth muscle hyperplasia and hypertrophy in the bronchial wall of patients with asthma are considered to be a consistent feature of bronchial remodeling. It is notably a possible dysfunction of newly formed smooth muscle bundles that deserves attention and more studies in this area are urgently required. The first works in children have shown that the increase in the airway smooth muscle mass in the bronchial wall might be associated with school age asthma. Lately, another study has described a negative correlation between the airway responsiveness at the age of 8 years and airway smooth muscle mass in infancy. However, this area of airway remodeling still remains poorly understood, especially with regard to its role in childhood asthma. Based on currently available data, reduced lung function at birth or in early childhood is apparently associated with the persistence of symptoms and the decrease in lung function in later life. However, it still has not been reliably confirmed whether this low lung function has any correlation with early signs of airway remodeling. More long-term follow-up studies are needed in pediatric patients comprising both tissue biopsies taken in early age followed by longitudinal long-term lung function monitoring.

**References**


#3 - NASAL AND SINUS DISEASE IN CYSTIC FIBROSIS

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Nasal and sinus disease is universal in cystic fibrosis (CF). Because nasal and sinus disease usually coexist, we will refer to this as "sinonasal disease". Since the mucosa of the sinuses and upper respiratory tract and the mucosa of the lower respiratory tract are similar, disease may be similar in both locations and sinonasal disease could influence the severity of pulmonary disease. This view of the "universal airway" has been demonstrated in patients with pulmonary conditions, such as asthma and COPD. In these diseases, an improvement in sinus health is reflected by an improvement in the lower airway disease. This has not been well studied in CF but the implications of this relationship combined with increasing life span makes an understanding of sinonasal disease important to the care of these patients.

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in CF carriers appear to be independently associated with a higher prevalence of sinonasal disease; 36% of carriers reported chronic rhinosinusitis compared to the 13–14% in the general population. The bacterial flora of the sinuses changes with patient age, can include anaerobes and fungi, and often mirrors the organisms present in the lower respiratory tract. A link between sinus infection and lower respiratory tract infection may contribute to morbidity following lung transplantation and immunosuppression. Somewhat surprisingly, the prevalence of otitis media in CF appears to be no greater than in an age-matched general population. Endoscopy and computerized tomography have broadened our understanding of how CF affects the sinuses. Endoscopic sinus exams are almost always abnormal and give a better indication of the presence of nasal polyposis than physical examination of the nose alone. Nasal polyps become more common with age and may represent a proliferative airway repair mechanism. Sinus CT has demonstrated several anomalies characteristic of sinonasal disease in CF such as bulging or displacement of the lateral nasal wall, demineralization of the uncinate process, and hypoplasia or aplasia of the paranasal sinuses. Serious complications of sinonasal disease in CF are rare and include mucoceles and periorbital abscesses. These usually require surgery.

There are few randomized, controlled trials evaluating medical or surgical treatments of CF sinus disease. Sinus surgery may provide some benefit, though there are no established selection criteria for appropriate candidates.
A recent meta-analysis demonstrated a relative risk reduction for intubation in the first 72 hours in the NIPPV group compared with NCPAP (RR 0.60, 95% CI 0.43, 0.83). The NIPPV trial was a large international multicenter randomized trial powered to study the important outcome of BPD, recruiting 1,009 extremely low birth weight babies, and it showed no difference between babies randomized to NIPPV compared with CPAP. SNIPPV vs. NCPAP for later use, post extubation at RDS resolution, as a “bridge” to spontaneous unsupported breathing, was shown to be more effective than NCPAP. A pooled meta-analysis showed that SNIPPV was more effective than NCPAP in preventing failure of extubation (RR 0.21 (0.10, 0.45)) and the number needed to treat was only 3 infants to prevent one extubation failure. SNIPPV vs. NCPAP post extubation, also tended to decrease the rate of BPD. SNIPPV may also be more effective than NCPAP for apnea of prematurity. A meta-analysis regarding apnea of prematurity suggests that SNIPPV is more efficacious with apnea that is frequent or severe. However, the studies performed addressed short-term outcomes and as such could not properly address the incidence of requirement for reintubation. Thus, more studies are needed before recommending SNIPPV as standard of care for apnea of prematurity. While non-invasive ventilation is probably safe, its success depends on gestational age. The data indicate that surfactant may still have a significant role in the treatment of RDS, especially in ELBW infants. Recent studies reported on an intubation rate of ~50% in their NCPAP group in ELBW infants. This leads us to the INSURE approach. This approach may allow the infant to benefit from both surfactant and NRS. A Cochrane review concluded that the INSURE approach with NCPAP compared with later selective surfactant administration, continued mechanical ventilation, and extubation from low respiratory support was associated with less need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes. Another option for surfactant application to the trachea without endotracheal intubation was described by using a thin catheter in spontaneously breathing preterm infants receiving NCPAP. This technique was reported to reduce the need for mechanical ventilation. There are ongoing trials with inhaled surfactant. To summarize, NCPAP is still the most common mode of non invasive respiratory support worldwide. The available evidence supports the preference of early or later use of NIPPV/SNIPPV compared to NCPAP because of minimizing the use and the length of endotracheal ventilation. There are data to suggest that this approach may also reduce the rate of BPD, however this has yet to be shown. The results of a large international RCT comparing both primary and post-extubation use of NIPPV with NCPAP, with a composite primary outcome of death or BPD at 36 weeks corrected age, indicate no additional benefit, or risk, conferred by NIPPV in comparison to NCPAP. Whether NIPPV/SNIPPV is more beneficial than NCPAP within the INSURE approach needs to be shown. Recently, heated, humidified high-flow nasal cannula (HHHFNC) is frequently used as a mode of NRS. High flows result in washout of anatomical and physiological dead space and contribute to improved fractions of alveolar gases with respect to carbon dioxide as well as oxygen and decrease the work of breathing and the energy cost of gas conditioning. HHHFNC probably creates positive end expiratory pressure (PEEP) that may contribute to its beneficial effect. However, the PEEP that is not monitored has raised concerns regarding the safety of HHHFNC in terms of air leak. Recent prospective studies support the notion that HHHFNC is as effective as NCPAP for early stages of RDS, post extubation and for apnea of prematurity. Yet, more studies, especially in the initial treatment of RDS and in ELBW infants, are needed before adopting HHHFNC as an alternative mode of NRS in these conditions. New modes of NRS such as neurally adjusted ventilator assist (NAVA), and nasal high frequency ventilation, need to be further studied before concluding on benefits for the short and long term outcomes in premature infants. Non-ventilatory measures in the treatment of RDS, such as caffeine, nutrition, fluid and PDA management and postnatal steroids in certain conditions should be included in the care of premature infants with RDS in order to minimize the rate of BPD.

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

References
#2 - TRANS-PLACENTAL TRANSMISSION OF RSV

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For many years, it has been generally accepted that the pathophysiology of RSV bronchiolitis is driven by the inflammatory response evoked by horizontal (i.e., interpersonal) transmission of the virus in the first few months after birth (1). However, a recently published study has brought to the forefront a striking new idea: RSV may be transmitted vertically from the respiratory tract of the mother to the lungs of the fetus (2). Until now, we
believed that when a pregnant woman got a cold, the developing fetus was protected by the placenta from RSV and other respiratory viruses. In this study, pregnant rats were inoculated with a recombinant RSV strain that could be tracked through expression of a red fluorescent protein (rrRSV). The same virus was subsequently found in 30 percent of fetuses exposed in utero, as well as in the lungs of 40 percent of newborn rats and 25 percent of rats born to inoculated mothers when tested in adulthood. These data provide proof of concept for the transplacental transmission of RSV from mother to offspring and the persistence of vertically transmitted virus in lungs after birth. Notably, the intratracheal RSV infection changed expression and function of critical neurotrophic pathways that control the development of cholinergic nerves in the budding airways and lung tissues (3).

These changes in cholinergic innervation of the fetal respiratory tract resulted in the development of postnatal airway hyperreactivity upon reinfection with the same virus (2). The airway smooth muscle tone was normal in the absence of stimulation and its contraction was normal in the absence of either maternal or neonatal infection. But in pups reinfeected with RSV after prenatal exposure to the virus, markedly potentiated contractile responses were measured after either electrical nerve stimulation or methacholine inhalation, suggesting the involvement of both pre- and postjunctional mechanisms. These findings are consistent and provide a plausible mechanism to the epidemiologic evidence that early-life RSV infection – or possibly reinfection – predisposes a subpopulation of children to recurrent wheezing and asthma that typically spans through the first decade of life even in the absence of atopic phenotype (4).

To our knowledge this is the first report of vertical transmission of RSV, or for that matter any common respiratory virus. A number of infectious agents, including herpesviruses and retroviruses, have been shown to cross the placenta and establish persistent infection in offspring. The new evidence extends this possibility to other infections, such as RSV, once regarded as temporary and localized and that instead may be longer lasting and more pervasive than we thought. Also, as shown for other viral pathogens, if RSV seeds the fetus before full T-cell maturation, this could lead to induction of prenatal tolerance and justify the limited synthesis of agents, including herpesviruses and retroviruses, have been shown to cross the placenta and establish persistent infection in offspring. The new evidence extends this possibility to other infections, such as RSV, once regarded as temporary and localized and that instead may be longer lasting and more pervasive than we thought. Also, as shown for other viral pathogens, if RSV seeds the fetus before full T-cell maturation, this could lead to induction of prenatal tolerance and justify the limited synthesis of interferon and other inflammatory cytokines that have been noted when newborns develop severe infections (5).

**Vertical RSV and asthma** – The general concept that we have been working under for decades is that nothing bad happens in the lungs until the baby is born — even with serious conditions such as cystic fibrosis – and that the lungs are “clean” of pathogens at birth. But if human studies replicate the findings from animal models outlined above, our understanding of the pathogenesis of RSV infections would be completely changed. It would turn back the clock of respiratory developmental diseases by months and mean that we would need to start thinking about lung development and pathology during pregnancy rather than at birth. This could create a paradigm shift by extending our focus on prevention from the first few years after birth to also include the last few months before birth. This new paradigm is in line with the emerging evidence that many (or most) chronic inflammatory, degenerative, and even neoplastic diseases plaguing adults have their origins from often-subtle events occurring during fetal life. The “foetal programing hypothesis” was originally formulated by Dr. David Barker more than two decades ago to explain the extensive reproduced and confirmed epidemiologic evidence that low birth weight predisposes to cardiovascular disease in late adulthood (6).

Dr. Barker died aged 75 in September 2013, leaving the legacy of this interesting controversy, but now widely accepted, idea that common chronic illnesses such as cancer, cardiovascular disease and diabetes result not always from bad genes and an unhealthy adult lifestyle, but from poor intrauterine and early postnatal health. In one of his last public speeches, he argued: “The next generation does not have to suffer from heart disease or osteoporosis. These diseases are not mandated by the human genome. They barely existed 100 years ago. They are unnecessary diseases. We could prevent them had we the will to do so.” We believe the same concepts can be extended to chronic obstructive airway diseases like asthma and COPD.

Asthma is the final product of complex interactions between genetic and environmental variables. Prenatal events like the intratracheal exposure to

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**2. VIRAL INFECTION IN INFANCY**

#1 - THE ROLE OF VIRAL PATHOGENS IN CHILDHOOD PNEUMONIA

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The incidence, severity and mortality from childhood pneumonia has declined substantially in the last decade due to improved socioeconomic conditions, better access to care, wider implementation of effective management and preventative strategies and development and availability of improved vaccines, particularly the pneumococcal (PCV) and \textit{H influenzae} type b (Hib) conjugate vaccines.[1] However, pneumonia remains the leading cause of childhood mortality globally outside the neonatal period and a major cause of morbidity and hospitalization despite good immunization coverage.[2,3] Further, early childhood pneumonia has increasingly been associated with the development of chronic non-communicable respiratory diseases into childhood and adulthood, such as asthma or chronic obstructive Airways disease (COPD).[4,5]

With improved global coverage of the newer conjugate vaccines, it is likely that viral causes of pneumonia may be responsible for an increasing proportion of pneumonia cases.[6] However, defining the etiology of pneumonia may be challenging as it can be difficult to distinguish colonizing from pathogenic organisms in respiratory specimens, blood culture rarely is positive and pneumonia, especially severe disease, may frequently be due to multiple co-pathogens. The development of better methods for specimen collection and of molecular diagnostics has provided more sensitive techniques to define potential etiologic agents but further compound the difficulty of ascribing pathogenicity.[7,8]

Despite these limitations, studies in the post-PCV era have reported an increasing predominance of viruses in childhood pneumonia cases, with a virus identified in 70–90% of cases.[9,10] In children vaccinated with 13-valent PCV (PCV13), RSV has been reported to be the predominant pathogen in case control analyses from both high income countries and low-middle country settings. However, there is frequent co-occurrence of other potential pathogens with RSV, including bacteria and other viruses.[9] Children under 6 months of age are at highest risk of RSV disease.[11]

To adequately interpret data on viruses in the context of childhood pneumonia, the prevalence of these in healthy control children must be considered. Using case control designs, viruses identified in association with pneumonia have been RSV, influenza virus and human metapneumovirus (hMPV); adenovirus, parainfluenza virus and coronavirus have been variably associated with pneumonia while the prevalence of rhinovirus has consistently been similar in cases and controls.[9,10,12,13] The use of quantitative measurements of viral load has not shown to be useful in distinguishing cases from controls except for RSV and for hMPV, but the presence of these alone is sufficient to ascribe etiology.

These studies indicate that RSV is a major cause of pneumonia in the era of conjugate vaccines for bacterial pathogens, particularly in young infants. However they also highlight the limitations of current diagnostic strategies, particularly the poor sensitivity of current tests for bacterial etiology and the potential for incorrectly assigning etiology based on molecular diagnostics. They also provide further data on the complexity of ascribing pneumonia etiology, showing interactions between multiple potential pathogens. Despite these limitations, the emerging data indicate that a key strategy for reducing the burden of childhood pneumonia lies in prevention of RSV disease in young children.

Identifying the etiology of pneumonia is key for initiating appropriate management strategies particularly use of antibiotics and to guide development of new vaccines. The reduction in bacterial pneumonia through conjugate vaccines underscores the need to reconsider the empiric treatment of pneumonia in settings where there are strong immunization programs. Case management with antibiotics for pneumonia or severe pneumonia in the World Health Organization Integrated Management of Childhood Illness (IMCI) program has been a highly effective strategy for reducing mortality prior to widespread conjugate vaccine availability[14], but defining the residual burden and identifying clinical or laboratory features that distinguish bacterial from viral pathogens will be important before any change in pneumonia strategy can be recommended globally.

References

3. HIGHLY PREVALENT CLINICAL ISSUES

#1 - LATE PREMATURITY: THE SHORT AND THE LONG-TERM PULMONARY OUTCOME

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Introduction
Late preterm (LP) newborns (born at 34+0/7 to 36+6/7 weeks gestational age) comprise the fastest growing subset of neonates, accounting for approximately 74% of all preterm births and about 8–9% of total births in the US.[1] “Late preterm” infants are born near term, but are “immature”.

The late prematurity birth interrupts normal \textit{in utero} fetal development during the last 6 weeks of gestation that are probably a “critical period” of growth and development of the fetal lungs[2]. Three factors play a role in the respiratory vulnerability of LP infants:[2]

1. Prematurity with its developmental and consequently physiologic components; 2. Heightened rate of respiratory morbidity in the neonatal period; 3.

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Susceptibility of LP infants to infection by such pathogens as respiratory syncytial virus (RSV).

**Short-term pulmonary outcome**

Respiratory complications are the prime morbidities of LP infants [2]. A large retrospective study [3] found that the odds of respiratory morbidity (respiratory distress syndrome [RDS], transient tachypnea of the newborn [TTN], pneumonia, respiratory failure, surfactant administration, and mechanical ventilation) decreased significantly with each advancing week of gestation up to 38 weeks compared with 39 to 40 weeks. Despite a relatively low absolute risk for RDS or TTN at 34 weeks compared with more premature infants, this rate poses an increased risk for LP infants when compared with term infants [2].

Acknowledgement of these morbidities led to studies aiming to decrease this burden. A recent large randomized controlled study [4] showed that administration of betamethasone to women at risk for late preterm delivery significantly reduced the rate of a neonatal composite of respiratory treatments in the first 72 hours (the use of continuous positive airway pressure or high-flow nasal cannula for at least 2 hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 hours, extracorporeal membrane oxygenation, or mechanical ventilation) or stillbirth or neonatal death within 72 hours after delivery. Of note, neonatal hypoglycemia was more common in the betamethasone group than in the placebo group.

**Long-term pulmonary outcome**

Late prematurity may affect the respiratory system in the long term [2]. Several studies reported an association of preterm birth (30–36 weeks’ GA) without clinical lung disease with altered lung development and function [2]. Friedrich et al. [5] in a longitudinal study found that despite normal lung volume, healthy preterm infants had persistently reduced airflow through the age of 16 months and concluded that preterm birth in itself was associated with altered lung development. A single study [6] showed a potential improvement, especially for large airway function, with advancing age.

A recent large prospective cohort study showed that the number of hospitalizations caused by respiratory problems during the first year of life was doubled in moderately late preterm (32–36 weeks’ GA) compared with term infants [7]. At preschool age, moderately preterm infants revealed more nocturnal cough or wheeze during or without a cold and increased use of inhaled steroids. At the age of 5 years, rates of respiratory symptoms between moderate and early preterm born (<32 weeks’ GA) children were similar; both were higher than in term born children. Whether LP birth is associated with airway disease such as asthma in early childhood remains controversial [2]. Different findings in published studies could result from the different methods of asthma diagnosis, age groups at diagnosis, and from the difficulties in diagnosing asthma in early childhood. A recent study [8] found that late preterm birth history is not independently associated with childhood asthma until 7 years of age.

LP infants are more vulnerable to viral respiratory infections, particularly RSV, which are more severe in these infants vs. term infants. The pernicious combination of RSV bronchiolitis affecting an *a priori* compromised lung/airways of LP infants may have a lasting effect on respiratory function and consequent long-term morbidity [2]. Long-term persistence of an early decrease in pulmonary function tests (PFT) was demonstrated by a longitudinal follow-up into early adulthood for an unselected random population in the Tucson Children’s Respiratory Study [9]. These observations suggest that the notion of a “critical developmental period” for the respiratory system does exist. Deficits in lung function during early life, especially if associated with lower respiratory illnesses (especially RSV), increase the risk for chronic obstructive pulmonary disease later in adult life [10].

**Summary**

LP infants are born during a “critical developmental time period” for the lungs. This may result in short and long-term pulmonary consequences.

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**References**


**#2 - A REVIEW OF CURRENT MANAGEMENT AND DIAGNOSIS CRITERIA OF TUBERCULOSIS IN CHILDREN**

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Globally, the burden of tuberculosis (TB) is immense, with an estimated one-third of the worlds population infected with *Mycobacterium tuberculosis*, and projections of almost 12 million new cases occurring annually. In 1993, the WHO declared TB a “global emergency” in public health. Despite the fact that TB data in children is sparse, in 2000, 11% of new cases occurred in children younger than 15 years of age. In 2012, WHO estimated 530 000 TB cases in children and 74 000 deaths worldwide, mainly in limited-resources countries. (1) Adequate TB control by 2015 was a main focus of the United Nations Millennium Development Goals. The key to achieving this goal is through better detection and successful treatment of those who are infected.

TB in children often occurs in highly TB-endemic communities, which commonly are disrupted because of poverty, malnutrition, high prevalence of HIV and/or a weak public health system. Despite all efforts, the global burden of TB remains extremely high worldwide, making this disease one of the most important public health problems in developing countries. In addition, TB control programs are still far from successful, probably because of the inability to detect sufficient numbers of cases before transmission to uninfected high-risk individuals has occurred. Many strategies in the fight against TB have been developed worldwide, all share the same aim: early identification and treatment of those with active disease.
and their contacts. In addition, to screen the population at high-risk for disease. Therefore, the effectiveness of early case finding should be a priority, but it depends on several factors such as health care system, contact tracing, and laboratory diagnosis.

**Diagnosis of Tuberculosis in Children:**

The diagnosis of TB in children is a common clinical challenge, and relies on a careful assessment of history of exposure, clinical examination, and relevant investigations.

The most recommended approach to the diagnosis of TB in both children and adults is based on the WHO guidelines recommendations from 2010 and 2014 (table 1). (2, 3)

| 1. Careful history (including history of TB contact and symptoms consistent with TB) |
| 2. Clinical examination (including growth assessment) |
| 3. Tuberculin skin test |
| 4. Chest x-ray (if available) |
| 5. Bacteriological confirmation whenever possible |
| 6. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB |
| 7. HIV testing |

Although some people develop active TB disease after an initial infection, almost all TB infections are asymptomatic and remain latent for many years (latent TB infection, LTBI). This itself is a great problem as LTBI provides a reservoir for future TB disease. Children, similar to adults, will develop latent TB infection after exposure. However, in contrast to adults, they have a much higher chance of developing active pulmonary tuberculosis (up to 30% in the first two years after infection). In children, the clinical manifestations of pulmonary TB vary broadly, from no clinical illness to moderate chronic or subacute illness. (4) The commonest form is pulmonary TB and this can be the most challenging to diagnose. Extrapulmonary TB accounts for around 20–25% of all childhood TB and the commonest forms are TB lymphadenitis, spinal TB, pleural effusion, abdominal TB, military TB and tuberculous meningitis.

Important factors to consider in all children with suspected TB is the endemic setting as well as the age and immune status of the child. In countries with a low incidence of TB, a positive contact with a case in combination with suggestive symptoms makes diagnosis more straightforward. In high TB endemic areas, a history of TB contact remains important, but is much less sensitive, given that transmission often occurs through unknown source cases. (5)

Laboratory tests for the diagnosis of infections can be grouped into two groups: detection of microbes (or components) and detection of components of the immune response to the microbe. The sensitivity of the first group will depend on the quality of the specimen and the concentration of microorganisms. This group includes microscopy, culture, ELISA, and nucleic acid detection (PCR). The second group measures the activity of the immune system against microbe-specific antigens in the possibly infected host. This category includes antibody detection and activated T cells. The gold standard for the diagnosis of TB is bacillary detection by smear or culture. In adults, microscopy can detect up to 60% – 70% of culture-positive samples. In children, this does not work as well due to limited access to appropriate body specimens, and also because children usually have paucibacillary disease, since cavitating disease is rare in children. Studies have shown that under best circumstances, acid-fast bacilli sputum smear is positive in only about 10–15% of children with TB while culture gives a better yield of 30–40%. Until recently, the diagnosis of LTBI has been based exclusively on the TST, which has relatively poor sensitivity and specificity. Despite these limitations, it remains the standard of care for diagnosis of LTBI worldwide, particularly in low-income countries. Interferon Gamma Release Assays (IGRAs) measure the in vitro response to specific *M. tuberculosis* antigens. Although they offer several advantages over TST such as better specificity, single visit, little inter-observer variability, and no boosting effect; they have not been found better than TST, and are not able to predict the risk of infected individuals developing active TB disease. Given their increased cost, replacing TST by IGRAs as a public health intervention in resource-constrained setting is not recommended.

Novel approaches to confirmation of TB have been developed. These include methods based on rapid culture techniques and genotypic techniques that improve detection of *M. tuberculosis*.

An example is the Xpert MTB/RIF assay, which is a fully automated real-time DNA based test that can detect both TB and rifampicin resistance in less than two hours. (3, 6, 7) As expected, it should be used rather than conventional microscopy and culture in children suspected of having MDR-TB.

**Treatment management of childhood TB:**

Treatment outcomes of childhood TB are usually good. However, young and immune-compromised children who are at high risk of disease progression and disseminated disease are at a higher risk of morbidity and mortality. The main goals of anti-TB treatment in children are to: cure the patient, prevent death or severe complications from TB disease, kill the bacilli, eliminate it from the host’s tissue to prevent relapse, prevent the development of drug resistance, and do all of these with minimal adverse effects. Treatment guidelines vary from region to region, however, all of these emphasize the need for multiple drugs for prolonged periods of time. The choice of treatment in active disease is empiric, as susceptibility data are usually not available. Five drugs are considered “first-line” for the treatment of drug-susceptible TB: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM). The new WHO guidance document emphasizes higher doses of these drugs, particularly in the young child, as age influences drug metabolism. (8)

Multidrug resistance TB (MDR-TB) is a major public health threat, and it arises due to improper use of anti-tuberculosis medications. Current guidelines have based their approach based on experience in adults. Initially, when MDR-TB is suspected, every effort should be made to confirm diagnosis by obtaining specimens for culture and drug susceptibility testing. Preventive therapy for contacts is not recommended; however, a close follow-up of asymptomatic children is recommended. Children with MDR-TB should be treated with the first line drugs to which their strain (or that of the contact) is susceptible, and use the same second-line drugs as the treatment in adults.

Contact tracing is important in TB. Prompt identification of TB cases, and secondary cases of active TB who would deserve treatment, and individuals with LTBI who will benefit from preventive therapy. High-risk children in close contact with a TB case include all children less than five years or HIV-positive children of any age. Careful clinical evaluation of household and close contacts for active TB should always be performed.

**Bibliography**


#4. IMAGING

#1 - IMAGING IN PTB

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The clinical diagnosis of primary TB in children remains challenging because of non-specific signs and symptoms and difficulty with acquiring diagnostic specimens. Because of this, the diagnosis of primary TB in practice, relies on a combination of clinical features and chest X-ray (CXR) findings. The detection of lymphadenopathy in the hilar and para-tracheal regions on the frontal CXR, supported by identification of subcarinal lymphadenopathy on the lateral CXR, represent a useful surrogate marker of TB at relatively low cost. However, sensitivity and specificity for identifying lymphadenopathy on CXR in children is relatively poor with significant inter-observer variation in the interpretation of radiographs, complicated further by poor quality of radiographs. Affecting both accuracy and observer agreement is the lack of standardized imaging criteria and lymph nodes size-criteria for a positive diagnosis of primary TB. Attempts are therefore being made to establish ‘objective’ chest radiograph signs backed up by a standard set of images as a guide.

Ultrasound is an especially attractive imaging alternative to CXR as it does not involve radiation or require sedation and because it is relatively cheap and mobile. Ultrasound of the mediastinum has been used to detect mediastinal lymphadenopathy and can also be used to detect extrapulmonary TB through abdominal imaging, at the same sitting. It is particularly useful in rural settings where no other imaging is available. The ability to store digital ultrasound images and cine-loops also enables tele-radiology support by expert interpretation and opinion, from a distance. Computed tomography (CT) and magnetic resonance imaging (MRI) are obvious diagnostic imaging considerations that will improve diagnostic accuracy of primary TB, but the radiation dose in CT, the need for anesthesia in MRI, the limited availability and high cost are real barriers to their clinical utility. MRI is preferred to CT because it does not involve ionizing radiation. However, the disadvantages of MRI for lung imaging (poor signal generated from the air in the lungs and movement artefacts from breathing), the cost and the requirement for the child to keep still for a prolonged period (requiring anesthesia) have slowed its use in thoracic infections. Yet, whole body MRI, including thoracic imaging is mainstream for detecting lymphadenopathy in childhood lymphoma. There are new ‘short-duration’ MRI protocols that do not require anesthesia and can be performed at a fraction of the cost. Diffusion-weighted imaging with background suppression (DWIBS) and Short Tau Inversion Recovery (STIR) are being performed in under 10-minutes, making MRI a more realistic problem-solving tool and a possible imaging gold standard. Unlike lymphoma, TB lymphadenopathy may demonstrate low signal intensity. This characteristic sign of caseous / gummatous necrosis may catapult diagnostic imaging, beyond its current role as a surrogate marker of TB, to being a true biomarker of primary tuberculosis.

Point-of-care imaging, low-risk non-invasive techniques, improved accuracy and high inter-observer agreement are key to diagnostic imaging, which continues to play a role in the diagnosis of TB, until such time that specimens can be acquired more easily from children to enable the accurate laboratory and clinical tests that are becoming available.

#2 - DYNAMIC IMAGING OF THE PEDIATRIC AIRWAY

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By virtue of the markedly different degree of attenuation of X-rays by air and soft tissue, chest radiography (CXR), fluoroscopy and computed tomography (CT) are effective methods for imaging the airways. Pathology may be directly visualized for large central airways or inferred for small peripheral airways on the basis of the imaging findings. Applications are broad and include suspected intraluminal obstruction (e.g. foreign body, bronchiolitis obliterans), intrinsic airway disease (e.g. tracheobronchomalacia, complete cartilaginous tracheal rings), or extrinsic compression (e.g. vascular rings and slings, crossing innominate artery, midline descending aorta). The preferred imaging technique varies with the suspected pathology and available equipment. Dynamic imaging techniques such as inspiratory/ expiratory CXR, fluoroscopy, and inspiratory/expiratory or cine CT permit the lungs and airways to be imaged at different phases of the respiratory cycle. Inspiratory/expiratory CXR and inspiratory/expiratory chest CT have long been the preferred initial imaging methods for detecting foreign body aspiration or bronchiolitis obliterans, respectively, on the basis of air trapping rather than direct visualization of the airway obstruction. Fluoroscopy has historically been the preferred noninvasive method for diagnosing tracheobronchomalacia due to its ease of performance, even in uncooperative patients, and its high specificity, but it is limited by its subjective interpretation, low sensitivity, poor depiction of the paratracheal structures, and inability to simultaneously display the anteroposterior and lateral walls of the airway and quantify luminal cross-sectional area1.

In infants and children too young to comply with breath-hold instructions, inspiratory/expiratory phases can be simulated by imaging during right/left lateral decubitus or prone/supine positioning. Controlled-ventilation CT under sedation or anesthesia also permits inspiratory/expiratory imaging of the lungs and airways in uncooperative patients. Dynamic cine CT technique allows the airways to be imaged sequentially during successive phases of the respiratory cycle, but coverage was initially limited to short (4 cm or less) segments of the airway, resulting in sampling misregistration and preventing synchronous evaluation of the true extent and severity of airway collapse during the same phase of the respiratory cycle1. Made possible by recent technologic advances including more rapid gantry rotation and wider detector arrays (up to 16 cm cranio-caudal coverage), dynamic volumetric cine CT now allows all or nearly all of the lungs and central airways to be imaged rapidly and sequentially throughout the respiratory cycle without the need for sedation or intubation. This technique is capable of providing multplanar, 3D and 4D information about the airways during normal tidal breathing or forced expiratory maneuvers, as well as depicting the relationship of the airways to the adjacent vasculature if intravenous contrast is administered2.

With dynamic volumetric cine CT, intrinsic and extrinsic causes of airway narrowing can be distinguished and fixed airway stenosis can be differentiated from expiratory central airway collapse due to tracheobronchomalacia (softening of tracheobronchial cartilage) or excessive dynamic airway collapse (inward bulging of the posterior membrane)3. Tracheobronchomalacia is primary (congenital) in approximately 1/200 children and often resolves in isolated mild to moderate cases by 2 years of age as the
Tracheobronchomalacia was originally defined as >50% reduction in airway cross-sectional diameter during coughing, but false positives are very common with this definition, especially for the bronchi in which physiologic expiratory airway narrowing is more pronounced than for the trachea. The shape and cross-sectional area of the airway lumen can be precisely determined by CT, but there is no current consensus on the optimal threshold degree of expiratory airway collapse for a diagnosis of tracheobronchomalacia among children of varying ages with or without coexisting lung disease during either tidal breathing or forced expiration. Expiratory collapse of normal airways can occur in the setting of obstructive lung disease such as asthma or bronchopulmonary dysplasia due to increased pleural pressure and increased peripheral airways resistance that reduces airway transmural pressure. Dynamic volumetric cine CT provides objective information to classify expiratory central airway collapse according to the FEMOS (functional status, extent, morphology, origin, severity) system, but it should be noted that the degree of luminal narrowing is only one factor in airflow limitation. Evidence of airway compression or expiratory collapse on imaging does not necessarily indicate a condition requiring therapeutic intervention, and correlation with the clinical symptoms, signs, risk factors, and pulmonary function tests is necessary to determine the functional significance.

In addition to the noninvasive nature, the advantages of dynamic volumetric cine CT over bronchoscopy include the ability to directly evaluate for vascular structures or soft tissue masses that impinge on the airway, depict the airways distal to a narrowing impassable by bronchoscope, and assess the lung parenchyma for conditions such as air trapping that may be associated with dynamic central airway collapse. A disadvantage of CT is the exposure to ionizing radiation. For perspective, dynamic airway CT incurs a radiation dose similar or less to than that from a year of natural background radiation exposure. Dynamic cine magnetic resonance imaging (MRI) avoids exposure to ionizing radiation and is capable of imaging the central airways and vasculature, but is limited by a longer scan time, more frequent need for sedation/anesthesia and less detailed depiction of the lung parenchyma compared to CT. Additional studies in children are needed to determine how the anatomic and functional information provided by dynamic CT is best applied to the diagnosis, treatment planning, and post-therapeutic monitoring of pediatric airway disorders.

References
7. Faust RA, Remley KB, Rimell FL. Real-time, cine magnetic resonance imaging for evaluation of the pediatric airway. Laryngoscope 2001;111:2187–2190
11. Faust RA, Remley KB, Rimell FL. Real-time, cine magnetic resonance imaging for evaluation of the pediatric airway. Laryngoscope 2001;111:2187–2190
13. Faust RA, Remley KB, Rimell FL. Real-time, cine magnetic resonance imaging for evaluation of the pediatric airway. Laryngoscope 2001;111:2187–2190
15. Faust RA, Remley KB, Rimell FL. Real-time, cine magnetic resonance imaging for evaluation of the pediatric airway. Laryngoscope 2001;111:2187–2190
17. Faust RA, Remley KB, Rimell FL. Real-time, cine magnetic resonance imaging for evaluation of the pediatric airway. Laryngoscope 2001;111:2187–2190


5. SLEEP DISORDERED BREATHING

#1 - ORTHODONTIC TREATMENT OF SLEEP DISORDERED BREATHING

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Obstructive sleep apnea syndrome (OSAS) is characterized by prolonged partial airway obstruction and/or intermittent complete obstruction (obstructive apnea) during sleep, affecting about 2% to 3% of children [1]. OSAS is a complex syndrome with multiple etiologic factors: the main causative factor is adenotonsillar hypertrophy while other conditions, such as craniofacial dysmorphism, obesity, hypotonic neuromuscular diseases, despite inducing reduction of the caliber of the upper airways, are commonly mistreated [2]. Adenotonsillectomy has been considered for many years the only treatment in children with OSAS although its efficacy remains uncertain, depending on the severity and on the presence of other co-morbidities. [3]. Since a residual OSA is reported in a large proportion of children after adenotonsillectomy [3], and children with OSA display a complex phenotype (mild or major craniofacial anomalies, and/or comorbid obesity, and/or adenotonsillar enlargement), a multi-therapeutic approach to pediatric OSAS and a defined timing of therapy are required [3,4]. A narrow upper airway accompanied by maxillary constriction and mandibular retrusion is commonly reported in children with OSAS [5]. The skeletal conformation showing hyperdivergent skeletal growth pattern associated with posterior displacement of the tongue base, increases the upper airway narrowing and craniofacial, intermaxillary, gonial and mandibular angles leading to a high-arched (ogival) palate [6].

Rapid maxillary expansion (RME) is the most common dento-facial orthopedic procedure used in young patients to treat maxillary transverse deficiencies, starting up to 4 years of age. Recently, it has been demonstrated to be efficacious to treat OSAS in children with a narrow palate and malocclusion: a significant reduction in the apnea-hypopnea index and in diurnal symptoms after six months of therapy with RME [7], and positive long-term effects in children with OSA and malocclusions treated with RME have been reported [8]. Similar results were obtained after one year of treatment with RME in 16 preschool and school-aged non obese children with OSAS and dental malocclusions with a significant drop in clinical symptoms as well as apnea-hypopnea index [8]. This study also demonstrated that starting treatment early when the bone is still extremely plastic and its growth rate is maximum increases the percentage of success of RME treatment. A two-year follow up after the end of the RME application was performed in the same population of children confirming a stable decrease in apnea-hypopnea index, an increase of mean overnight oxygen saturation and a persistent improvement in clinical symptoms [9]. Finally, a recent randomized study showed preliminary results regarding the effect of RME applied before adenotonsillectomy compared to the effect of RME applied after surgery, in children with OSA. No significant differences between the two different approaches were described [10].

In conclusion, orthodontic treatment is a valid treatment for OSA, improving clinical symptoms, respiratory parameters measured during PSG and long lasting effect. The widening of the maxilla, the corrections of dental malocclusions and the correct relationships between maxillary and mandibular arches with respect to the anterior cranial base, are the main craniofacial changes induced by RME that may explain the efficacy of orthodontic therapy. Orthodontic therapy should be encouraged in pediatric OSAS, and an early approach may permanently modify nasal breathing and respiration, thereby preventing obstruction of the upper airway.

References

#2 - NEUROCOGNITIVE CONSEQUENCES OF SLEEP-DISORDERED BREathing IN CHILDREN

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Towards the turn of the century, David Gozal’s group published a series of papers that raised important questions. In a sample of 297 1st grade pupils whose school performance was in the lowest decile of their class ranking, they found that 18% had sleep-associated intermittent hypoxia and/or hypercapnia; school performance improved in those whose parents had opted for adenotonsillectomy (1). They then showed that 13% of 14–15 year olds with poor school performance had parent-reported snoring at age 4–5, compared to only 5% among those with good school performance (2). Finally, a group of first graders with snoring, but no obstructive sleep apnea, i.e. an obstructive apnea index <1, performed worse on measures related to attention, social problems and visuospatial function than non-snorers, suggesting that simple snoring may not be as benign as hitherto widely believed (3).

Against this background, we set out to perform the Hannover Study on Sleep Apnea in Childhood (HASSAC), a community-based cross-sectional study on several aspects of sleep-disordered breathing (SDB) in 1144 primary school children incorporating a two-phase sequential screening procedure: Participants were screened for symptoms and signs of SDB using an SDB-questionnaire and home pulse oximetry (HPO), those with outlying results
on either screening method subsequently underwent an abbreviated home polysomnography (hPSG) for a final diagnosis of obstructive sleep apnea syndrome (OSAS). Overall, participants were representative of the underlying population of third-graders in the study region. We found that 10.1% of this cohort were habitual snorers, while the population prevalence for OSAS was 2.8% (4, 5).

We then wanted to know how these symptoms affected behavior and academic achievements. For this, we used parental questionnaires and collected teachers’ ratings, and defined poor school performance as grade 4 or worse in the last school report form, or requirement for special assistance, with this classification roughly corresponding to the lowest quintile of a class. We found that children with habitual snoring, compared to those who never snored, had 3–10 times the odds for daytime symptoms such as hyperactivity, difficulty concentrating, falling asleep while watching TV or at school or having peer problems, and 2–3 times the odds for poor school performance in mathematics, science and spelling (4, 6). There was a clear dose-effect gradient, i.e. the proportion of children with poor school performance increased with increasing frequency of parent-reported snoring. Considering its high prevalence, and assuming a causal link to disturbed behavior, habitual snoring appeared to be a substantial public health problem in primary school children.

Given this association, we wanted to know how this is mediated, i.e. whether this is mainly through detrimental effects of intermittent hypoxemia or more likely due to recurrent arousal. Contrary to our hypothesis, the increased odds for poor school performance or daytime symptoms associated with habitual snoring stayed the same once children exhibiting intermittent desaturation in their overnight pulse oximetry recording had been excluded, suggesting that even so-called benign snoring, i.e. snoring without hypoxemia, may in fact not be benign. If not via intermittent desaturation, could the relationship with poor school performance be mediated via frequent arousals elicited by recurrent obstructive apnea? To address this question, we took advantage of the fact that children with an abnormal questionnaire score in our HASSAC study also underwent hPSG. Thus, we re-analyzed our data on the relationship of snoring with daytime symptoms and poor school performance after excluding all children with a mixed-obstructive apnea/hypopnea index (MAOHI) ≥0.5, but again, the risk for poor school performance was not reduced among snorers after excluding those with recurrent apneas.

Given that simple snoring has such a strong association with daytime symptoms – are these reversible? In our HASSAC study, we could collect 1-year follow-up data in 82 snorers and 80 controls. Among these, 42 snorers (51%) had stopped snoring. While their scores for emotional problems, hyperactivity and problems with peers improved, their school performance did not (6). This is in line with other data suggesting that reduced scores in executive functioning and IQ seen in children prior to adenotonsillectomy may not improve following this operation (7). Similarly, in the Avon longitudinal study on parents and children (ALSPAC), even those whose SDB symptoms peaked at age 30 months and abated thereafter still had almost twice the odds for hyperactivity and 60% higher odds for behavioral problems at age 7 years (8).

Taken together, there is now a growing body of evidence that frequent snoring in children may not be as benign as previously thought, but may instead be associated with impaired behavior and poor academic achievements. These problems may even persist after snoring ceases, which – if these statistical associations were confirmed as causal – would argue for their early recognition and treatment. Here, it is encouraging to see that in another longitudinal study on snoring and daytime symptoms, the proportion of children who did not snore at age 2 and 3 years was 42% in those who were breastfed for less than 1 month, but 83% in those who were breastfed for 12 months or longer (9), suggesting that breastfeeding may reduce the risk of snoring during early childhood. In addition, given the limited availability of sleep labs, we urgently need better and easier-to-perform screening methods to identify those who may need treatment for their snoring, e.g. in whom poor school performance can be predicted from a screening test (10). Also, interventions such as nasal steroids, monochlukast or orthodontic treatment may deserve further study.

### References


### #3 - SLEEP-DISORDERED BREATHING – YEAR IN REVIEW 2015

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This last year has seen a number of significant advances in the field of pediatric sleep-disordered breathing. The following is a personal selection of a few publications.

#### Diagnosis of sleep-disordered breathing

Overnight polysomnography (PSG) is considered necessary to diagnose children suspected of sleep-disordered breathing (SDB). In practice, however, most children do not have access to overnight PSG, due to the lack of sleep laboratories worldwide. The quest for a simpler means to diagnose SDB, or at least to prioritize children for referral to a sleep laboratory, remains a high priority.

**Questionnaire.** In a prospective study in children aged 5 to 9 years with obstructive sleep apnea syndrome (OSAS), Rosen et al. ¹ found that, conversely to PSG, the Pediatric Sleep Questionnaire results reflect OSAS-related impairment in behavior, quality of life and sleepiness as well as predict their improvement post-adenotonsillectomy (AT). The authors concluded that while PSG is needed to diagnose OSAS, results from a careful clinical assessment provide important adjunctive information on comorbidities and their improvement after surgery.

**Overnight oximetry in OSDB children.** Kaditis et al. ² performed a systematic analysis of the literature on the use of nocturnal oximetry in children with obstructive SDB (OSDB) from primary snoring to OSAS. Their conclusion confirmed that overnight oximetry (SpO₂) is useful for diagnosing OSDB and for predicting post-AT complications in a child with a history suggestive of OSDB. Overall, a desaturation index (≥4%) higher than 2 episodes/hour can predict both mild and moderate-to-severe OSDB, while criteria based on clusters of desaturation such as the McGill oximetry score can predict moderate-to-severe OSDB.

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**Pediatric Pulmonology**
Diagnosis of OSAS using home respiratory polygraphy (HRP). Alonso-Alvarez et al. prospectively assessed the diagnostic reliability of HRP in children aged 2 to 14 years with a clinical suspicion of OSAS. They found a sensitivity of 91% and a specificity of 94% and concluded that HRP emerges as a potentially useful and reliable approach for the diagnosis of moderate/severe OSAS in children.

Drug-induced sedation endoscopy (DISE) aims to reproduce upper airway obstruction during sleep and is gaining increasing popularity, with the hope of guiding efficient surgery and cure OSDB children. In a meta-analysis, Galluzi et al. concluded that DISE may benefit a minority of children with OSAS, and should only be used in children with unremarkable clinical evaluation or upon persistent OSAS after AT.

Obstructive sleep-disordered breathing and obesity
Pathogenesis of OSAS in obese adolescents. Literature on the pathogenesis of OSAS in adolescents is very limited. Schwab et al. prospectively compared upper airway magnetic resonance imaging in 137 adolescents aged 12 to 16 years. Results indicated that lymphoid tissue, rather than other soft tissue components (tongue, lateral pharyngeal walls, parapharyngeal fat pads), are the primary upper airway anatomical risk factors for OSAS. While the pathogenesis of OSAS is clearly multifactorial (e.g., decreased upper airway reflexes in OSAS obese adolescents) and often require additional treatment, the results are clinically important since they suggest that obesity should still be considered as the first-line treatment in adolescents with OSAS.

OSDB and metabolic syndrome. In a systematic assessment of the literature on the interactions between sleep, OSDB, obesity and disruptions of metabolic homeostasis in children and adolescents, Hakim et al. concluded that obesity and OSDB appear to contribute to the initiation and progression of each other, and that both are linked to the metabolic phenotype. One intriguing mechanism postulates that OSDB/disrupted sleep as well as other factors favoring obesity, such as high-fat/fructose diet, disrupt the gut microbiome and lead to increased systemic levels of lipopolysaccharides, in turn promoting inflammation and metabolic dysfunction.

Treatment of sleep-disordered breathing in children
Watchful waiting. Chervin et al. followed 192 children aged 5 to 9 years with mild/moderate OSAS after seven months of watchful waiting only. They found resolution of OSAS in 42% of the children. Independent predictors of resolution were lower AHI and normal waist circumference. The authors concluded that, in practice, a baseline low AHI and normal waist circumference, or low Pediatric Sleep Questionnaire and snoring score, may help identify an opportunity to avoid AT.

Myofunctional therapy (MT). Camacho et al. performed a meta-analysis of the use of MT as a treatment for OSAS in adults and children. Although the total number of patients (especially children, n=25) was low, the effects were highly significant. Overall, MT decreased AHI by 50–60% in pediatric and adult patients. In children, a positive effect was reported when used as the only treatment in mild OSAS as well as to consolidate OSAS cure after AT + rapid maxillary expansion. The authors concluded that MT could be an adjunct to other OSAS treatments in patients of all ages.

Evolution of obstructive sleep-disordered breathing in children
Evolution in preschool children with OSDB. Walter et al. investigated the long-term evolution of OSDB in preschool-aged children with normal weight. Half of the preschoolers with OSDB were treated, most often by adenoidectomy and/or tonsillectomy. Overall, OSDB resolved in half of the children, either spontaneously (35%) or with treatment (57%). However, 40% still had OSAS, similarly to observations in school-aged children. Intriguingly, complete resolution of OSDB at three years post-treatment was more likely in preschoolers with moderate/severe OSAS compared to those with mild OSAS or primary snoring.

Long-term evolution of OSAS. Spilsbury et al. reported results on both remission and incidence of OSAS in 490 participants who underwent PSG at 8–11 and 16–19 years of age. The authors first observed that OSAS in middle childhood usually remitted by adolescence. Secondly, while habitual snoring and obesity predicted OSAS at each time point, distinct additional risk factors for OSAS were found in middle childhood vs. adolescence. Hence, prematurity, a disadvantaged neighborhood or African-American origin also predicted OSAS in middle childhood, while risk factors in adolescents included male sex and previous AT. Finally, obesity, but not habitual snoring, in middle childhood predicted adolescent OSAS. These results confirm that prevention and treatment of obesity appears of utmost importance in the fight against pediatric OSAS.

Evolution of OSAS after treatment. Lee et al. performed a meta-analysis of PSG findings after AT for OSAS in 3413 obese and non-obese children. The overall success rate was 51% for postoperative AHI < 1 event/h (34% for obese vs. 49% for non-obese). Postoperative AHI was positively correlated with AHI and body mass index before surgery. The authors concluded that residual OSAS after AT persists in about 50% of children, especially in children with severe OSAS and obesity.

References
III. YOUNG INVESTIGATOR ORAL COMMUNICATIONS

#A96 - AIRWAY MOLECULAR PHENOTYPING IN PREMATURITY IDENTIFIES INTRINSIC SECRETORY SIGNATURES LINKED TO TH2 INFLAMMATION AND AIRWAY REMODELING

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Rationale: We have recently demonstrated that infants born severely premature (<32 wks) exhibit enhanced airway secretion of Th2 cytokines during rhinovirus (RV) infection and a relative airway Th2 bias (lower IFNγ/IL-4 ratio) during RSV and human metapneumovirus infections. Premature infants with RV-induced “Th2 high” responses had a more severe respiratory phenotype characterized by recurrent hospitalizations in early life. In this study we investigated if the airways of premature infants also exhibit a baseline upregulation of Th2-promoting molecules and cytokines/growth factors known to promote airway fibrosis, angiogenesis and chronic airway obstruction.

Methods: Nasal airway secretions were obtained from children (<3 y/o) born severely premature or full term (n=42) using standard nasal lavage technique. Samples were analyzed with viral multiplex PCR to identify RV and other common respiratory viruses and then were analyzed for protein levels of 30 molecules of interest including periostin (POSTN), VEGF, Angiopoietin-2, Endothelin-1, FGFα, FGFβ, TGFβ1, TGFβ2, EGF, TGF-alpha, PDGF, OPN, SPARC, Follistatin, MMP/TIMP panels and Th1/Th2 pro-remodeling cytokines using multiplex immunoassays. Demographic and clinical variables were obtained by electronic medical record review.

Results: In the absence of viral infection, children born premature had increased nasal airway levels of two strong Th2-promoting molecules: POSTN (preterm 0.36 pg/ml vs. term: 0.13 pg/ml; p <0.05) and VEGF (preterm: 376 pg/ml vs. term: 181 pg/ml; p <0.05). POSTN and VEGF levels correlated with the secretion of pro-asthmatic Th2 cytokines (e.g. IL-4) and airway pro-remodeling molecules (e.g. TIMP/MMP), all of which were further increased during RV infection. Multivariate analysis demonstrated that the association between prematurity and higher levels of POSTN and VEGF was independent of gender, age and race.

Conclusion: We identified a novel intrinsic airway secretory signature in premature children characterized by enhanced secretion of molecules linked to Th2 inflammation (POSTN and VEGF). This prematurity-related airway secretory signature was further increased during RV infection suggesting that respiratory viruses could potentially exacerbate airway Th2 inflammation and remodeling in prematurity leading to long-term lung function deficits in this vulnerable population.

IMPACT: This study presents a novel airway molecular phenotyping approach in prematurity that has the potential to provide new insights into the phenotypic heterogeneity of this condition. The latter will improve risk stratification and our ability to predict responses to therapies (e.g. corticosteroids) leading to a dramatic reduction in morbidity, mortality and increasing lifelong costs of 15 million children born premature in the world every year.

#C19 - THE ROLE OF PROCALCITONIN IN UNCOMPLICATED PNEUMONIA AND COMPLICATED PNEUMONIA IN CHILDREN 3 MONTHS TO 5 YEARS OLD ADMITTED IN HOSPITAL

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OBJECTIVE: Procalcitonin (PCT) is a potential biomarker for differentiating Uncomplicated Pneumonia and Complicated Pneumonia. The main objective of this study is to correlate initial procalcitonin levels taken on admission with the presence of complications and outcome of Pediatric Community Acquired Pneumonia among children aged 3 months-5 yrs old admitted in the Philippine General Hospital.

DESIGN/METHODOLOGY: A prospective cohort study conducted in the Pediatric Emergency Room which recruited 70 children aged 3 months to 5 years old diagnosed with Pediatric Community Acquired Pneumonia, classified as Uncomplicated Pneumonia (n = 35) and Complicated Pneumonia (n = 35) based on chest X-ray study findings read by a single radiologist. Quantitative PCT determination was performed on admission and measurements of blood leukocyte and neutrophil counts were collected. Patients were then followed up 3 days after admission for short term outcome and 7 days after admission for long term outcome as follows: non-survivor; survivor-discharged, stable still admitted in the ward, deteriorated without mechanical ventilator, deteriorated requiring mechanical ventilator, readmitted.

RESULTS: The mean initial PCT level among Complicated Pneumonia was higher than Uncomplicated Pneumonia but was not statistically different (p = 0.0531). PCT levels were higher among non-survivors of pneumonia than survivors at short term and long term outcome but not statistically significant. The initial PCT level in non-survivors of Uncomplicated Pneumonia was statistically higher than survivors at long term outcome (p = 0.0326). No difference in mean PCT among survivors and non-survivors of Complicated Pneumonia was observed at short and long term outcome. Among survivors at short and long term outcome, PCT levels were observed to be highest among those who deteriorated and were intubated than those who were not intubated, stable but still admitted in the ward, readmitted, and discharged. There was no correlation between PCT and blood leukocyte count or between PCT and neutrophil count. The odds of requiring mechanical ventilation was twice on admission, short term outcome, and anytime on admission when PCT was high. The likelihood of dying was fourfold at long term outcome when PCT was high.

CONCLUSION: Procalcitonin can predict the likelihood of dying among Uncomplicated Pneumonia at long term outcome but not the presence of complications in Pediatric Community Acquired Pneumonia and disease outcome in Complicated Pneumonia. However, PCT can better predict unfavorable outcome than blood leukocyte and neutrophil count.

RECOMMENDATION: Additional studies with more pneumonia subjects are needed to determine if indeed there is no difference in initial procalcitonin levels between Uncomplicated and Complicated Pneumonia. Also a repeat procalcitonin level may be performed at time of follow up on either short term outcome or long term outcome to compare the change with outcome status.

#F93 - DO INFLAMMATORY BIOMARKERS PREDICT PULMONARY EXACERBATION IN PATIENTS WITH CYSTIC FIBROSIS?

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Background: Cystic fibrosis (CF) lung disease is characterized by chronic bacterial infection beginning in early childhood and continuing throughout life. The association between oxidative stress and neutrophilic inflammation
in CF lung disease is well recognized. Patients with CF have increased oxidative stress in the airways. New inflammatory biomarkers have recently been used to predict lung inflammation in CF. Calprotectin and isoprostanes are biomarkers which may play an important role in lung inflammation. Objective: The aim of this study was to provide a non-invasive approach for direct measurement of oxidant stress in the lungs and predict lung inflammation of patients with CF. Methods: A prospective cohort study was conducted. Fifty children with CF and 25 healthy controls aged 6–18 years were evaluated. Sputum cultures, concentrations of 8-isoprostane and calprotectin in breath condensate and sputum samples were obtained; lung functions and inflammatory serum markers were also compared. Results: The mean age of the CF patients and healthy controls was 10.6 ± 3.2 years and 10.5 ± 3.2 years, respectively. Fifteen patients had pulmonary exacerbation during the study. 8-isoprostane levels in the breath condensate of CF patients were similar to controls (p = 0.05). Calprotectin was not detected in the breath condensate of patients in both CF and control groups. 8-isoprostane levels in breath condensates and sputum samples were similar within the pulmonary exacerbation and stable phases of CF patients; however 8-isoprostane levels in breath condensates decreased significantly after treatment for pulmonary exacerbation (p < 0.05). Sputum 8-isoprostane and calprotectin levels were measured in only 2 patients and these results were not significant for assessment. There was no correlation between FVC%, FEV1%, FEF25-75%, CRP levels and 8-isoprostane levels in breath condensate and sputum samples of patients. Sputum calprotectin levels were also similar within the pulmonary exacerbation and stable phases of CF patients. 8-isoprostane levels displayed a positive correlation between breath condensate and sputum samples (r = 0.35). Conclusions: Lipid peroxidation and oxidative stress are increased in pulmonary exacerbations of patients with cystic fibrosis, as reflected by increased 8-isoprostane concentrations in breath condensates and decreasing after antibiotic therapy. Although sputum calprotectin and 8-isoprostane levels do not predict pulmonary exacerbation of patients with CF, 8-isoprostane levels in breath condensate may be a useful marker for assessing treatment response.

#J61 - PRIMARY CILIARY DYSKINESIA AND CYSTIC FIBROSIS: SIMILARITIES IN LUNG STRUCTURE AND FUNCTION.

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Introduction
Few studies have comparatively assessed the expression of primary ciliary dyskinesia (PCD) versus cystic fibrosis (CF) in order to highlight similarities and differences between the two conditions. The aim of our study was to compare chest magnetic resonance imaging (MRI), spirometry and sputum culture results in patients with PCD or CF.

Methods
Twenty PCD patients (12 males; age, 15.1 ± 11.1 years; range, 8–29.4 years) and 20 subjects with CF (13 males; age, 16 years; range, 8–26 years; 70% with pancreatic insufficiency) were prospectively assessed when clinically stable by means of chest MRI, spirometry and sputum culture. Chest MRI scans were scored using the modified Helbich scoring system.

Results
Mean chest MRI total scores were 11.6 ± 0.7 in PCD and 9.1 ± 1 in CF patients. Median FEV1 and FVC Z scores were −1.75 (range, −4.6–0.7) and −0.6 (−3.9–1.8) in PCD and −0.9 (range, −5.4–2.3) and −0.3 (−3.4–2.5) in CF subjects, respectively. We found no differences in lung function or structure between the two groups, although the MRI subscore of collapse/consolidation was higher in PCD than in CF (1.6 ± 0.1 and 0.6 ± 0.2, respectively; p < 0.001). Despite respiratory symptoms occurring earlier in PCD than in CF (0.1 years versus 0.6 years, respectively; p = 0.02), PCD was diagnosed significantly later (9.9 years versus 0.6 years, respectively; p = 0.03). Spirometry and MRI findings were confirmed even after adjustment of data for the diagnostic delay. Pseudomonas aeruginosa and Staphylococcus aureus were more frequently isolated in CF than in PCD (p = 0.05 and p = 0.003, respectively).

Conclusion
Our results suggest that PCD and CF patients may have similar lung function and structure, thus indicating that PCD may be more severe than previously thought. These similarities are unlikely determined exclusively by the relevant diagnostic delay of PCD. Comparative studies of PCD and CF may help to develop PCD-specific protocols not derived from CF.

#L105 - ALTERED INTRACELLULAR PROTEOME CHARACTERIZATION OF A549 HUMAN LUNG CARCINOMA CELLS AFTER MYCOPLASMA PNEUMONIAE INFECTION

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Objective: While the pathogenesis of M. pneumoniae infection has been studied extensively, the molecular mechanisms underlying M. pneumoniae pathogenesis are still not fully understood. Therefore, in the present study, in order to seek certain pathogenesis-related proteins, we investigated the effects of M. pneumoniae infection on the intracellular protein expression profile of A549 human lung carcinoma cells. Methods: A549 cells were infected with 10 CFU/cell M. pneumoniae for different time intervals (2h, 8h and 24h, respectively). Thereafter, 2-dimensional gel electrophoresis (2-DE) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique were applied to identify and characterize the members of the A549 intracellular proteome during M. pneumoniae infection. Finally, the altered expression of some of the identified proteins was validated by Western blot analysis, while bioinformatics analysis (including BINGO, KEGG and STRING) was employed to further explore the biological characteristics of these differentially expressed proteins. Results: Based on 2-DE-LC-MS/MS, thirty-eight protein spots were successfully identified, of which 17 proteins were up-regulated and 22 proteins were down-regulated in the M. pneumoniae-infected group compared to the untreated group. Subsequent Western blot results confirmed that the expression of LaminA/C and Ruvb12 were consistent with the proteomic results, indicating the accuracy of the proteomic study. Additionally, BINGO cellular compartment analysis showed that the differentially expressed proteins were mainly related to the cytoplasm, macromolecular complex, cytoskeleton and nuclear matrix. The molecular function of the differentially expressed proteins was associated with glycerol-3-phosphate dehydrogenase (NAD+)- activity, phosphopyruvate hydratase activity, protein homodimerization activity and identical protein binding, while the biological process of these proteins was linked to cellular process and DNA recombination. Furthermore, STRING analysis revealed that 15 of these differentially expressed proteins were able to interact with each other, and mainly formed one protein-protein interaction network which is consistent with cellular metabolic proteins. Moreover, KEGG database search revealed that the 39 differentially expressed proteins were involved in 28 biological pathways, including metabolism (e.g. Glycolysis/ Gluconeogenesis, purine metabolism, pyrimidine metabolism), RNA degradation, spliceosome and MAPK signaling pathway, suggesting that these differential proteins might act as important mediators during M. pneumoniae infection. Conclusion: M. pneumoniae infection may affect protein expression profiles in A549 cells. Using a proteomics approach to investigate the differential proteome of A549 cells is a feasible strategy to understand the pathogenesis of M. pneumoniae infection. Further functional experiments conducted on the identified differentially expressed proteins may elucidate M. pneumoniae pathogenesis in a more detailed manner based on bioinformatics analysis.
#L128 - HUMAN ANAPHYLATOXIN C5A RECEPTOR KNOCK-IN MICE ACQUIRE SENSITIVITY TO STAPHYLOCOCCUS AUREUS PANTON VALENTINE LEUKOCIDIN IN A PNEUMONIA MODEL

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Introduction
Methicillin-resistant Staphylococcus aureus strains have become an increasingly important and frequent cause of severe, necrotizing community-acquired pneumonia (CA-MRSA). The majority of the CA-MRSA isolates carry the gene encoding Panton-Valentine leukocidin (PVL), a pore-forming toxin that lyses polymorphonuclear leukocytes. However, the role of PVL on the pathogenicity of CA-MRSA necrotizing pneumonia is contradictory, which can partially be attributed to the strong species-specificity of this toxin. Although human cells are susceptible to PVL, those of mice are resistant. The basis for the species-selectivity is due to the receptor for PVL, the human anaphylatoxin C5a receptor (C5aR). To address the need for a mouse model suitable for studying human disease, we have generated a human C5aR knock-in (hC5aR-KI) mouse strain to study the pathogenicity of PVL both in vitro and in vivo.

Methods
Humanized C5aR (hC5aR-KI) mice were created using standard homologous recombination techniques. Wild-type mice and hC5aR-KI littermates were inoculated with 107 CFU/animal of either a MRSA USA300 strain that carries PVL or isogenic strains deficient in PVL (dPVL) or alpha-toxin (dHla). Six hours later, the lungs were harvested and assessed for bacterial burden, myeloperoxidase (MPO) and cytokines.

For in vitro experiments, bone marrow cells of WT and hC5a-R-KI mice and human PMNs were assessed for 1) expression of hC5aR, 2) affinity for PVL, 3) calcium influx with PVL, 4) PVL-mediated cell permeabilization, and 5) cellular viability with LDH release assay.

Results
1) HC5aR-KI mice had impaired clearance of the MRSA strain bearing PVL compared to their wild-type littermates. Infections with the isogenic dPVL strain deficient in PVL were cleared equally well by both mouse strains, and lung burden was not significantly different from wild-type mice infected with normal MRSA carrying PVL. Interestingly, there were no differences in MPO or cytokines.

2) Given that alpha-toxin is reported to be an important virulence factor in murine pneumonia, we were concerned that this toxin can overwhelm the toxicity of PVL. HC5aR-KI mice given MRSA deficient in alpha-toxin (dHla) exhibited a significantly impaired ability to clear the bacteria compared to the wild-type littermates, as well as increased lung inflammation (lung MPO and IL-6).

3) HC5aR-KI mouse bone marrow cells had similar affinity for the LukS subunit of PVL as human PMNs, while wild-type mouse exhibited no binding. However, hC5aR-KI cells had significantly reduced LDH and mobilization of calcium relative to human PMNs with PVL, and had reduced hC5aR expression on the cell surface.

Conclusion
Although hC5aR-KI mouse cells have decreased C5aR receptor expression and are less susceptible to lysis by PVL, these animals nonetheless demonstrate newly acquired sensitivity to infection with PVL+ MRSA, and can serve as a potential tool to study the role of PVL in CA-MRSA pneumonia.
Conclusion: The proportion of adolescent patients being poorly compliant with inhaled steroids is high. While previous studies have shown parental concern towards cost and medication side-effects leading to poor compliance amongst parents, these concerns are not necessarily shared by adolescent patients themselves who perceive the treatment as more of an inconvenience. Educating patients in this age group is crucial towards achieving good compliance.

A27 - THE ROLE OF SOLUBLE VASCULAR CELL ADHESION MOLECULE-1 IN THE FORMATION OF THE INFLAMMATORY PROCESS IN CHILDREN WITH BRONCHIAL ASTHMA

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Bronchial asthma (BA) is a major public health problem worldwide. It is regarded as a chronic inflammatory disease of the airways.

Objective: To evaluate the role of soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) in inflammation formation in children with asthma.

Materials and Methods: 69 children aged from 6 to 17 years with persistent BA in exacerbation were examined. Among these, there were 34 patients with mild persistent BA (1st group), 22 patients with moderate persistent BA (2nd group) and 13 patients with severe persistent BA (3rd group). Fifteen healthy children were included in the controls.

Ultrasonography was used to investigate the thickness of the intima-media (I-M) complex. The serum levels of sVCAM-1 were determined by enzyme-linked immunosorbent assay (ELISA, catalog #BMS232, Austria). The level of circulating immune complexes (CIC) was determined by V. Haskova. Statistical analyses were performed with StatSoft STATISTICA Version 8 (Tulsa, OK).

Objective: To determine the endothelial function status in children with asthma.

Chong CS., Ramamurthy MB., Goh DY., Van Bever HP., Lim MT.
Khoo Teck Puat-National University Children’s Medical Institute, National University Hospital – Singapore, Singapore

Objectives: In adolescence, denial of chronic illness has been well documented. This can affect adherence to treatment at a time when patients are expected to take more responsibility toward administering their own medication. We investigated the compliance rate with inhaled corticosteroid therapy amongst adolescent patients with asthma in Singapore.

Methods: Questionnaire survey of adolescent asthma patients using inhaled corticosteroids attending the pediatric asthma clinic at the National University Hospital Singapore over a 5-month period. Data on compliance with medications over the preceding two weeks were obtained.

Results: Twenty-five patients were interviewed during the study period (age 12 to 23 years, median 17 years). There were 10 males (40%) and 15 females. Only 6/25 patients (24%) were fully compliant with regular inhaled steroid therapy. Of the 19 patients who missed prescribed doses, 10 (53%) missed more than 25% of their prescribed doses. 10/19 patients (53%) had forgotten to take their medications, the most common reason. 4/19 patients (21%) found the medications inconvenient. 5/19 patients (26%) did not think that the medications were beneficial, despite 3 of the 5 patients having “poorly controlled” asthma based on their Asthma Control Test scores. 2/19 patients (11%) ran out of medications and did not replenish their supply. None of the patients attributed their non-compliance to the worry of side-effects or cost of medication.

A38 - INTERRELATIONSHIP OF ENDOTHELIAL FUNCTION PARAMETERS IN CHILDREN WITH BRONCHIAL ASTHMA

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The endothelium plays an important role in the development of the local inflammatory process in the pathology of various organs and systems.

Objective: To determine the endothelial function status in children with bronchial asthma (BA) and evaluate its role in disease formation.

#A27 - THE ROLE OF SOLUBLE VASCULAR CELL ADHESION MOLECULE-1 IN THE FORMATION OF THE INFLAMMATORY PROCESS IN CHILDREN WITH BRONCHIAL ASTHMA

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Materials and Methods: 69 children aged from 6 to 17 years with persistent BA in exacerbation were examined. Among these, there were 34 patients with mild persistent BA (1st group), 22 patients with moderate persistent BA (2nd group) and 13 patients with severe persistent BA (3rd group). Fifteen healthy children were included in the controls.

Ultrasonography was used to investigate the thickness of the intima-media (I-M) complex. The serum levels of sVCAM-1 were determined by enzyme-linked immunosorbent assay (ELISA, catalog #BMS232, Austria). The level of circulating immune complexes (CIC) was determined by V. Haskova. Statistical analyses were performed with StatSoft STATISTICA Version 8 (Tulsa, OK).

Objective: To determine the endothelial function status in children with asthma.

Chong CS., Ramamurthy MB., Goh DY., Van Bever HP., Lim MT.
Khoo Teck Puat-National University Children’s Medical Institute, National University Hospital – Singapore, Singapore

Objectives: In adolescence, denial of chronic illness has been well documented. This can affect adherence to treatment at a time when patients are expected to take more responsibility toward administering their own medication. We investigated the compliance rate with inhaled corticosteroid therapy amongst adolescent patients with asthma in Singapore.

Methods: Questionnaire survey of adolescent asthma patients using inhaled corticosteroids attending the pediatric asthma clinic at the National University Hospital Singapore over a 5-month period. Data on compliance with medications over the preceding two weeks were obtained.

Results: Twenty-five patients were interviewed during the study period (age 12 to 23 years, median 17 years). There were 10 males (40%) and 15 females. Only 6/25 patients (24%) were fully compliant with regular inhaled steroid therapy. Of the 19 patients who missed prescribed doses, 10 (53%) missed more than 25% of their prescribed doses. 10/19 patients (53%) had forgotten to take their medications, the most common reason. 4/19 patients (21%) found the medications inconvenient. 5/19 patients (26%) did not think that the medications were beneficial, despite 3 of the 5 patients having “poorly controlled” asthma based on their Asthma Control Test scores. 2/19 patients (11%) ran out of medications and did not replenish their supply. None of the patients attributed their non-compliance to the worry of side-effects or cost of medication.
Materials and Methods: 60 children aged from 6 to 17 years with persistent BA in exacerbation were examined. Groups depending on BA severity were formed: 1st group – patients with mild persistent BA (n = 29), 2nd group – with moderate persistent BA (n = 21) and 3rd group – with severe persistent BA (n = 10). The control group included 15 healthy children. Ultrasonography was used for investigation of the intima-media thickness (I-M) complex and for calculation of the percent increase in flow-mediated dilatation (FMD%). The serum levels of S-nitrosothiol and FMD% (r = 0.81, p = 0.0001) and sVCAM-1 and I-M complex (r = 0.81, p = 0.0000) were determined with enzyme-linked immunosorbent assay (ELISA, catalog BMS232, Austria). Statistical analysis was performed with StatSoft STATISTICA Version 8 (Tulsa, OK). Non-parametric variables are reported as median (interquartile range). Differences between groups were tested using the Mann-Whitney test. Results: The thickness of the I-M complex was significantly increased in the patients of the 3rd group (1.2 (0.2; 1.3) mm), compared with children of the 1st (0.9 (0.8; 1.0) mm), p1-3 = 0.0000, 2nd (1.0 (1.0; 1.2) mm), p2-3 = 0.0004) groups and controls (0.6 (0.5; 0.7) mm), p3-3 = 0.0000). The indices of FMD% were significantly diminished in the patients of the 1st, 2nd and 3rd groups, compared with controls (respectively 7.31 (6.38; 8.64)%), 6.40 (6.12; 6.98)% and 5.57 (4.81; 5.86)% with 19.35 (17.00; 21.00)%, p < 0.001. Serum S-nitrosothiol levels were significantly diminished in the patients of the 1st (0.17 (0.15; 0.22) mmol/l), in the patients of the 2nd (0.14 (0.12; 0.15) mmol/l) and in the patients of the 3rd (0.11 (0.08; 0.11) mmol/l) groups, compared with controls (0.33 (0.28; 0.37) mmol/l), p1-3 = 0.0000, pc-1 = 0.0000, pc-2 = 0.0002). Serum sVCAM-1 was significantly increased in the patients of the 1st, 2nd and 3rd groups, compared with controls (respectively 1000.41 (850.24; 1100.32) ng/ml; 1180.62 (1070.09; 1300.72) ng/ml; 1630.92 (1510.45; 1870.84) ng/ml, compared with 745.60 (690.82; 790.19) ng/ml, p < 0.001). It was demonstrated that levels of S-nitrosothiol (H = 41.29, p = 0.0000), FMD% (H = 44.52, p = 0.0000) and SVCAM-1 (H = 56.63, p = 0.0000) were dependent on BA severity. The correlation between levels of S-nitrosothiol and FMD% (r = 0.81, p = 0.0001) and sVCAM-1 and I-M complex (r = 0.80, p = 0.0003) were determined. It was shown that the degree of endothelial dysfunction was dependent on asthma severity.

Conclusions: in children with asthma, there are signs of endothelial dysfunction, its extent of which depend on the severity of the disease.

#A41 - URINARY EOSINOPHILIC PROTEIN X AT AGE THREE YEARS AND THE DEVELOPMENT OF WHEEZING THROUGHOUT CHILDHOOD.

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Background: Wheezing is common in early life, but most children stop wheezing by school-age. At present there is no biomarker which can predict wheeze/asthma persistence. Eosinophils play a crucial role in airway inflammation, and markers of eosinophil activation such as Eosinophilic Protein X (EPX) may be associated with asthma development.

Objective: To investigate whether urinary (u)-EPX in children at age 3 years is a useful biomarker for the prediction of future wheeze persistence and asthma development.

Methods: u-EPX/creatinine ratio (µg/mmol) was measured using radio immunoassay at age 3 years in 906 participants in the population-based birth cohort. Children attended further clinical follow ups at ages 5 (n = 856), 8 (n = 815), 11 (n = 746) and 16 years (n = 610). Based on longitudinal data, children were assigned to different wheeze phenotypes (never, transient, late-onset, persistent). Current asthma at age 16 years was defined as a positive response to any 2 of the following 3 questions: Has a doctor ever told you that your child has or had asthma?; Has your child had wheezing or whistling in the chest in the last 12 months?; In the past 12 months has your child had wheezing or whistling in the chest?

Results: u-EPX levels differed significantly between children with different wheeze phenotypes (p = 0.005; ANOVA), with those with Persistent wheeze having the highest u-EPX. The post hoc analysis (Scheffe) revealed statistically significant difference between children with Persistent and “No wheeze” phenotypes (u-EPX µg/mmol, GM [95% CI]: 87 [96–101] vs. 67 [63–72], p = 0.005, persistent vs. no wheeze) There were no statistically significant differences between other wheeze phenotypes (Transient early: 75 [66–86]; Late-onset: 80 [70–90]). Of 610 children with follow-up information at age 16 years, 133 (21.8%) had asthma. uEPX at age 3 years was significantly higher among children who had asthma at age 16 compared to those without asthma. This was the case in the whole cohort, and among children with physician-confirmed wheeze in the first 3 years of life (p < 0.001 and p = 0.03 respectively). U-EPX ≥ 97 µg/mmol at age 3 years was a significant predictor of asthma at age 16, but the discriminative ability was moderate (Receiver operating characteristic curve, AUC = 0.646).

Conclusions: Early-life u-EPX differs significantly between children with different wheeze phenotypes, however its discriminative ability for asthma prediction is moderate.

#A64 - SAFETY AND TOLERABILITY OF ONCE-DAILY TIOTRIPUM RESPIMAT® ADD-ON THERAPY IN CHILDREN WITH SEVERE SYMPTOMATIC ASTHMA

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3. Pediatric Department, University of Verona – Verona, Italy
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Background: Tiotropium Respimat® (tioR) add-on therapy has been shown to have safety and tolerability comparable with those of placebo Respimat® (pboR) in adult and adolescent Phase III and pediatric Phase II trials in patients with symptomatic asthma. We present safety and tolerability data from the first Phase III study of tioR add-on therapy in children with severe symptomatic asthma.

Methods: A 12-week, randomized, double-blind, parallel-group trial (NCT01634152) in children aged 6–11 years with severe symptomatic asthma. We recruited 610 children with physician-confirmed asthma. The study was randomized to receive tioR 5 µg (two puffs, 2.5 µg) or 2.5 µg (two puffs, 1.25 µg), or pboR (two puffs), as add-on to high-dose inhaled corticosteroid (ICS; >400 µg budesonide or equivalent) maintenance therapy plus at least another controller (e.g. long-acting β2-agonist [LABA] and/or leukotriene receptor antagonist [LTRA]) or medium-dose ICS (200–400 µg budesonide or equivalent) plus at least two other controllers (e.g. LABA and/or LTRA and/or sustained-release theophylline). Patients were required to have ≥6-month history of asthma, defined as symptomatic at screening and before randomization by interviewer-administered Asthma Control Questionnaire mean score ≥1.5. Patients with a significant disease other than asthma were excluded. Primary and key secondary efficacy end points: peak and trough forced expiratory volume in 1 second responses, respectively, at Week 12. Adverse events (AEs) were recorded.

Results: 401 patients were randomized and 400 were treated: 130 received tioR 5 µg, 136 received tioR 2.5 µg, 134 received pboR. Baseline demographics and disease characteristics were balanced among treatment groups. 69.8% of patients were male, mean age (± standard deviation [SD]) was 9.0 ± 1.6 years, mean treatment exposure

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(±5D) was 86.1 ± 9.1 days. Incidence of AEs was comparable between treatment groups, with a low incidence of drug-related AEs, AEs leading to discontinuation and serious AEs (Table); no deaths occurred. Asthma, decreased peak expiratory flow and nasopharyngitis were the most frequently reported AEs, by preferred term, and occurred less frequently with tioR versus pboR. Conclusion: In children aged 6–11 years with severe symptomatic asthma, the safety and tolerability of once-daily Tiotropium Respimat add-on to at least ICS are comparable with those of placebo Respimat.

#A74 – PREVALENCE SURVEY AND RISK FACTORS FOR ASTHMA AMONG CHILDREN AGED 0–14 YEARS IN HANGZHOU: A CROSS-SECTIONAL SURVEY.

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Background: Asthma is a global problem. Prevalence varies among different countries and cities. We aimed to obtain the prevalence of childhood asthma in Hangzhou, to describe the characteristics of childhood asthma, and to discover factors that may relate to asthma in Hangzhou.

Methods: This cross-sectional study was conducted in Hangzhou, the capital of Zhejiang Province in the southeast coast of China. The subjects were children born between July 1st, 1996 and June 30th, 2010, and living inHangzhou at least one half-year for children older than six months, or lived in Hangzhou since birth for children younger than six months. A control group of non-asthmatic children matched for age and sex with each asthmatic patient individually was also randomly selected and interviewed. International Study of Asthma and Allergies in Childhood and National Epidemiology study of Asthma and Allergies in China questionnaires were used in this survey.

Results: A total of 13,878 children were actually surveyed. In these children, 665 (4.8%) children were diagnosed with asthma. The prevalence of asthmatic children was higher in boys than that in girls in some age groups (Fig 1).

In 85.1% asthmatic children, respiratory tract infection was a trigger of asthma attacks. Other causes included cold air (53.1%), house dust (20.3%), exercise (14.6%), fish and shrimp (14.0%), pollen (11.1%), and other, and Table 1). We compared the prevalence of triggers between four different age groups. Exercise, house dust, pollen, decoration, smoke, moldy smell, odor of cooking oil, mosquito-repellent incense, pet, and perfume were factors having statistically different prevalence among different age groups (p < 0.05). The 12–14 year age group had the highest prevalence in most of these triggers (Fig 2).

Conclusions: In conclusion, we conducted an epidemiological study in Hangzhou. The prevalence of childhood asthma was 4.8%. The use of ICS was only 46.2%. Risk factors of asthma may include caesarean birth, concomitant allergic diseases, including atopic dermatitis, food allergy, allergic rhinitis and urticaria as well as certain conditions occurring in the child, including drug allergy, food allergy and atopic dermatitis. Exclusive breastfeeding within the first six months might represent a protecting factor of asthma.

#A75 - SERUM LEVELS OF VITAMIN D AND ITS IMPACTS ON RECURRENT WHEEZING IN THE FIRST FIVE YEARS OF LIFE

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Objective: To analyze the impact of vitamin D (vitD) on recurrent wheezing in the first five years of life.

Methods: This is a prospective and transversal study that included children up to four years of age with recurrent wheezing who were treated at the...
Pediatric Pulmonology Outpatient Clinic at the Clinic Hospital of the University of Campinas Medical School, in Brazil. A questionnaire was administered regarding the children’s personal and family background, clinical manifestations and laboratory investigations. In addition, their parents were asked regarding how controlled were the crises of wheezing in the past four weeks and three months. On the same day, a 2 ml sample of blood was collected to measure the 25(OH)D serum level. A vitD deficiency was considered when lower than 20 ng/ml, insufficiency between 20 and 30 ng/ml and normal when higher than 30 ng/ml. To ascertain the levels, questions were drawn with regard to sun exposure and the use or not of sunscreen. Chi-square, Fisher-Freeman-Halton and Mann-Whitney tests were used for statistical analysis (p < 0.05).

Results: In total, 92 patients were interviewed. 12 were excluded because of unsuccessful sampling. Out of the remaining 80 patients, 67.5% were male. The mean age in months was 22.09±11.30, with a median of 21.00 (5–48) months. In our study, 13 (16.3%) infants had a vitD deficiency, 36 (45.0%) had insufficient levels and 31 (38.8%) had a normal vitD level. During 2015, 67 (83.8%) blood samples were taken in autumn or winter and 13 (16.5%) in summer or spring, although no difference between the levels of vitD was observed when comparing seasons; hence, for this reason, the groups were not separated based on the seasons. There was no association between vitD levels and sun exposure when analyzing frequency and duration of sun exposure, the period of the day and if the child used sunscreen or not. Out of the 13 infants that had a vitD deficiency, 6 (46.2%) did not have sufficient sun light exposure. There was no association between the levels of vitD and wheezing episodes in the last four weeks. Results showed that 49 (61.3%) children had at least one wheezing episode in the last four weeks, 8 of whom (16.3%) had a vitD deficiency and 22 (44.9%) had an insufficient serum vitD level. With regard to atopy, 37 (46.3%) were classified as atopic and there was no statistical difference with vitD levels or with wheezing in the last four weeks. Of these atopic children, 12 (32.4%) had a normal serum vitD level and 24 (64.9%) presented wheezing episodes.

Conclusion: In the present study, there were no significant impacts between vitamin D serum levels and the factors related to recurrent wheezing, such as gender, ethnicity and atopy. There was also no influence of seasons, sun exposure and use of sunscreen on vitamin D levels.

#A81 - LONG-TERM OUTCOME OF BRONchodilATOR-RESISTENT AIRWAY LIMITATION IN SEVERE CHILDHOOD ASTHMA

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Background: Persistent airflow limitation in asthma may be an early sign of ACOS (Asthma COPD Overlap Syndrome). Epidemiological studies have shown that there may be a loss in lung function by the age of 14 years in children with severe asthma, but the loss did not progress into adult life (1). Aim: To determine the outcome profiles and determinants of “bronchodilator-resistant” airway limitation from the age of 7 years to 18 years in severe asthma (ATS/ERS criteria).

Material & Methods: This retrospective study was conducted in 2 tertiary-care University Hospitals (1/1/2014 to 6/30/2014). Patients with severe asthma were included. They were identified via a computer-based patient registry. Patients with an associated disorder and/or premature infants were excluded. Non-reversible (NR) bronchial obstruction was defined according to the following (>1 criteria): post-salbutamol (400 μg) FEV₁ z-score < -1.96, and/or FEF₂₅₋₇₅ < -1.64, identified in at least 2 LFT (VMAX Sensormedics plethysmograph) performed at least 3 months apart. Data collected included standard demographic, allergy, asthma phenotype, LFT and treatment data.

A chi² (Yates correction) or ANOVA (Bonferroni correction) test was used as appropriate. A p-value < 0.05 was considered significant.

Results: 31 patients were included in the study (male sex, 73 %; familial /personal atopy, 63 %; ever admitted for acute asthma; 40 %). We identified 3 severe asthma groups according to LFT profiles throughout the entire childhood period: Normal LFTs (N, n = 10), Intermittent NR Airway Limitation (INRAL, n = 13), Permanent NR Airway Limitation (PNRAL, n = 8). Compared to the “N” group, “INRAL” patients had greater cumulative doses of inhaled steroids (58639 vs. 5558 μg beclomethasone eq., p < 0.05) (there was a trend towards early-onset persistent wheeze (<3 yrs), elevated blood eosinophils and IgE, more hospital admissions for asthma, more frequent montelukast administration). In the “PNRAL” group, there was a trend towards lower BMI, less atopy, later onset asthma (>3 yrs), longer duration of therapy by montelukast).

Conclusion: Some children with early-onset persistent “bronchodilator-resistant” airway limitation (INRAL) may improve with prolonged treatment. The identification of the determinants of such improvement requires further studies.
Conclusions: TNF-α level does not depend on BA severity and is associated with PFT parameters in the period of exacerbation and remission. The significant increase in TGF-β1 level in remission and emergence of associations of TGF-β1 level with PFT parameters in remission may reflect its role in airway remodeling in children suffering from severe asthma.

#A88 - MARKERS OF ENDOTHELIAL DYSFUNCTION IN CHILDREN WITH MILD PERSISTENT ASTHMA

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The aim of the study is to determine endothelial function in patients with mild persistent asthma during periods of exacerbation and remission. Methods: 43 children aged 6 to 17 years with BA in exacerbation (1st group) and remission (2nd group) were examined. Seventeen healthy children composed the control group. Ultrasound assessment of endothelium-dependent dilatation of the brachial artery with evaluation of its diameter increase (FMD%) (D.S. Celermajer et al., 1992) was carried out. The serum levels of S-nitrosothiol were determined spectrophotometrically. Statistical analysis was performed with StatSoft STATISTICA Version 8 (Tulsa, OK). Non-parametric variables are expressed as median (interquartile range). The current clinical data study was approved by the Medical Ethics Committee of the Kharkiv National Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants and their parents gave written informed consent.

Results: The indices of FMD% were significantly diminished in patients of the 1st and 2nd groups, compared with control: 8.42 (6.95; 15.00)% and 9.73 (8.42; 15.33)% respectively compared with 19.35 (17.00; 21.00%), p < 0.001. A significant FMD% increase in remission compared to the period of exacerbation (p1–2 = 0.0000, T = 0) was revealed, but remained below the normative values (p–c = 0.0000). Serum S-nitrosothiol levels were significantly decreased in patients of the 1st and 2nd groups, compared with control: 0.21 (0.17; 0.26) and 0.27 (0.23; 0.33) mmol/l respectively compared with 0.33 (0.28; 0.37) mmol/l, p < 0.001. This index increased in the period of remission compared with the period of exacerbation (p1–2 = 0.0000, T = 0), but remained significantly lower than in children of the control group (p–c = 0.0036).

Relationship between FMD% and S-nitrosothiol in children with mild persistent asthma and disease duration was not revealed.

Conclusions: Presence of endothelial dysfunction in children with mild persistent bronchial asthma was determined both in the period of exacerbation and remission. It was demonstrated that these indices increase in dynamics although their values remain nevertheless lower than the norm. Results testify to the long term pathological process which leads to sustained alterations of vessel walls without regard to duration of the illness.

#A91 – PREVALENCE AND RISK FACTORS FOR BRONCHIAL ASThma IN SCHOOL-GOING CHILDREN OF SEMI-URBAN AREA OF INDIA

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Aims: To determine the prevalence of asthma in school-going children and identify the possible risk factors in semi-urban area.

Methods: The cross sectional study was conducted in randomly selected schools from semi-urban area. Minimal sample was (n = 598) assuming a prevalence of asthma of 15% with 95% level of confidence, 20% precision and 10% non-response rate. School-going children from 6th to 10th standard/grade were included in this study. Prior permission was received from school authorities. A modified International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire was used and translated to local language Hindi. The questionnaire was back-translated to English and expert opinion was taken for validity and reproducibility for field use. The questions related to severity of asthma were excluded. Those who answered yes to any of the questions were identified as cases of asthma and others were identified as control for the purpose of this study. A semi-structured proforma was introduced to elicit information regarding risk factors. Age of the child was taken as completed years. Information regarding various risk factors including family history of asthma, type of fuel used, placement of kitchen in the house, number of windows in sleeping room, pet animals (cat and dogs), smoking among family members, birth order, and smoke outlet was collected.

Results: A total 620 subjects were analyzed with a response rate of 95%. The prevalence of bronchial asthma among study subjects was 20.3%. Mean age of study subjects was 12.98 (1.58) years. Male to female ratio was 1.59:1. Baseline characteristics including age, gender, weight and height were similar in both cases and controls (Table 1). Factors associated with presence of asthma were family history of asthma, smoking, pet animals and food allergy (Table 2). Factors such as cooking fuel, number of windows in sleeping room, location of kitchen and smoke outlet were not significant on statistical analysis.

Conclusion: Bronchial asthma is a significant problem in semi-urban areas of India. Family history of asthma, smoking, pet animals and food allergy are significant factors for the presence of asthma.

#A100 - POTENTIAL RISK FACTORS OF BRONCHIAL ASTHMA DEVELOPMENT IN CHILDREN

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The aim of the study was to study the influence of perinatal data and comorbidity on the development of bronchial asthma (BA) in children. Methods: We analyzed data (demographic and perinatal data, comorbidity) from 164 children who have had previous health care visits caused by wheeze or cough, current wheeze, and chronic cough (cough without colds or cough at night) at the age of 1 to 3 years. Among these, at the age of 5 to 6 years, 44 patients (1st group) had BA, 120 children (2nd group) — without asthma. Asthma diagnosis was confirmed based on GINA. The current study was approved by the Medical Ethics Committee of the Kharkiv National Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki. The Fisher exact test was used to compare characteristics of children with and without the outcome. Odds ratio was calculated for assessment of risk factor significance.

Results: The relative number of boys in the 1st group was significantly higher than in the 2nd group (65.9% and 42.5%, p < 0.01). The complicated course of pregnancy was found in 79.5% of patients of the 1st group and 58.3% of children of the 2nd group (p < 0.05). Pathological first trimester of pregnancy was detected in 40.1% of cases in the 1st group, 17.5% in the 2nd group (p < 0.01). The incidence of children with early formula-feeding (who were on breastfeeding less than 6 months) was significantly higher in the 1st group (77.3%), compared with the 2nd group (45.0%) (p < 0.001). The incidence of allergic rhinitis in children was significantly higher in the 1st group (65.9%) compared to the 2nd group (5.8%) (p < 0.001). The occurrence of gastrointestinal disease among observed children was higher in the 1st group (20.5%) compared to 2nd group (5.8%) (p < 0.01).

Conclusion: The development of BA in preschool children who presented to primary care with recurrent wheeze or cough was associated with male sex (OR 2.61 [95%CI 1.27–5.38]; p < 0.05), complicated course of pregnancy (OR 2.78 [95%CI 1.23–6.29]; p < 0.005), first trimester pregnancy pathology (OR 3.26 [95%CI 1.52–7.00]; p < 0.01), early formula feeding (OR 4.16 [95%CI 1.88–9.17]; p < 0.001), allergic rhinitis (OR 31.21 [95% CI 11.65–83.62]; p < 0.001) and gastrointestinal disorders (OR 4.15 [95% CI 1.44–11.96]; p < 0.001).
### #A106 - AIRWAY EOSINOPHILIC INFLAMMATION ASSESSED BY INDUCED SPUTUM AND LUNG FUNCTION IN ASTHMATIC CHILDREN

**Ghezzi M, Kantar A.**

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**Rationale:** Eosinophilic airway inflammation is predominant in paediatric asthma phenotype, and its assessment by induced sputum (IS) is increasingly recognized as an important diagnostic tool but actually there is no consent about the best cut-off to diagnose the presence of eosinophilic inflammation. We investigated the correlation of IS eosinophils with lung function parameters.

**Methods:** We conducted a retrospective analysis based on electronic medical records review of all allergic asthmatic children. 222 children with well-controlled asthma under inhaled corticosteroid treatment were included into the analysis, with an age range 4–18 years. We included children who underwent lung function test, IS and FeNO in our Centre and with IS eosinophils percentage greater than 2.5.

**Results:** Median IS eosinophil percentage was 10.5 (5 – 22.25), median FeNO level was 15.3 (8.9 – 24.0) ppb. There was no correlation between IS eosinophils and FeNO. FeNO didn’t show any correlation with spirometric function parameters. IS eosinophil percentage was weakly correlated with FEV1 (r = -0.25) and MMEF (r = -0.19). IS eosinophil percentage greater than 10 showed a stronger correlation with FEV1 (r = -0.44) (Graph 1) and MMEF (r = -0.41).

**Graph 1:**

Conclusion: FeNO didn’t show correlation both with IS eosinophils and spirometric parameters among patients with well-controlled asthma under inhaled corticosteroid treatment. IS eosinophil percentage showed weakly correlation with FEV1 and MMEF but among patients with IS eosinophil percentage greater than 10, we achieved a good correlation with FEV1 (r = -0.44).

### #A119 - THE VIRTUAL ASThma CLINIC FOR CHILDREN: A COST-EFFECTIVENESS ANALYSIS

**Van den Wingaert LS,1,2 Kievit W,2 Roukema J,1 Boehmer AL,3 Brouwer ML,4 Hugen CA,5 Niers LE,6 Sprij AJ,7 Rikkers-Mutsaerts ER,8 Rottier BL,9 Verhaak CM,10 Pijnenburg MW,11 Merkus PJ.1**

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6. Paediatrics, Maxima Medical Centre – Veldhoven, Netherlands
7. Paediatrics, Juliana children’s Hospital, Haga Hospital – Den Hague, Netherlands
8. Paediatrics, Leids University Medical Centre, – Leiden, Netherlands)
9. Paediatrics, University Medical Centre Groningen – Groningen, Netherlands
10. Psychology, Radboud University Medical Centre – Nijmegen, Netherlands
11. Paediatrics, Sophia Children’s Hospital, Erasmus Medical Centre – Rotterdam, Netherlands

**Purpose of the study**

The primary aim of the study was to assess whether asthma control could be improved through a virtual asthma clinic (VAC) for children with asthma, while reducing the regular visits to the outpatient clinic by 50%. Alongside this randomized controlled trial, an a-priori defined cost-effectiveness analysis was carried out to determine whether the clinical benefits gained with the VAC were attained at reasonable costs.

**Methods**

Randomized controlled, prospective, 8-center study of 16 months duration in children with asthma (6–16 yrs). Usual care consisted of 4-monthly outpatient visits and a digital age-specific questionnaire on asthma control (C-ACT: 6–12 yrs; ACT: 12–16 yrs) at 0, 8 and 16 months. In the VAC group, children were followed online with a monthly ACT and were seen at the outpatient clinic every 8 months. The primary outcome measure was asthma control. Costs were assessed from both healthcare and societal perspectives. Mean incremental costs were weighted against the mean incremental effect in terms of ACT. Ninety-five percent uncertainty boundaries in the incremental cost effectiveness ratio were determined non-parametrically using bootstrapping (1000 replications with replacement).

**Results**

Two-hundred ten children (mean age 11.3 yrs (± SD 2.8 yrs; 60% male) were included. After 16 months of follow-up, asthma control measured with the C-ACT was significantly better in the VAC-group compared to the UC-group (1.56 points (95% CI 0.18 to 2.94, p = 0.03). There was no difference in ACT-score (0.28 points (95% CI 1.67 to 2.23), p = 0.78). The total healthcare costs were lower in the VAC group, with a mean difference of €280.39 and 95 percentiles ranging from €-686.93 to €126.16. The difference in societal cost was estimated at €454.13 (95% percentiles €94.46 to €332.21), in favor of the VAC. Figure 1 presents the results from the 1000 bootstrapped replications concerning ACT and costs (direct and indirect) for a 16-month study period. A 98% of the 1000 bootstrapped replications resulted in cost savings with a mean cost saving of €473.00 (95 percentiles €-46; €-1068).

**Conclusion**

The virtual asthma clinic for children is an effective e-health innovation to improve asthma care and is cost-effective.

**- See more at: [http://www.cipp-meeting.org/en/abstracts/relectures#sthash.xv2cyA0U.dpuf](http://www.cipp-meeting.org/en/abstracts/relectures#sthash.xv2cyA0U.dpuf)**
**#A122 - MICROBIAL COMMUNITIES IN THE UPPER RESPIRATORY TRACT (URT) OF CHILDREN WITH ATOPIC BRONCHIAL ASTHMA (BA)**

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2. Department of Pediatrics, Institute of SB – Nizhny Novgorod, Russia
3. Department of Pulmonology, Institute of Pediatrics – Moscow, Russia

The state of the microbiome is an important component of human health; however studies on the relationship of the microbiome and asthma in Russia are scarce. We studied the microbiome of the URT in patients aged 5 to 17 years with atopic BA with the use of the culture method: the microbiome of the mucous membrane of the nasal cavity was studied in 174 children while that of the mucous membrane of the posterior wall of the pharynx was studied in 170 children.

The mucous membrane of the nasal cavity: 17.82% of patients (31/174) had pathogenic and conditionally pathogenic flora that was non-selected, 45.40% (79/174) had selected *S. aureus*, 29.31% (51/174) of children had *S. epidermidis*, while other variants of pathogenic and conditionally pathogenic microorganisms were isolated from patients, including *H. influenzae* (3 patients), *K. pneumoniae* (3 patients) and *S. pneumoniae* (4 patients), *Proteus* (2 patients).

The mucosa of the posterior pharyngeal wall: 74.71% patients (127/170) had pathogenic and conditionally pathogenic flora that was non-selected, 4.71% (8/170) had selected *S. aureus*, 17.06% (29/170) of children had fungi of the genus *Candida* (one receiving therapy with the inclusion of corticosteroids in 17 patients), children with single *Escherichia coli* (1 patient), *K. pneumoniae* (3 patients), *S. epidermidis* (2 patients).

*H. influenzae* (3 patients), *K. pneumoniae* (3 patients) and *S. pneumoniae* (4 patients) and *Proteus* (2 patients).

The level of total IgE in serum was: in the group of patients with the mucous membrane of the nasal cavity in which pathogenic and conditionally pathogenic flora was non-selected, 179 ± 143 U/ml in the group of patients with the mucous membrane of the nasal cavity which highlighted *S. aureus*, 316 ± 283 U/ml, in the group of patients with the mucous membrane of the nasal cavity were selective for *S. epidermidis* – 353 ± 356 U/ml, in the group of patients with other variants of conditionally pathogenic and pathogenic flora – 163 ± 108 U/ml, p = 0.023. Differences in the level of total immunoglobulin E, depending on the characteristics of the microbiome of the throat in patients with asthma, were not established.

Thus, the condition of the mucous URT microbiome, especially of the mucous membrane of the nasal cavity, the relationship with and typically the control of asthma in the previous month was unacceptable in 42%. Vitamin D prophylaxis was incomplete in 8 cases. A familial history of allergy was found in 10 patients. A personal history of atopy was present in 12 patients.

Domestic pollution was correlated with asthma exacerbations in 8 children exposed to passive smoking. Urban atmospheric pollution was a triggering factor. Measurement of emanation of atmospheric CO in Tunis City was strongly associated with asthma exacerbation hospitalizations during February and March (7 hospitalizations/month). The exacerbation was severe in 15 cases, moderate in 35 cases. Mean hospital stay was about 4 days.

**Conclusion**

This study underlines the need to strengthen the efforts to encourage improvement of the therapeutic education of asthmatic children in order to decrease the risk of hospitalization for exacerbation of asthma and to avoid triggering factors.

## C. BRONCHOPULMONARY AND PLEURAL INFECTIONS (INCLUDING TUBERCULOSIS)

**#C6 - BRONCHOALVEOLAR LAVAGE IS USEFUL FOR THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN CHILDREN**

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2. Pediatrics, Kaohsiung Chang Gung Memorial Hospital – Kaohsiung, Taiwan

**Objective:** To compare the mycobacteriological yield from self-expectorated sputum (SP), gastric lavage (GL) and bronchoalveolar lavage (BAL), in children with pulmonary tuberculosis (TB). Methods: Twelve children with culture- or PCR-positive pulmonary TB were retrospectively enrolled in this study. These patients had undergone SP collection, GL and/or BAL through flexible bronchoscopy. Positive culture yield rates from these three methods were compared. Results: The positive bacterial yield from BAL (85.7%; six of seven patients) was significantly higher than specimens from SP (75.0%; six of eight patients) and GL (60.0%; six of ten patients). Combining BAL and SP or BAL and GL increased culture positivity to 100% (10 of 10 patients, and seven of seven patients, respectively). Conclusion: Flexible bronchoscopy with BAL is an effective tool for diagnosis of pulmonary TB in children. When combinations of BAL and SP or BAL and GL are used, a higher rate of diagnosis of pulmonary TB can be achieved. Flexible bronchoscopy with BAL and GL can be used for patients who cannot expectorate, or for patients whose sputum is negative for acid-fast bacilli (AFB).

**Table 1. Diagnostic tests list of the 12 pulmonary Mycobacterium tuberculosis infection patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>SP</th>
<th>SP/C</th>
<th>BAL</th>
<th>BAL/G</th>
<th>GL</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>M</td>
<td>-</td>
<td>0/2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/0 (BAL)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>F</td>
<td>-</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>1/0 (BAL)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>M</td>
<td>0/3</td>
<td>0/3</td>
<td>1/1</td>
<td>1/1</td>
<td>0/0</td>
<td>1/0 (BAL)</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>F</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/0</td>
<td>0/0 (BAL)</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>M</td>
<td>1/0</td>
<td>1/0</td>
<td>1/1</td>
<td>1/1</td>
<td>0/0</td>
<td>1/0 (BAL)</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>F</td>
<td>1/0</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0 (SP)</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>M</td>
<td>0/3</td>
<td>0/3</td>
<td>1/1</td>
<td>1/1</td>
<td>0/0</td>
<td>1/0 (BAL)</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>F</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0 (BAL)</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>M</td>
<td>-</td>
<td>0/3</td>
<td>0/3</td>
<td>1/0</td>
<td>0/0</td>
<td>1/0 (GL)</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>F</td>
<td>0/3</td>
<td>0/3</td>
<td>1/0</td>
<td>1/0</td>
<td>0/0</td>
<td>1/0 (SP)</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>F</td>
<td>2/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0 (GL)</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>M</td>
<td>3/0</td>
<td>3/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0 (GL)</td>
</tr>
</tbody>
</table>

*SP: sputum smear; SP/C: sputum culture; BAL/S: bronchoalveolar lavage smear, BAL/G: bronchoalveolar lavage culture, GL/S: gastric lavage smear, GL/C: gastric lavage culture. The numerator means how many positive results in the total number (denominator).**

**Pediatric Pulmonology**
Colistin inhalations are effective in young children, as monitored by sputum and disruption of biofilm formation in non-CF CLD. We have shown that treatment plays an important role for symptom relief, exacerbation reduction and toxicity. Colistin inhalations have been shown to be efficacious in adults with chronic infection, 9 (64%) were eradicated. In most cases, the incidence of P. aeruginosa is frequently successful, particularly in short intermittent inhalations (1–2 months per cycle) and 14 were maintained on chronic therapy (more than 2 months continuously). Median duration of treatment was 14.9 (range 0.25–200) months. Of 14 patients with short term or intermittent P. aeruginosa infection, 11 (79%) were eradicated. Of 14 patients with chronic infection, 9 (64%) were eradicated. In most cases, subjective improvement was noted, at least temporarily.

Conclusion:
Colistin inhalations led to clinical improvement in non-CF CLD. Eradication of P. aeruginosa is frequently successful, particularly in short term or intermittent infection.

Reflections:
Adult studies indicate that sputum surveillance and targeted antibiotic treatment play an important role for symptom relief, exacerbation reduction and disruption of biofilm formation in non-CF CLD. We have shown that Colistin inhalations are effective in young children, as monitored by sputum cultures, either expectorated or induced. Prospective, randomized controlled trials, akin to those performed in adult populations, are needed in children.

#C55 - A MULTICENTER STUDY OF CLINICAL CHARACTERISTICS AND ETIOLOGY OF HOSPITALIZED CHILDREN WITH ACUTE LOW RESPIRATORY TRACT INFECTION

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Objective: To investigate the epidemiology, clinical characteristics and etiology of hospitalized children with acute low respiratory tract infection (ALRTI) in the New Century.

Methods: 1116 cases of ALRT during January 2014 to November 2014 were collected. All patients were divided into 4 groups, namely younger than 1 year old group, 1 to 3 years old group, over 3 years of age and less than 6 years old group, more than or equal to 6 years old group, and were subsequently compared. The drug resistance gene of 20 patients with MP infection in throat swab specimens was detected by using nested PCR and DNA sequencing.

Results: Wet cough, fever and wheeze were main manifestations of the patients with ALRI; these incidence rates were 82.7%, 76.1% and 37.4%, respectively. The incidence of wheeze, auscultation of the lungs wheeze, anemia and granulocytopenia in the group of patients less than 1 year old were higher than the older groups (P = 0.007, 0. 001, 0.000, 0.001). Conversely, the incidence of fever, long stay in hospital, pleural effusion, higher rate of CRP and D-dimer in the group of patients more than 6 years old were higher than the younger groups (P = 0.000, 0.006, 0.000, 0.001, 0.027). The pathogen-positive rate among all these samples was 72.5% (441/608). Virus was the dominant pathogen, about 53.6% (326/608). Among viral infections, RSV was the most common, about 66.7% (217/326), followed by the influenza virus (25.5%, 83/326) and parainfluenza virus (7.1%, 19/326). The positive rate of bacterial infection was 38.9% (236/608), including gram negative (G-) bacteria, 50.4% (125/248) and gram positive (G+) bacteria, 49.6% (123/248). The five most common bacterial pathogens included S. pneumoniae, S. aureus, K. pneumoniae, E. coli. H. influenzae. Mycoplasma (MP) positive rate was 29.1% (177/608) and drug resistance was 65.0% (13/20), especially A to G mutation at position 2063, about 50.0% (10/20).

Conclusion: Children under 3 years of age have a high risk for ALRI. Younger children are prone to wheezing and anemia, whereas older children usually have high fever time and inflammatory index. Bacterial and viral infections are more common in infants and young children with ALRI. With increasing age, the Mycoplasma infection rate increased and the percentage of drug resistance of MP also increased.

#C67 - COMPARISON OF BRONCHOSCOPY AND SPUTUM BACTERIOLOGY IN PATIENTS WITH PRIMARY CILIARY DYSKINESIA

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2. Clinical Microbiology, Hacettepe University Faculty of Medicine – Ankara, Turkey

Introduction: In patients with primary ciliary dyskinesia (PCD), impaired mucociliary clearance leads to an accumulation of secretions in the airways and susceptibility to repeated bacterial infections. While chronic infections of the PCD airways are strongly associated with morbidity and mortality, relatively little is known about their bacterial composition. Our aim was to analyze the lower airway bacteriology in PCD and to compare the results with those of the sputum samples to evaluate whether a correlation existed between sputum and BAL microbiology in PCD cases.

Methods: We retrospectively analyzed the microbiology of the flexible bronchoscopy and sputum samples of 114 patients diagnosed with PCD in

Pediatric Pulmonology
Cystic congenital thoracic malformation in a management of pulmonary disease in PCD.

Sputum culture did not always reflect the lower airway microbiology in the BAL specimens and that BAL culture results supported the view that the sputum samples were not obtained simultaneously from the same patient. We conclude that negative sputum microbiology results should be evaluated before the sputum analysis. Since this was a retrospective study, the detection in sputum could be attributed to the antibiotic treatment of some patients before the sputum analysis. The low rate of microorganism was the second common pathogen in BAL and sputum samples. There were no significant correlations with age and the positive microbiology of BAL and sputum samples.

Microbiology Sputum sample Positive n (%) Sputum sample Negative n (%).

Bronchoalveolar lavage sample Positive (n = 72): 44(61.1%) 28(38.9%).

Bronchoalveolar lavage sample Negative (n = 42): 10(23.8%) 32(76.2%).

Conclusions: The most commonly cultured pathogens were H. influenzae and S. pneumoniae in PCD patients. We found higher microbiological yields in BAL compared to the sputum samples. The low rate of microorganism detection in sputum could be attributed to the antibiotic treatment of some patients before the sputum analysis. Since this was a retrospective study, the most important limitation was that the BAL samples and the sputum samples were not obtained simultaneously from the same patient. We conclude that negative sputum microbiology results should be evaluated cautiously since the rate of bacterial and fungal yield was found to be higher in BAL specimens and that BAL culture results supported the view that the sputum culture did not always reflect the lower airway microbiology in the management of pulmonary disease in PCD.

Clinical Case: 17-year-old boy, with irrelevant family and personal history, admitted at the emergency department with a one-week history of cough and pleuritic left-sided back pain, without fever or dyspnea. Physical examination identified decreased breathing sounds over the left lower lobe without other findings. Chest X-ray revealed a consolidation in left lower lobe, with a liquid level suggesting an abscess. Contrast-enhanced computer tomography showed enlarged left hilar lymph nodes and a consolidation in left lower lobe with multiple cystic lesions, the largest (7 cm) with a fluid level. Blood sample test presented mild elevation of C-reactive protein (3.73 mg/dL), without leukocytosis or other abnormalities. The patient started treatment with amoxicillin-clavulanic acid and then ertapenem, without radiologic improvement.

Bronchoscopy disclosed purulent secretions from the left lower lobe (negative direct microscopic examination) and pulmonary function tests were normal. Subsequently, after a 4-week treatment with ertapenem, the patient underwent a left lower lobectomy by left thoracotomy. Microscopic examination of the lobectomy specimen consisted of extensive necrotizing granulomatous inflammation with acid-fast bacilli. In peripheral zones, there were cystic lesions lined by respiratory epithelium, compatible with a cystic CTM. Approximately 6 weeks after hospital admission, cultures from sputum, selective bronchial aspirate and bronchial washing were positive for Mycobacterium xenopi.

Treatment with rifampicin, ethambutol and isoniazid was started. Serologies for VIH were negative and immunoglobulins and serum protein electrophoresis were in normal range.

Conclusion: the present case is unusual due to the late diagnosis of this cystic CTM without prior recurrent chest infections and also due to an infection by an uncommon agent. Mycobacterium xenopi is a slow-growing nontuberculous mycobacteria considered an emergent pulmonary pathogen with significant morbidity and mortality in immunocompromised patients. However, Mycobacterium xenopi infection has also been associated with patients with preexisting pulmonary disease.

Background: Noninvasive ventilation (NIV) refers to the administration of mechanical respiratory support without the use of endotracheal intubation. In adults with acute respiratory failure, NIV is superior to standard treatment in preventing intubation and reducing the risk of mortality. The use of NIV in children has increased significantly over the last decade, but few studies have assessed its usefulness in infants with acute respiratory failure.

Objectives: The aim of the study is to determine whether NIV reduces the need for endotracheal intubation or slows the clinical progression of acute respiratory failure.

Materials and methods: We prospectively recorded and retrospectively analyzed the medical records of inpatient infants who were initially diagnosed with acute respiratory failure and received NIV between February 2010 and June 2015 (5 years 4 months).

Results: In total, 11 infants received NIV for respiratory failure. 10 infants were male and 1 was female. The median age was 74 days (interquartile range (IQR) 51.5–90.5). All cases were diagnosed as acute bronchitis, and 9 cases (89%) were respiratory syncytial virus-positive. The treatment in all cases consisted of intravenous fluid therapy, prednisolone 2 mg/kg/day and oxygen therapy, and in 4 cases (36%) administering antibiotics. The median lag time between the onset of symptoms and initiation of NIV was 4 days (IQR 3–7.5). The median respiratory rate and heart rate before NIV was 70/min (IQR 62.5–74.5) and 180/min (IQR 176.5–187.5). At the moment of NIV, a blood gas analysis showed median pH of 7.34 (IQR 7.3–7.37) and median venous PCO2 of 61 mmHg (IQR 47.5–62). None of them presented episodes of apnea or major complications related with NIV. Nine cases (82%) were removed from NIV after recovery and 2 cases (11%) were deemed ineffective 5 hours and 12 hours after initiation of NIV and therefore required intubation. Of the variables obtained before NIV treatment, pH (<7.3) was a significant factor associated with NIV failure. Of the variables obtained after 1 hour of NIV treatment, heart rate (>180/min), respiratory rate (>70/min), pH (<7.3) and venous PCO2 (>65 mmHg) were significant. The presence of persistent severe tachycardia, tachypnea and acute respiratory acidosis after 1 hour of NIV treatment was associated with NIV failure.

Conclusion: NIV appears to be effective in the treatment of infants with acute respiratory failure. The improvement of vital signs and blood gas analysis after 1 hour of NIV may be a predictive factor for the success of the treatment.

Pediatric Pulmonology
#C107 - THE CLINICAL CHARACTERISTICS AND PREDICTORS OF REFRACTORY MYCOPLASMA PNEUMONIAE PNEUMONIA IN CHILDREN

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Objective: To analyze the clinical characteristics of refractory Mycoplasma pneumoniae pneumonia (RMPP), and explore the related factors predicting RMPP.

Methods: Retrospective analysis was performed on 634 children with Mycoplasma pneumoniae pneumonia (MPP) hospitalized in our hospital between January 1, 2011 and December 31, 2014. The clinical features, laboratory data, radiological findings between the RMPP group and the general Mycoplasma pneumoniae pneumonia (GMPP) group were compared and the predictive values of related factors were analyzed.

Results: The median age of the RMPP patients (n = 145) was much older than that of the GMPP patients (n = 489) (P < 0.01). We also found more severe presentations, higher incidence of extra-pulmonary complications and more serious radiological findings in the RMPP group, which needed oxygen more often, longer antibiotics administration and intensive care (P < 0.05). Meanwhile, the levels of C-reactive protein (CRP), lactic dehydrogenase (LDH), immunoglobulin A (IgM), interleukin (IL)-6, IL-10, interferon gamma (IFN-γ) and the percentage of neutrophils, CD4+ in the RMPP group were significantly higher than those in the GMPP group (P < 0.05); while the levels of prealbumin (PAB) were lower than that in the GMPP group (P < 0.01). In ROC curve analysis, the percentage of neutrophils, CRP, LDH, PAB, IL-6, IL-10 and IFN-γ were useful for differentiating patients with RMPP from those with GMPP.

Multiple logistic regression analysis showed that CRP ≥ 16.5 mg/L, LDH > 417 IU/L and IL-6 > 14.75 pg/ml were significant predictors regarding RMPP.

Conclusions: CRP ≥ 16.5 mg/L, LDH ≥ 417 IU/L and IL-6 ≥ 14.75 pg/ml are significant predictors of RMPP in children, which can aid in early recognition of RMPP.

#C113 - OUTCOME OF WHOOPING COUGH IN INFANTS: A COHORT OF 14 PATIENTS

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Introduction

Whooping cough (pertussis) is a vaccine-preventable disease that still remains a serious infection in neonates and young infants. It is poorly controlled, with the highest rates of morbidity and mortality among infants. In Tunisia, a recent resurgence of pertussis in young infants has been observed in 2013. The aims of this study were to describe clinical characteristics and the outcome of infant pertussis and to determine risk factors associated with severe forms and prolonged hospitalization and cough.

Patients and methods:

This is a retrospective study including cases of pertussis in children and conducted in the department of pediatrics of the Children’s Hospital of Tunis, over a period of one year (January 2013- December 2013). The diagnosis of pertussis was confirmed by RT-PCR. All survivors were followed during two years.

Results

Fourteen patients were included. The median age was 2.25 months (15 days-21 months). The sex ratio was 0.57. Pertussis vaccination was performed in 5 infants. The source of infection was identified in 8 cases. Fever was present in 5, cough with cyanosis in 13 cases, dyspnea in 11 cases, and seizures in two cases. Chest radiography was normal in 4 cases. Viral or bacterial co-infection was found in 4 cases. Leukocytosis was observed in 13 cases with an average number of white blood cells at 52,807 / mm3. Ten infants developed a severe form and were transferred to ICU. The outcome was fatal in 3 cases. The median duration of the oxygen therapy was 21.14 days (0–66 days). The median length of hospitalization was 24 days (6–69 days). The median duration of cough was 3.8 months. At two years follow-up, 2 infants developed recurrent wheezing and asthma.

Death was associated with leukocytosis, hemodynamic disorders and seizures. The duration of hospitalization was associated with tachycardia, neurological disorders, severe forms, lymphocytosis, duration of the intubation, duration of oxygen therapy and coinfection. Prolonged coughing was associated with female gender and the presence of bilateral alveolar infiltrates on chest X-ray. The duration of cough was not associated with: age, severe cases, hospitalization in ICU, duration of oxygen therapy, leukocytosis or coinfection.

Conclusion

Pertussis is a public health problem, with a highest rate of mortality and morbidity among young infants. Pertussis adult vaccination should be included in the national immunization schedule.

D. NON-INFECTIONOUS RESPIRATORY DISORDERS

#D17 - PRESENTATION AND MANAGEMENT OF DIFFERENT CAUSES OF CHYLOTHORAX IN CHILDREN: ONE MEDICAL CENTER EXPERIENCE

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Background: Chylothorax in children is a relatively rare cause of pleural effusion in most children. However, it is usually a common complication of cardiothoracic operations such as open-heart surgery. Other etiologies for chylothorax, such as trauma or malignancy, occur more commonly in adults but rarely in children.

Objectives: To explore the etiologies of chylothorax in children, this study analyzed these patients admitted in a medical center.

Methods: We retrospectively reviewed the medical records of the pediatric patients admitted to our tertiary transfer center during the period of 1995 to 2005 with a diagnosis of chylothorax.

Results: A total of 22 patients (15 females and 7 males) with chylothorax were enrolled in our study. The etiologies for chylothorax were: a complication of cardiothoracic surgery in 14 patients (63.6%), congenital chylothorax in 5 patients (22.7%), association with neuroblastoma in 2 patients (9.1%), and congenital nephrotic syndrome in 1 patient (4.6%). All patients required medical therapy. Chest tube drainage was undertaken in twenty patients, and surgical intervention was performed in 3 patients. Four patients died (18.2%) due to other causes.

Conclusions: Cardiothoracic surgery was the most common cause of chylothorax in children at our institution. Medication and chest tube drainage were effective in most patients. Early recognition, medication, and performing surgical intervention when necessary are important measures to avoid a catastrophic outcome.

#D17 - PULMONARY CAPILLARY HEMANGIOMATOSIS: A RARE CASE OF PULMONARY HYPERTENSION

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Introduction: Pulmonary capillary hemangiomatosis (PCH) is a rare cause of pulmonary arterial hypertension (PAH), with centrilobular ground-glass nodules as a characteristic imaging finding. We report a case of a girl with typical features of PCH and severe PAH with rapidly progressive failure.

Pediatric Pulmonology
Case presentation: An 8-year old caucasian girl presented initially with symptoms of fatigue, decreased exercise tolerance and shortness of breath on exertion 4 months ago. She had stayed in the ICU in the last month because of breathlessness reported by her mother. Since then, she was under 2.0–2.5 liters of oxygen/min, hydrochlorothiazide, spironolactone and sildenafil. Initial physical examination: discreet perioral cyanosis, saturation of 89% with oxygen. She had a loud P2 and normal pulmonary auscultation. Echocardiogram: severe pulmonary hypertension with pulmonary artery pressure of 100 mmHg. Chest radiography depicted an enlargement of the pulmonary arteries and scattered small pulmonary opacities (image A). A CT scan of the lungs demonstrated diffuse centrilobular ground-glass nodules (images B, C and D). Spirometry showed a mild restrictive pattern. Sildenafil was suspended due to the subsequent risk of pulmonary edema and death. Before a surgical biopsy could be performed, her symptoms worsened with hypoxia and hypotension and the patient was admitted to the ICU, where she was submitted to invasive mechanical ventilation, with no improvement and progression to death. Unfortunately, her family did not allow a post-mortem examination to confirm the diagnosis.

Discussion: PCH is a rare lung disease in which progressively worsening pulmonary hypertension is the most common presenting symptom and is often fatal. The definitive diagnosis can be made by lung biopsy. However, the latter is too invasive and brings a high risk for patients with PCH, mainly children. Therefore, noninvasive approaches need to be considered. Radiologic manifestations are important tools for PCH suspicion: multiple large centrilobular ground-glass nodules, septal lines and mediastinal lymph node enlargement may be seen on CT scan. Chest radiograph demonstrates PAH with diffuse pulmonary opacities. The prognosis is poor. Diuretics, ACE inhibitors, corticosteroids, warfarin and interferon alpha 2a are the current available treatment. Hypoxia becomes worse with prostaglandins, causing pulmonary edema and eventually death. The definitive treatment is lung transplantation.

Conclusions: The purpose of this case report is to emphasize the clinical radiological importance to diagnose rare and rapidly progressive diseases like PCH, mainly in children with PAH in whom the biopsy presents a higher risk. By recognizing the PCH, we can indicate lung transplantation as soon as possible and manage PAH properly.

#D21 - PULMONARY HEMANGIOMATA AND KASABACH-MERRITT SYNDROME TREATED WITH INTERFERON ALPHA 2 IN AN INFANT.

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3. Paediatric Surgery, Christian Medical College Hospital – Vellore, India
4. Radiology, Christian Medical College Hospital – Vellore, India
INTRODUCTION: Pulmonary hemangiomata causing Kasabach–Merritt syndrome is a rare entity. Here we present the case of a young infant with extensive hemangiomata in the lung who had no response to treatment with steroids and propranolol and was successfully treated with Interferon alpha 2a.

CASE:
Eight-month old otherwise well, male infant presented with blood stained saliva noted from 4 months of age. He had required packed red cell transfusions for anemia. On examination, there was a faint erythematous macule over the nape of the neck. Respiratory system was normal on examination and systemic examination was unremarkable except for the presence of cushingoid features. Investigations revealed thrombocytopenia in the range of 10,000 to 20,000/cumm and significant anemia. CXR and CT chest showed hemorrhages and extensive nodular shadows. A lung biopsy was done uneventfully with platelet transfusion and presence of hemangiomata was demonstrated on histopathology. There was no response to steroid therapy in the past and a trial of propranolol did not help. Ongoing hemoptysis, anemia and worsening chest imaging features necessitated the use of anti-angiogenic drugs. The infant was treated with alpha 2 interferon. Over a period of 6 months, there was significant clinical and radiological improvement. The platelet count increased to 75000/cumm. This child is now 5 years old and has normal neurological and physical development.

CONCLUSION
Hemangiomata in the lung and Kasabach-Merritt syndrome is a rare differential diagnosis for hemoptysis in infants. Confirmation of pulmonary hemangiomata by lung biopsy involves significant risk when there is thrombocytopenia. However histopathological diagnosis is essential before initiation of therapy with anti-angiogenic agents.

Key words: Pulmonary hemangiomata, Hemoptysis, Kasabach-Merritt syndrome, Interferon alpha 2

Serial chest X-rays, CT images and histopathological photomicrograph will be included in the poster.

- See more at: http://www.cipp-meeting.org/en/abstracts/relectures#sthash.if1RRPyc.dpuf

#D23 – PULMONARY MANIFESTATIONS OF PROLIDASE DEFICIENCY.

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Prolidase deficiency is a rare autosomal recessive disease, in which pulmonary manifestations have been sporadically reported. We have encountered two patients who presented with severe pulmonary cystic lesions leading to respiratory failure. This led us to retrospectively evaluate pulmonary involvement in patients with prolidase deficiency treated in our hospital.

Out of 21 patients, 12 had a history of recurrent pulmonary infections and 10 were diagnosed as having chronic lung disease. Out of 7 chest CT scans performed, 4 patients had subpleural cysts, 2 patients had bronchiectatic changes and one had diffused ground glass attenuation and minor linear atelectasis. Three patients died, with all deaths being attributed to respiratory insufficiency.

Prolidase deficiency is frequently associated with various pulmonary manifestations including extensive cystic changes that may be life-endangering. The differential diagnosis of bilateral progressive cystic changes should include prolidase deficiency and pulmonary evaluation should be performed in patients with prolidase deficiency.

<table>
<thead>
<tr>
<th>Patients</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M)</td>
<td>11(52%)</td>
</tr>
<tr>
<td>Age (years) mean ± SD</td>
<td>21.5 ± 6.5 [20, 10–33]</td>
</tr>
<tr>
<td>Median Range</td>
<td></td>
</tr>
<tr>
<td>Recurrent pulmonary infections</td>
<td>12(57%)</td>
</tr>
<tr>
<td>Chronic lung disease CT (n-7)</td>
<td>10(47%)</td>
</tr>
<tr>
<td>Cystic changes n-4 Bronchiectasis n-2diffused ground glass attenuation, linearatelectasis n-1</td>
<td></td>
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<tr>
<td>Lung biopsy (n-1)</td>
<td>Lipoid pneumonia</td>
</tr>
<tr>
<td>PFT(n-4)</td>
<td>FEV1- range 21%-93% (2,44,63,93) FVC-range 22%-95% (22,49,59,95)</td>
</tr>
<tr>
<td>Outcome</td>
<td>3 died — pulmonary insufficiency</td>
</tr>
</tbody>
</table>

#D27 - STUDY OF LARYNGOMALACIA, PHARYNGOMALACIA AND PHARYNGOLARYNGOMALACIA


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Purpose: To present and compare the characteristics of patients diagnosed with laryngomalacia, pharyngomalacia, and pharyngolaryngomalacia.

Background: Our institution performs bronchoscopies in search of airway diseases in neonates and infants. Laryngomalacia is known to be the leading cause of congenital stridor, but we have reported that pharyngomalacia causes symptoms similar to laryngomalacia. There are reports of pharyngomalacia associated with severe laryngomalacia, and some infants have both laryngomalacia and pharyngomalacia although there are only a few reports comparing patients with these diseases.

Patients and methods: Thirty-four patients diagnosed with pharyngomalacia as the sole airway disease, 154 patients diagnosed with laryngomalacia as the sole airway disease, and 25 patients diagnosed with at least both laryngomalacia and pharyngomalacia (pharyngolaryngomalacia) as airway diseases from 2003 to 2015 were included in the study. The characteristics...
and clinical course of patients in each group were reviewed from medical records retrospectively.

Results: The median (interquartile range) of birth weight and gestational age was 2945 g (2548 to 3212 g) and 38.7 weeks (37.9 to 39.9 weeks) in laryngomalacia, compared to 2670 g (1757 to 3137 g) and 37.9 weeks (34.3 to 39.9 weeks) in pharyngomalacia, and 2596 g (2010 to 2878 g) and 37.3 weeks (36.0 to 40.0 weeks) in pharyngolaryngomalacia. Patients with laryngomalacia had a significantly greater birth weight and gestational age compared to pharyngomalacia and pharyngolaryngomalacia (p < 0.05). Inspiratory stridor was the most common symptom in laryngomalacia, found in 91.9% of patients, whereas obstructive apnea or hypoapnea was most common in pharyngomalacia found in 73.5% and pharyngolaryngomalacia found in 76.0%. The average age in months at onset of symptoms was youngest in laryngomalacia (0.2 months) compared to pharyngomalacia (0.6 months) and pharyngolaryngomalacia (0.7 months), whereas the average age in which symptoms and clinical findings resolved was youngest in pharyngomalacia (5.7 months) followed by pharyngolaryngomalacia (6.3 months) and laryngomalacia (10.3 months) in patients where the disease resolved during follow-up. Surgery was performed in 2.9% of patients with pharyngomalacia, 11.0% of patients with laryngomalacia, and 24.0% of patients with pharyngolaryngomalacia. The percentage of patients with underlying diseases of either chromosomal, neuromuscular and any type of multiple malformation syndrome was 11.9% in pharyngomalacia, 3.2% in laryngomalacia, and 36.0% in pharyngolaryngomalacia. Conclusion: These results suggest that pharyngolaryngomalacia is not a severe type of laryngomalacia but may be associated with systemic diseases, and that pharyngomalacia and laryngomalacia sometimes coexist, but are separate and independent diseases.

**#D32 - CLINICAL CHARACTERISTICS OF 51 PRIMARY CILIARY DYSKINESIA PATIENTS: SINGLE-CENTER EXPERIENCE**

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Introduction: Primary ciliary dyskinesia (PCD) is a genetically heterogeneous, rare lung disease which leads to chronic upper and lower airway infections, organ laterality defects, and fertility problems. Even though patients often have classical findings, sometimes it can be accompanied by different findings. The aim of this study was to describe the clinical characteristics of PCD patients who were followed-up at Gazi University Hospital.

Method: We analyzed clinical characteristics, radiological and laboratory findings and complications of PCD patients in the Gazi University Hospital Pediatric Pulmonology Department.

Results: Between 2007–2015, 51 patients were followed up with the diagnosis of PCD in the Gazi University Hospital Pediatric Pulmonology Department. The mean age of diagnosis was 8.08 ± 4.6 years, and 27 (52%) were male. Consanguinity was present in 36 (70%) patients. The most common initial symptoms were chronic cough, recurrent pneumonia and chronic rhinitis. Only five patients had respiratory problems in the neonatal period. Organ laterality was present in 27 (52%) patients and 7 (13%) patients had other cardiac abnormalities such as ASD, PDA. Five patients had recurrent otitis, 11 patients had sinusitis, 5 patients had nasal polyposis and 4 of them had conductive hearing loss. Atelectasis was detected in 21 patients and bronchiectasis in 21 patients. Primary immunodeficiency was accompanied in 3 patients and hematological malignancy in 2 patients. Pulmonary function tests were obtained from 26 patients and the most common finding was small airway obstruction. Lobectomy was performed in 3 patients and 1 patient had sinus surgery.

Conclusion: Although PCD has classical clinical findings, sometimes these can be accompanied by other system abnormalities such as immunodeficiency and hematological malignancies. With increasing understanding of the pathogenesis and improvement in the diagnosis of the disease, new situations could be described in the course of the disease.

**#D33 - NEUROENDOCRINE CELL HYPERPLASIA OF INFANCY: IS BIOPSY NOT NEEDED?**

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2. Pediatric Pulmonology and Allergy, Children’s Hospital, Ludwig Maximilians University – Munich, Germany

Introduction: Neuroendocrine cell hyperplasia of infancy (NEHI) is a newly described diffuse lung disease with unknown etiology. Usually it affects infants under two years, characterized by tachypnea, retractions, crackles, and hypoxia. It was reported that with typical clinical and radiological findings, it could be diagnosed and there is no need for biopsy in these patients.

Case presentation: A four-month-old boy patient was admitted to the pediatric pulmonology clinic with complaint of failure to thrive and tachypnea.

Physical examination revealed tachypnea, retractions and crackles on both lungs. It was learned that one of his brothers had died at the age of 18 months with similar complaints. Hyperaeration and diffuse ground-glass opacities in different lobes which included right middle lobe and lingual were detected on computerized tomography. Open lung biopsy was performed and reported as NEHI. Steroid treatment was started. Because of no improvement, it was stopped after the first month. At the last control, he was two years old, physical examination was normal except pectus excavatum.

Although the findings of the sibling, who had similar symptoms and pathognomonic radiological findings which were compatible with NEHI, had died when he was 18 months-old because of pulmonary hypertension.

Conclusion: Death has previously not been reported in NEHI. It could suggest that differences may reside in the underlying course of the disease or there could be another interstitial lung disease with similar findings. Lung biopsy should be performed in patients who have serious clinical symptoms due to interstitial lung disease, although the radiological findings were compatible with NEHI.

**#D36 - SURFACANT METABOLISM DISORDERS: TWO CASES WITH DIFFERENT FINDINGS**

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Introduction: Surfactant metabolism disorders are a specific group of lung diseases which lead to interstitial lung disease in childhood, especially in infancy. Herein, we report two patients with surfactant metabolism disorders with different clinical findings and mutations.

Case 1

The first case is a 17-month-old female infant with malnutrition, recurrent lower respiratory tract infections and failure to thrive since three months of age, diagnosed as surfactant protein C deficiency with I173T mutation. Diffuse, giant and life-threatening pneumatoceles developed during the course of the disease. They were treated with empiric drug treatment and oxygen support, and resolved rapidly. Large-giant pneumatoceles can develop in the course of surfactant protein C deficiency and may be associated with biopsy.

Case 2

The second case is a 2.5 month-old boy patient with respiratory distress after birth, tachypnea, failure to thrive and suspected seizure history. He was diagnosed with surfactant metabolism disorder with newly defined homozygous c.3134A>G(p.Q1045R) ABCA3 mutations. There is a standard treatment recommendation for these patients. Response rate is expected in 28 days to 3 months based on the drugs. His clinical findings were not improved although he is on the fourth month of treatment.

Conclusion: Childhood interstitial lung diseases have a very different clinical spectrum even in the same disease groups. Children with respiratory complaints, recurrent lower respiratory tract infections, gastrointestinal symptoms, and growth retardation should be evaluated in terms of surfactant metabolism disorders. Large-giant pneumatoceles can develop in the course of surfactant protein C deficiency and may be associated with biopsy. They can resolve with medical treatment. If available, genetic testing should be

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attempted as a first step for diagnosis. The rate of treatment response can differ in these patients and the reasons that affect the rate of treatment response should be investigated.

- See more at: http://www.cipp-meeting.org/en/abstracts/relectures#shash. if1RRPYc.dpuf

**#D65 - A CASE OF NEONATAL RESPIRATORY INSuffICIENCY WITH A NON-DESCRIBED HOMOzyGous VARIant OF THE ABCA3 GENE**

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**Background**

Childhood Interstitial Lung Disease (ChILD) involves a heterogeneous group of conditions that affect the pulmonary parenchyma and interfere with gas exchange. Surfactant dysfunction is included in this group and usually manifests in full term infants, few hours after birth, as acute respiratory distress. It can also present later in childhood or adulthood in a milder form of the disease.

Surfactant dysfunction affects genes encoding surfactant proteins B and C and the phospholipid transporter, ABCA3 (ATP-Binding Cassette). ABCA3 protein is involved in surfactant storage and transport to the alveolar space, and its dysfunction has been associated with lung disease. ABCA3 gene is localized on chromosome 16q13, and homozygous or compound heterozygous mutations can cause disease. Although association between ABCA3 mutation and lung disease is considerably recent, more than 150 distinct mutations have been identified to date. These are inherited as autosomal recessive disorders.

We report a clinical case of interstitial lung disease in a newborn, with a homozygous variant of the ABCA3 gene.

**Clinical case**

Female gender patient, gestational age of 39 weeks, AI 9/10 (5',10'). No relevant familiar antecedents and absence of consanguinity. Clinical onset of respiratory distress, tachypnea, retraction, cough and cyanosis, a few hours after birth. Crackles were audible at auscultation. Immediate oxygen supplementation was needed.

Clinical evolution was characterized by maintenance of respiratory distress, dependence of oxygen support and failure to thrive. Chest radiography revealed bilateral diffuse interstitial pattern. CT scan revealed bilateral ground glass opacification and zones of air trapping. Infectious and cardiac causes were excluded.

Due to the early onset of respiratory insufficiency and strong possibility of ILD, DNA analysis of ABCA3, SFTPB and SFTPC was made, and revealed a homozygous variant in the ABCA3 gene c.4442C>T. This mutation is localized in a highly conserved residue of the gene, and for this reason, is more likely to be a deleterious mutation. This is also a mutation not described in the literature.

Pulmonary biopsy revealed areas of atelectasis, septal thickening, pneumocyte hyperplasia and iron-laden macrophages, findings suggestive of chronic pneumonitis of infancy.

**Conclusion**

Although rare, surfactant dysfunction diseases cause significant morbidity and mortality. Our findings suggest that this variant can be pathologic. On the one hand, the mutation is located in a highly conserved residue of the gene, therefore more likely to be deleterious. On the other hand, the clinical features are highly suggestive of a surfactant disorder, and the histopathological findings support the diagnosis of ILD. The pattern found on the biopsy is frequently found in ABCA3 mutation patients already described in the literature. The description of unknown mutations is essential for better understanding of this condition and for prenatal screening.

**#D84 - MUCOEPIDERMoid CARCinoma OF THE BRONCHUS IN 8 CHINESE CHILDREN**

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Objective: To review the Mucopidermoid Carcinoma (MEC) of the bronchus in children and to make early diagnosis and appropriate therapy for the disease. Method: A retrospective study was performed on MEC patients diagnosed in the Beijing Children’s Hospital (BCH). The clinical features, image characteristics, bronchoscopic manifestations, therapy and prognosis information were reviewed. Results: Eight MEC cases were diagnosed in BCH in the last seven years (2008.12–2015.12). Patient age ranged from 4 years and 6 months to 12 years and 5 months. The main clinical features were cough (8/8), intermittent fever (4/8) and hemoptysis (3/8). Chest computed tomography (CT) showed circular mass in respiratory tract, atelectasis or emphysema, bronchiectasis. Half of the cases had a neoplasm located in the left bronchus (left main bronchus 3 cases and the lower basal segment 1 case), while the other half were in the right bronchus (right bronchus intermedius 2 cases, right middle 1 case and right middle-inferior lobar bronchus 1 case). Six of the eight cases were diagnosed with the biopsy by bronchoscope, only inflammatory cell infiltration was shown in the biopsy specimen in one case. While the biopsy specimen of another one case could not be retrieved by bronchoscope because of bleeding tendency, MEC was finally diagnosed after surgery. Five patients had resection surgery of the affected bronchi and lobectomy while another three had neoplasm resection with interventional bronchoscopy. None of the patients were given chemotherapy. The follow-up of all these cases was generally good up to this report. Conclusion: MEC were rare in children and the clinical features were non-specific; Biopsy by bronchoscope is a good choice for the diagnosis of bronchial mucopidermoid carcinoma. Bronchoscopic intervention was effective in the treatment of non-operative carcinoma. The MEC patients generally had good prognosis.

Key words: Mucopidermoid Carcinoma (MEC); Bronchus; Children

**#D87 - BRONCHOSCOPY FINDINGS IN CHILDREN WITH HEMOPTYSIS: A 5-YEAR EXPERIENCE**

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**INTRODUCTION:** Hemothysis is defined as expectoration of blood or blood tinged-sputum due to bleeding from the respiratory tract. The objective of this study was to determine the indications and to evaluate the findings of bronchoscopy of children admitted to Hacettepe University İhsan Dogramaci Children’s Hospital with the complaint of hemothysis. **METHOD:** We searched for the ICD code of hemothysis in our hospital network and found patients admitted to hospital with hemothysis between June 2010 and June 2015. There were 34 patients under 18 years of age who had hemothysis. Bronchoscopy was not performed in patients who were diagnosed with polyarteritis nodosa disease (n = 1) during hospitalization, cystic fibrosis (n = 1) with acute exacerbation or had severe congenital heart disease (n = 4). We retrospectively examined the records of 28 children who had consulted in Pediatric Pulmonology with hemothysis and underwent flexible bronchoscopy between June 2010 and June 2015.

**RESULTS:** The mean age was 13.6 (7–18) years and female/male ratio: 42.9 (67.8%). Twenty-seven of the 28 children were examined with Thorax CT scan or chest X-ray. Twenty of these children (71.4%) had a neoplasm (n = 12) or other irregular findings (n = 8). Twenty-five children (89.3%) had a neoplasm resection with interventional bronchoscopy. Five patients had neoplasm located in the left bronchus (left upper 1 case and left middle 4 cases). Six children (21.4%) were reported as normal. The most frequent findings of bronchoscopy of children admitted to Hacettepe University İhsan Dogramaci Children’s Hospital were cough (84.3%), intermittent fever (50%) and hemoptysis (67.8%). Twenty-seven of the 28 children were examined with Thorax CT and 12 of 27 children (44.4%) were reported as normal. The most frequent findings in Thorax CT were nonspecific nodules, consolidations, granular patterns and hilar lymphadenopathies. 

Initial diagnosis before bronchoscopy was pulmonary hemosiderosis in 1 patient. We found acute bleeding in 2 children (7%), hypervascularity in 10 children (35.7%), purulent secretion in 7 children (25%) and serous secretion in 8 children (28.5%). Bronchoalveolar lavage (BAL) examination revealed that 7 patients had a wide range of PMNL and 5 patients had different proportions of hemosiderin-laden macrophages. 3 had normal lavage findings. BAL aerobic cultures of three children were positive and all of the specimens

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were negative for acid fast staining examination and Mycobacterium tuberculosis culture. We determined hemosiderin-containing macrophages in 1 patient (3.5%). Two patients were diagnosed with pulmonary hemosiderosis (7.1%), 2 patients diagnosed with gastroesophageal reflux (7.1%), 4 patients with pneumonia (14.2%), 8 patients with latent TB (14.2%), 2 patients diagnosed with gastroesophageal reflux in 1 patient (3.5%). Two patients were diagnosed with pulmonary hemosiderosis in the differential diagnosis of hemosiderosis. It is concluded that flexible bronchoscopy is useful for diagnosing patients with hemosiderosis.

**E. FETAL AND NEONATAL RESPIRATORY DISORDERS**

**#E4 - CASE REPORT: A LONG-TERM RESPIRATORY CARE FOR A 1-YEAR-OLD INFANT WITH TRACHEAL BRONCHUS AND TRACHEOBRONCHOMALACIA: CHOICE OF nBiPAP OR HHHFNC?**

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**Introduction**
Tracheal bronchus (TB) is a congenital abnormality of the tracheobronchial tree, which is an aberrant bronchus arising from the lateral tracheal wall superior to the carina. The incidence of TB is approximately 2% of the general population. Most of the time, TB is asymptomatic and incidentally diagnosed by bronchoscopy. TB may affect the respiratory system by recurrent pulmonary infections in childhood.

A case of a right-upper-lobe (RUL) TB with tracheobronchomalacia (TBM) was diagnosed. Rather than receiving any surgical procedure, the patient was treated by nasal bi-level positive airway pressure (nBiPAP) or heated, humidified high-flow nasal cannula (HHHFNC) as non-invasive respiratory support (NRS). After discharge, the patient suffered from recurrent pulmonary infections and hospital readmission on several occasions.

**Case report**
A 1-year old male preterm infant with maternal premature rupture of membranes delivered by emergency caesarean section for intrauterine growth restriction at 31 weeks gestation. The patient developed respiratory distress and required intubation in the delivery room. Due to poor activity, tachypnea and extremely low body weight (810g), this patient was transferred to the NICU. Desaturation and frequent episodes of bradycardia were observed under NRS after extubation several times, with the patient being re-intubated five times. The CXR revealed RUL atelectasis. RUL TB at 1 cm above the carina associated with bilateral TBM and left side vocal cord palsy were diagnosed by computed tomography (CT) and bronchoscopy (Fig-1). Given the difficult weaning of the ventilator, increased work of breath (WOB) and airway resistance caused by airway anomalies, the patient was treated by nBiPAP with inhalation and chest physical therapy after extubation. Through 106 hospital admission days with full-time ventilator support, the patient developed ventilator dependency and was discharged from hospital with eventual home care nBiPAP support.

After discharge, patient was readmitted 3 times due to bronchopneumonia within a half year. Patient felt irritable and uncomfortable during nBiPAP, the interface such as nasal mask or nasal prong making him crying and angry. We opted to substitute nBiPAP for HHHFNC, which provided similar efficiency but less invasive compared with nBiPAP. Finally, the patient was stable under HHHFNC support and discharged from hospital.

**Conclusion**
Congenital airway abnormalities such as TB may induce respiratory distress. However, the use of NRS decreases the WOB and airway resistance in infants with airway abnormalities, especially TB. Nowadays, there are still no guidelines with regard to NRS for patients with tracheal bronchus with upper airway abnormality. In this case, nBiPAP and HHHFNC appears to provide the same efficiency. Therefore patient’s comfort is the main consideration.

We hope the experience of respiratory care of this patient who was diagnosed with RUL TB and NRS can offer other clinical staff a new option.

**#E11 - MANAGEMENT OF NOSOCOMIAL RSV BRONCHIOLITIS IN A PRETERM INFANT WITH HIGH FREQUENCY JET VENTILATION: CASE REPORT**

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**Introduction**
RSV bronchiolitis is one of the most common illnesses in the first year of life with a high disease burden worldwide. A great deal of literature in the past has explored the severity of RSV disease in the population of ex-preterm infants. Our case report differs in that we describe acute management of nosocomial RSV bronchiolitis in a 33-weeks corrected gestational age infant prior to discharge home from the NICU.

**Case Description**
A previously well 21-day-old female ex 30+2 week infant was transferred to our tertiary care NICU with apneic spells and desaturations requiring intubation. A full septic work-up was negative for bacterial pathogens and viral testing was performed due to significant respiratory secretions. Viral testing results were positive for RSV; an unexpected result given this infant had only been exposed to the NICU environment, had no siblings and both visiting parents were well.

**Discussion**
A wealth of literature exists documenting the high disease burden of RSV in the preterm infant population but the majority of this literature describes RSV disease in ex-preterm infants once they are discharged home from the NICU. During the management of our infant, we performed a literature review and were unable to find any reports of similar cases or advice regarding ventilation strategies. In this case report, we detail the clinical challenges we faced including hypoxemic respiratory failure, tachycardia, pulmonary toileting, irritability and the implications of isolation precautions in the context of an NICU. We outline management strategies employed for effective ventilation of our patient, and discuss various ventilation strategies employed. We conclude that HFJV in combination with adequate sedation and efficient pulmonary toileting may be used for cases of hypoxemic respiratory failure due to nosocomial RSV pneumonia in the preterm infant population.

**#E20 - THE INFLUENCE OF THEOPHYLLINE AND CAFFEINE ON THE RESPIRATORY CENTER IN PREMATURE INFANTS: AN ANALYSIS USING THE VENTILATORY RESPONSE TO CO2**

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**Introduction**
The effectiveness and adverse events of theophylline and caffeine for the treatment of apnea of prematurity have been reported in the past, but none have reported the influence of both drugs on the respiratory center. The ventilatory response to CO2 (VRCo2) is a test measuring the increase in minute ventilation in response to an increase in
CO2, and it is possible to assess the responsiveness of the respiratory center quantitatively. Therefore, we studied the influence of both drugs on the VRCO2.

Patients and methods: During August 2009 to October 2015, the VRCO2 before and after drug administration was available in 42 infants in whom theophylline or caffeine was used for apnea of prematurity. The VRCO2 was measured by rebreathing gas composed of a mixture of 5% CO2 and 95% O2 in a closed circuit, where CO2 accumulated continuously. In the past, we have reported the average VRCO2 in normal infants as 40.4 ± 14.8 (ml/min/ kg/mmHg). The VRCO2 and clinical course were reviewed from medical records retrospectively.

Results: Twenty-three patients were included in the theophylline group (median gestational age (GA): 28.9 weeks, median birth weight (BW): 1047 g), and 19 patients were included in the caffeine group (median GA: 27.7 weeks, BW: 979 g). The median age of drug administration was 11 days in the theophylline group, and 13 days in the caffeine group. Twenty-two patients (95.6%) in the theophylline group, and 13 patients (68.4%) in the caffeine group were intubated, and in all these patients, treatment for apnea of prematurity was started while the patient was intubated. There was no statistically significant difference in the number of days under nasal continuous positive airway pressure (CPAP) ventilation, and reintubation was needed in 1 patient in the caffeine group. The VRCO2 in the theophylline group increased from 7.37 ± 13.3 to 21.6 ± 15.1, and from 14.8 ± 14.3 to 20.0 ± 15.0 in the caffeine group. There was a significant increase in the theophylline group, but not in the caffeine group. In regard to adverse events, abdominal distension was significantly more common in the theophylline group.

Discussion: Treatment was started while the patient was intubated in most patients, thus the effect of both drugs on apnea was difficult to judge. There was no statistically significant difference in the number of days under nasal CPAP ventilation and the number of patients needing reintubation, hence there seems to be no clinical difference in the effect of both drugs. On the other hand, the VRCO2 increased significantly after theophylline administration such that theophylline appears to have a better effect on the respiratory center. There were fewer adverse events in the theophylline group which is consistent with previous reports. Caffeine is recommended for the treatment of apnea of prematurity due to the fewer number of adverse events, but in cases where the response of the respiratory center is poor, it may be necessary to consider changes in treatment.

#E25 - INFANT PULMONARY FUNCTION TESTS AT ONE YEAR OF LIFE IN EXTREMELY LOW GESTATIONAL AGE INFANTS CORRELATE WITH EARLY NEONATAL FACTORS

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Background: Extremely low gestational age infants (less than 29 weeks gestation) are at high risk for pulmonary morbidity in the first year of life. Yet currently there are no host factors or biomarkers that predict chronic respiratory disease at 1 year. The NHLBI-funded Prematurity and Respiratory Outcomes Program (PROP) enrolled infants from 11 medical centers to prospectively evaluate the factors related to chronic lung disease at 1 year corrected age.

Hypothesis: We hypothesized that infant pulmonary function tests (iPFTs), specifically the raised volume rapid thoracoabdominal compression technique (RVRTC), will be a sensitive measure to detect chronic lung disease. We evaluated neonatal host factors that correlated with airflow obstruction (FEF25-75 and FEF75), and with tidal breathing measures.

Methods: A total of 109 infants had iPFTs performed between 9-20 months corrected age at five medical centers including Duke University, Indiana University Riley Children’s, University of Rochester, Cincinnati Children’s, and Washington University. Tidal breathing measures and RVRTC measures were obtained based on ATS/ ERS standards. Data were expressed as z-scores based on normative data of full-term infants with different length, weight, and sex. The risk factors evaluated included demographic data, respiratory support and medications used, and comorbidities during the NICU course. The association between each measure and each risk factor was tested using linear regression adjusted for center difference.

Results: The average gestational age was 26.7 weeks, with 50.5% male, 58.7% White and 39.4% Black race distribution. Overall, all RVRTC measures were decreased in this cohort compared to term infant normative data, even when corrected for weight, length, and gender. Significantly decreased FEF25-75 and FEF75 were associated with lower gestational age, male gender, presence of patent ductus arteriosus or pneumonia, the PMA at which invasive and non-invasive ventilation and oxygen support ended, and surfactant and diuretic treatment in the NICU. Decreased Tpef/Te was associated with lower gestational age and duration of ventilation. There was no correlation between iPFT results and the diagnosis of bronchopulmonary dysplasia (BPD), maternal prenatal smoking, parental asthma, or private vs. public insurance.

Conclusions: Airflow obstruction occurs in premature infants at 1 year of age and is more severe in males, earlier gestational age infants, and in infants with more severe respiratory disease, suggesting that airway abnormalities are the major sequelae of lung disease of prematurity.

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#E71 - VENTILATION/PERFUSION RATIO, RIGHT SHIFT OF THE OXYHEMOGLOBIN DISSOCIATION CURVE AND RIGHT TO LEFT SHUNT IN HEALTHY NEWBORN INFANTS

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Background: A number of studies have non-invasively measured oxygenation impairment in sick newborn infants by the degree of right-to-left shunt, right shift of the oxyhemoglobin dissociation curve and ventilation/perfusion (V/Q) inequality. However, normal values have not been reported with this method. We aimed to measure shunt, shift and V/Q in healthy infants with no history of respiratory conditions. These measures could serve as reference to quantify the severity of conditions such as BPD or pulmonary failure and be used as outcome variables in future clinical studies.

Methods: We analyzed data from 64 healthy infants without respiratory conditions previously collected during hypoxic challenge in a UK tertiary perinatal centre. Transcutaneous oxygen saturation (SpO2) was recorded at a fraction of inspired oxygen (FiO2) of 0.21 and 0.15. We used a previously published computer software algorithm (Dassios T. Neonatology 2015;107(4):283–8) which analyzes and fits paired data for FIO2 and SpO2 and derives a curve which represents the best fit of shift and shunt for each infant’s data and calculates the shunt, shift and V/Q.

Results: Mean (SD) gestational age was 38 (1.7) weeks, weight was 2978 (472) g and median (range) postnatal age at measurement was 2(1–9) days. Mean (SD) rightwards shift of the oxyhemoglobin dissociation curve was 5.8 (1.1) kPa and V/Q ratio was 0.89 (0.18). None of the infants had any degree of right to left shunt.

Conclusion: We report normal values of right-to-left shunt, right shift of the oxyhemoglobin dissociation curve and ventilation/perfusion (V/Q) ratio in healthy newborn infants that could be useful as reference outcome measures in quantifying oxygenation impairment in newborn infants.
F. CYSTIC FIBROSIS

#F3 - SWEAT CONDUCTIVITY IS AN ACCURATE DIAGNOSTIC TEST TO RULE IN AND RULE OUT CYSTIC FIBROSIS IN VERY YOUNG INFANTS

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Objective: To assess the accuracy of sweat conductivity for the diagnosis of cystic fibrosis (CF).

Methods: In this diagnostic test study, coulometry (Gibson & Cooke/Chloride Analyzer, model 4425000, Labconco) was taken as gold standard to verify the reliability of sweat conductivity (Macroduct/Sweat Check Conductivity Analyzer, model 3120, Wescor). Infants with two subsequent tests for immunoreactive trypsinogen higher than 70 ng/mL were eligible. After informed consent signed by parents, sweat samples were collected during the same appointment and analyzed in a blind fashion by independent technicians. Conductivity was measured directly and converted to a NaCl molarity. We calculated sensitivity, specificity, positive and negative predictive value (PPV and NPV), positive likelihood ratio (LR +), and the area under the ROC curve.

Results: CF was ruled out/ruled in 508 and 30 infants, respectively (only 3, i. e. 0.6%, with doubtful results) aged 34 to 68 days old (median 45 days); the median sweat chloride and conductivity values were 10.5 (7.8–14.2) and 29.0 (26.0–33.0) mmol/L, respectively. Conductivity cut-off values to rule in or rule out CF were 40.5 and 66.0 mmol/L, respectively. Conductivity values above 66.0 mmol/L had 100% sensitivity, 99.4% specificity, 100% PPV, 100% NPV, and 166.7 LR + to diagnose CF. The area under ROC curve was 0.99 (95% CI, 0.99–1.00; p < 0.001).

Conclusions: The sweat conductivity test yielded a high degree of diagnostic accuracy. Conductivity measurement seems to be as reliable as conventional quantitative sweat chloride analysis to diagnose or exclude CF.

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#F60 - A STUDY OF THE PHENOTYPE AND GENOTYPE OF CHILDREN WITH CYSTIC FIBROSIS DIAGNOSED AT A TERTIARY HOSPITAL IN SOUTH INDIA

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PURPOSE OF THE STUDY

Exact prevalence of cystic fibrosis (CF) in India is not known and CF is being underdiagnosed due to lack of awareness. The objective of this study is to study the clinical profile and CF transmembrane conductance regulator protein (CFTR) mutations of children diagnosed with CF at a tertiary hospital in South India.

METHODS

A retrospective descriptive study was conducted at a tertiary care referral hospital in South India between January 2008 and June 2015. Inclusion criteria were children aged less than 18 years at diagnosis with clinical features suggestive of CF and 1) Positive sweat chloride test (>60 mEq/l) or 2) Presence of disease causing mutations of CFTR gene. Medical records of children who met the inclusion criteria were reviewed and analyzed.

RESULTS

Out of 17 children with CF, 9 (52%) were girls and 8 (48%) were boys. Nine (52%) children were less than 6 months of age at diagnosis, 2 (12%) were between 6 and 12 months, 4 (24%) were between 1 and 5 years and 2 (12%) were above 5 years of age at diagnosis. Mean age at diagnosis was 24.7 months ± 45 months and median age was 6 months.

History of poor weight gain (17 children, 100%), respiratory symptoms in the form of cough and shortness of breath (16 children, 94%) and oily stools (14 children, 82%) were the most common clinical features at presentation. Thirteen children (74%) had the clinical triad of all these three features. Four children (24%) had consanguineous parents and 4 (24%) had siblings diagnosed with CF. As per Revised Indian Academy of Pediatrics growth chart 2015, all 17 children weighed less than 3rd centile for age and sex and 11 children (65%) had length/height less than 3rd centile for age and sex.

Pseudomonas aeruginosa was grown in respiratory secretions of 15 (88%) children with CF (in 8 children at the time of diagnosis and in 7 during follow-up). Staphylococcus aureus was the second common organism (6 children, 35%).

Genetic analysis for ΔF508 mutation was positive in 8 (47%) children (7 homozygous and 1 heterozygous). Of 9 ΔF508 negative children, CFTR gene sequencing was performed in 4 children (24%). 1 child (6%) had homozygous C53+1G>T mutation, homozygous p.R.75X, C223C>T mutation, homozygous c.C343, c.1029delC mutation and homozygous R1162 mutation. CFTR gene sequencing could not be performed in the remaining five ΔF508 negative children due to financial constraints.

CONCLUSION

Our study shows that CF, though not very common, does exist in South India. Awareness among pediatricians regarding the above-mentioned clinical features and a high index of suspicion are essential for early diagnosis of CF.

REFLECTIONS AND CONCRETE PROPOSALS FOR ACTION

A multicentric study on CF with larger sample size is required to establish the CF phenotype and genotypes prevalent in India with higher degree of confidence. Inclusion of CF in Indian neonatal screening programs will help in diagnosing more children with CF at an earlier age.

#F72 - SOMATIC AND RESPIRATORY MUSCLE FUNCTION IN CHILDREN AND YOUNG ADULTS WITH CYSTIC FIBROSIS: EPIDEMIOLOGIC AND GENETIC FACTORS

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Background

Somatic skeletal and respiratory muscle function is impaired in children and young adults with cystic fibrosis (CF). Chronic malnutrition, airway obstruction and chronic infection impact negatively not only on respiratory muscle function, but also on peripheral skeletal muscle strength and endurance. We hypothesized that duration of CF disease would be related to indices of somatic and respiratory muscle function. We also tested whether the most prevalent CFTR gene mutation (F508del) is an independent predictor of somatic or respiratory muscle function in CF.

Methods

Upper arm muscle area (UAMA), maximal inspiratory (PImax) and expiratory (PEmax) pressures and the tension time index of the respiratory muscles (TTImus) were measured in 147 children and young adults with CF. Subjects were classified into three categories according to genomic DNA mutation analysis: Homozygous for F508del, heterozygous for F508del and other mutations.

Results

Mean (SD) disease duration was 12 (6) years and age at testing 14 (5) years. Mean (SD) PImax was 71(27) cmH2O, PEmax 72 (30) cmH2O, TTImus 0.19 (0.15) and UAMA 2730 (1100) mm2. Mean (SD) UAMA in homozygous...
subjects for F508del (n = 52) was 2702 (1028) mm², in heterozygous subjects for F508del (n = 65) was 2865 (1202) mm² and in subjects with other mutations (n = 30) was 2578 (998) mm². TTTmax in homozygous subjects for F508del was 0.185 (0.145), in heterozygous subjects for F508del was 0.189 (0.149) and in subjects with other mutations 0.200 (0.151). After adjustment for age, disease duration was significantly related to TTTmax (p = 0.015, r = -0.335) and UAMA (p = 0.014, r = 0.296) but not to Pmax (p = 0.096, r = 0.220) and PEmax (p = 0.321, r = 0.134). Pmax, PEmax, TTTmax and UAMA were not significantly different in subjects homozygous for F508del, subjects heterozygous for F508del and subjects with other mutations.

Conclusions
Disease duration is significantly and negatively related to somatic and respiratory muscle function in children and young adults with CF. These findings probably reflect the dynamic relation between the age-related increase in muscle mass and the evolving myopathy in patients with CF. Somatic and respiratory muscle impairment is not particularly related to presence of the F508del mutation.

#F104 - A CASE REPORT OF CEPACIA SYNDROME

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A review of the literature on “Cepacia Syndrome” is limited to case reports. The patients with this condition are patients with cystic fibrosis with exacerbations caused by Burkholderia cepacia. The patients are very unwell and the mortality rate is high. Management of the condition is usually achieved with antibiotics, both intravenous and nebulized. The addition of immunosuppressive agents has been tried.

We report on a young Vietnamese girl with known bronchiectasis since the age of 12 yrs old who was admitted for an infective exacerbation. The initial bronchoalveolar lavage performed grew Escherichia coli. She was started on Piperacillin/Tazocin and Ceftazidime with an inadequate response. Her condition continued to deteriorate despite being on intravenous antibiotics and nebulized Gentamycin for 2 weeks. She was diagnosed to have Cepacia Syndrome and was started on intravenous methylprednisolone and nebulized Gentamycin. Her condition deteriorated and she was eventually intubated. She required high ventilatory support. Frequent bronchoalveolar lavages were performed for airway toilet as the secretions were thick and tenacious causing plugging of the airways. Her fever and respiratory symptoms worsened and a repeat sputum culture showed Burkholderia cepacia which was multidrug resistant. Her condition deteriorated and she was eventually extubated. She required high ventilatory support.

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

#G35 - CHURG-STRAUS SYNDROME IN CHILDREN: CASE REPORT

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Churg-Straus syndrome (CSS) is rare disease in children. At the moment, only several decades of observations are described. However, due to severe course and unfavorable prognosis, it attracts focused attention of specialists. CSS is systemic disorder which is characterized with severe bronchial asthma, pulmonary infiltrates, hypereosinophilia and systemic vasculitis. Frequency of CSS in adults is 2.4 /1 mln/year; data regarding its frequency in children are absent due to its rarity. This disease manifests with allergic rhinitis, bronchial asthma, eosinophilic infiltrative disease, and systemic vasculitis with granulomatous infiltration. Outcome is fatal if not treated. Predominant causes of death are cardiac, renal, cerebral failure, and perforation or bleeding in gastrointestinal tract. Diagnostic criteria of SCS proposed by the American College of Rheumatology are: bronchial asthma, eosinophilia, mono- or polychrothropy, affection of accessory sinuses, eosinophilic extravasates on biopsy.

A clinical case of CSS is presented. A girl, 11 years old, suffered from quickly progressive bronchial asthma on the background of hypereosinophilia and elevated IgE level. Quickly progressive bronchial obstruction syndrome with unusual course appeared:
- with abundant passage of mucous-purulent sputum
- with local fine crackles and crepitation predominantly in basal and lower parts which appeared and disappeared during the day
- with catarhal-purulent diffuse endobronchitis on bronchoscopy

A large quantity of eosinophils was found in sputum (up to 80%). In sputum, bacterial culture fungi of Candida spp. and streptococci in diagnostically
significant titers were revealed, IgE – 710 mcg/ml. Preliminary diagnosis: bronchial asthma. Infiltrative changes in lungs on X-ray and CT scan were detected. In biopsy of skin and muscles from the back and left foot, systemic productive vasculitis, granulomatous inflammatory infiltration and muscular calcification were revealed allowing to diagnose Churg-Strauss systemic vasculitis. Lethal outcome occurred due to perforative enteritis, perforation of esophagus, generalized peritonitis and cardiac-pulmonary failure.

Summary. The rarity of the pathology (1–3 cases/1 000 000) makes it difficult to diagnose. Nevertheless, in presence of bronchial asthma, eosinophilia and affection of inner organs, it is necessary to keep in mind Churg-Strauss vasculitis. Latest developments of immunomodulatory therapy and early beginning of the treatment allow to improve outcome of the disease.

#G123 - ENDOGENOUS LIPOID PNEUMONITIS IN TWO CHILDREN WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH BIOLOGIC DRUGS

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Objective

Emphasize the need of making a broad differential diagnosis in juvenile idiopathic arthritis patients treated with biologic drugs regarding possible pulmonary complications other than infection.

Methods

We reviewed and summarized the clinical course of 2 children affected with SJIA treated with biologic drugs who developed an endogenous lipid pneumonitis (ELN).

Case Description

The first case was an eleven-month-old boy diagnosed with SJIA and treated with anakinra. One year after, he was admitted because of a pneumonia. Intravenous antibiotics were started. Blood cultures and bronchoalveolar lavage were negative for bacteria. Lobar condensation resolved in a week and at that time an interstitial pattern seemed to be more evident. A CT scan showed a diffuse alveolar-interstitial pattern. Cultures remained negative for virus, bacteria, mycobacteria and fungus. Pathology showed clusters of cholesterol crystals invading or substituting the alveoli. ELN was diagnosed and high dose steroid treatment was started. He received steroid therapy and anakinra until the age of 5. At this point, a change of treatment from anakinra to tocilizumab was needed because of a new IJA flare. At the age of 8 years, a chest CT was performed, showing septal thickening in the upper lobes and lower left lobe, an atelectasis in the middle lobe was also observed. Nowadays, at 11 years of age, he is asymptomatic, is on low-dose budesonide/formoterol, and has normal forced spirometry and body plethysmography.

The second case was a ten-month-old boy diagnosed with SJIA, treated with tocilizumab. At the age of 3 years, he was diagnosed with a macrophage activation syndrome. One year later, he was admitted because of pneumonia. He received intravenous antibiotics. Blood cultures were negative. A chest CT scan showed small peripheral nodules in the right lower lobe. Cultures remained negative for virus, bacteria, mycobacteria and fungus. Pathology showed alveolar macrophages laden with cholesterol crystals and a PAS-positive material. ELN was diagnosed and high dose steroid treatment was started. Six months latter a chest CT scan showed a small atelectasis of the right middle lobe, without interstitial involvement. At the age of 9 years, he presented with a new flare, and pathology showed more fibrosis and fewer alveolar macrophages laden with cholesterol crystals. Nowadays, at 11 years of age, he remains on chronic low dose oral steroid therapy, tocilizumab and mycophenolic acid. He is asymptomatic, on chest examination he has persistent crackles in the right lower base, and his forced spirometry is normal.

Conclusion

Patients with SJIA treated with biologic drugs often develop pulmonary complications. A first step requires the exclusion of an infectious etiology, however non infectious complications must be ruled out. Endogenous lipid pneumonitis is recognized as a different disease process with unclear relationship to the treatment and/or the underlying inflammatory disease.

H. NEUROMUSCULAR AND CHEST-WALL DISEASES (INCLUDING SIDS)

#H8 - CHANGE IN PULMONARY FUNCTION IN PATIENTS WITH DUCHEENNE MUSCULAR DYSTROPHY

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Introduction: Declining respiratory muscle function increases the susceptibility of patients with Duchenne muscular dystrophy (DMD) to recurrent chest infections, sleep-disordered breathing and respiratory failure. Pulmonary function testing at regular intervals allows doctors to identify deteriorating respiratory function early, and put interventions in place at the appropriate times to minimize the risk of respiratory complications as a result of loss of respiratory muscle strength. A regular multidisciplinary neuromuscular clinic has been in place at the National University Hospital Singapore since 1995 to provide care to patients with DMD.

Objective: To analyze the respiratory function decline over time in patients with DMD managed at a tertiary pediatric unit in Singapore, using non-invasive measurements of respiratory function.

Method: This was a retrospective review of all patients with DMD attending a multidisciplinary neuromuscular clinic at National University Hospital Singapore between December 1995 and February 2014.

Results: There were a total of 39 male patients. The age range of patients during lung function measurements was 6 to 25 years old. The mean age of diagnosis was 5.9 years (standard deviation 2.3 years). The mean age at which lung function testing was first conducted was 10.4 years (SD 3.5 years). Ten patients were ambulant, and 29 became wheelchair-dependent by the end of the study period. The mean age of becoming wheelchair-bound was 9.6 years (SD 2.5 years). The mean annual declines in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and inspiratory vital capacity were 4.16% predicted, 3.45% predicted and 4.70% predicted, respectively. There was a mean fall in sniff nasal inspiratory pressure (SNIP) of 1.06 cmH2O per year. Maximal inspiratory pressures and maximal expiratory pressures exhibited similar falls in values, with a drop of 1.46 cmH2O and 1.50 cmH2O per year, respectively.

Conclusions: Our study describes the natural decline in pulmonary function test parameters in a population of patients with DMD. There is a decline in both inspiratory and expiratory muscle function in these patients over time with current strategies in managing their respiratory health. These data will be useful as a baseline for future interventions when comparing changes in lung function in patients with DMD.

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

#I12 - RELATIONSHIP BETWEEN EXPOSURE TO BETA-GLUCAN AND ENDOTOXIN AND THE DEVELOPMENT OF ASTHMA AND ATOPY IN CHILDHOOD

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Pediatric Pulmonology
Background: The role of beta-glucans (biologically active polysaccharides with pronounced immunomodulation activities) in the development of asthma and allergic sensitization is unclear, with several studies reporting differing and often contradictory findings.

Objective: To examine the relationship between exposure to beta-glucan and endotoxin in early childhood on the development of wheeze, asthma and atopic sensitization by school-age.

Methods: Beta-glucan and endotoxin content was measured by a kinetic limulus assay in domestic dust samples collected from living room floor at age 5 years in 428 participants in a population-based birth cohort. At ages 5, 8 and 11 years, we assessed children for allergic sensitization (skin prick tests), parentally-reported symptoms and medication use (validated questionnaires). We transcribed primary health care records for all children, and based on the longitudinal data on parentally-reported and physician-confirmed wheezing, assigned children to wheeze phenotypes (never, transient, late-onset, persistent controlled and persistent troublesome; latent class analysis). Asthma at each age was defined as current wheeze, doctor-diagnosed asthma ever and current use of asthma medication.

Results: There was a statistically significant difference in beta-glucan concentration between the five wheeze phenotypes (p = 0.046), with significantly higher levels in the late-onset (mcg/g, GM [95% CI]: 7.65 [7.54–7.76]) and persistent troublesome wheeze classes (7.60 [7.38–7.82]), compared to no wheeze (7.42 [7.35–7.49]), transient early (7.46 [7.30–7.61]) and persistent controlled wheeze classes (7.38 [7.24–7.51]). However, there was no significant association between beta-glucan exposure at age five years with wheeze (OR [95% CI]: 0.72 [0.40–1.30]), asthma (0.74 [0.37–1.50]) and atopic sensitization (1.30 [0.82–2.01]) at age 11. In the multivariate longitudinal generalized estimating equation model, we found no significant association between beta-glucan exposure and the development of wheeze (1.06 [0.73–1.53], p = 0.77), asthma (0.99 [0.60–1.66], p = 0.99) and sensitization (1.24 [0.88–1.76, p = 0.22). The risk of sensitization significantly decreased with increasing endotoxin exposure (0.82 [0.70–0.96], p = 0.016).

Conclusion: High exposure to beta-glucan was associated with late-onset wheezing and persistent troublesome wheezing, but not with asthma or allergic sensitization. The risk of the development of atopic sensitization during childhood decreased with increasing endotoxin exposure.

#I46 - PRESENCE OF RESPIRATORY INFECTIONS IN THE PEDIATRIC AMBULANCE

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Introduction: Respiratory infections are the most common reason for visiting the pediatrician. Viruses are their most common cause for children under the age of 3 in 95%, and among older children in 85%.

Aim of the study: To determine the number of patients who were treated with the diagnosis of respiratory infections, their age and gender.

Study method: Retrospective analysis of electronic records for the month of March 2015, when 1118 curative views were performed.

Results: Respiratory infections were present in 61% (682). Boys were 52% (355), girls 48% (327).

Distribution in the diagnosis was as follows: J00, 24% (165); J02 35% (240); J03 8% (54); J04 4% (27); J05 14% (95); J21 8% (54); J10/J11 3% (20); J18 1% (7); J45 3% (20).

Representation by age: from 0 to 3 years, 245 (36%); from 4 to 7 years, 286 (42%); from 8 to 11 years, 48 (10%); 12–15 (7%) and over 16, 35 (5%).

Conclusion: Respiratory infections in pediatric clinics are expected and more often represented in the winter. The most common were upper respiratory tract infections in 74%.

#I83 - FEASIBILITY OF A PEER-LED ASTHMA AND SMOKING PREVENTION PROGRAM (ASPP) IN AUSTRALIAN SCHOOLS WITH HIGH INDIGENOUS YOUTH

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Background: The burden of tobacco smoking and asthma among Indigenous Australians remains high. Indigenous Australians are 3 times more likely to die from asthma and have poorer outcomes than other Australians. The frequency of smoking also remains higher in this population. Targeting adolescents is important as smoking behaviors are often established in youth. Asthma management is often suboptimal in this group which may impair quality of life. Despite this burden of illness, there are few prevention intervention strategies specifically for Indigenous Australians. We undertook a pilot study in two Darwin schools in 2014 to determine the feasibility of an innovative, peer-led school-based education program ASPP to improve asthma management and prevent the uptake of tobacco smoking in schools with high numbers of Indigenous youth.

Methods: ASPP is founded on an evidence-based 3-step program (Triple A) using standard manuals addressing asthma, enriched with a smoking prevention module. The program uses a student-centered approach where students (peer leaders) become teachers and deliver ASPP to year 7 students using activities, videos and games. Students completed questionnaires related to asthma and smoking.

Results: Of 203 students involved, 56 (28%) were Indigenous. Self-reported asthma was high (19%) compared to the national average of 10.2%. While previous smoking was reported in 10%, exposure to cigarette smoking at home (63%) far exceeded national data (7.8%). Thirty-seven students who reported asthma and/or respiratory symptoms were invited for further clinical evaluation. Of the 22 who consented (59%), 41% were Indigenous. Asthma severity varied: mild (63%), moderate (25%) and severe (12%). Induced sputum from 17 students showed that 15 (88%) had sputum neutrophilia, 12 (71%) had eosinophilic asthma, 10 (59%) had cilia dysfunction and 7 (41%) had hypomotility.

Conclusion: Our pilot study was well received by both students and staff and illustrates the potential of further school-based prevention and interventions in an at-risk group. Implementing ASPP in schools with high numbers of Indigenous youth would facilitate improvement in asthma management and preventing the uptake of tobacco smoking.

#I90 - FOREIGN BODY ASPIRATION IN CHILDREN: RESULTS OF NATIONWIDE SERIAL SURVEYS IN JAPAN,
Methods: The first survey was conducted in 2005–06 and the second conducted in 2015 by sending a questionnaire to tertiary hospitals throughout Japan. We also asked doctors of the hospitals to fill out a case card of FBA-diagnosed cases during the survey period.

Results: During the 1st survey period, 163 cases were reported from 169 hospitals and the results were published in 2009. During the 2nd survey period, 112 cases were reported from 419 hospitals. Age range of the 1st survey was from 2 months to 15 years, and 128 cases (78.6%) were under 3-years of age, meanwhile age range of the 2nd survey was from 6 months to 13 years, and 76 cases (72.3%) were under 3-years of age. Male gender was predominant: 66.5% in the 1st survey and 66.0% in the 2nd survey. Regarding the type of FB, 73.6% of 1st survey cases were organic in nature. In relation with age, organic materials accounted for 85.3% of FB in children aged <3 years old, meanwhile in children aged ≥3 years old, non-organic materials accounted for 65.7% of FB. Similar trends were observed in the 2nd survey. Peanuts and other types of nuts were predominant in the organic materials, followed by beans. More than half of non-organic materials were dental prostheses and toys in both surveys. Elapsed time until diagnosis ranged from within one hour to few months. Although approximately half of the cases of both surveys were diagnosed within 24 hours, 21.9% of the 1st survey and 14.4% (16 cases) of the 2nd survey took more than 7 days until diagnosis. Delayed-diagnosed cases had been treated under the diagnosis of other respiratory diseases; croup, prolonged cough, asthma, pneumonia/atelectasis. The predominant location of FBs was main bronchi in both surveys; 73.9% in the 1st survey and 68.6% in the 2nd survey, followed by trachea (10.3% and 15.1%) and larynx (2.5% and 8.1%). Severe consequences were reported; one death in the 1st survey and three deaths in the 2nd survey. Respiratory and neurological sequelae were also reported in several cases.

Conclusion: Clinical features of FBA cases showed similar trends even 10 years apart in Japan. Further educational programs for caregivers and extensive nation-wide campaigns should be offered to prevent FBA incidents.

Acknowledgment: We thank all the physicians who replied to the questionnaire of our surveys. This study was supported by the Japanese Society of Pediatric Pulmonology.

#I95 - COST-EFFECTIVENESS OF HOME MECHANICAL VENTILATION IN CHILDREN LIVING IN A DEVELOPING COUNTRY
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Background: Home mechanical ventilation is a promising option for children requiring long-term mechanical-assisted ventilation, while data on cost-effectiveness of this approach is limited.

Aims: To investigate the cost-effectiveness of home mechanical ventilation in children requiring long-term mechanical-assisted ventilation.

Methods: A retrospective cohort was conducted on 36 children (16 girls, 44.4%) requiring mechanical-assisted ventilation. Underlying diseases of children were congenital airway malformations in 11, cystic fibrosis in 2, severe laryngomalacia in 10, poly neuropathy syndrome in 3, mitochondrial myopathy in 5, hypoxic ischemic encephalopathy in 4, and cerebral palsy in 1. Children were admitted in pediatric intensive care units (ICU) for 2 weeks. After discharge, they were on home mechanical ventilation and were followed for 1 year. Data on daily costs of admission at ICU, rehospitalizations, weaning, educational performance and muscle strength were gathered.

Results: Mean age of children at time of initiation of mechanical-assisted ventilation was 5.8 years (ranged from 2 months to 15 years). Mean number of re-hospitalizations was 3.4 ± 4.9 times with mean duration of 9.44 ± 2.53 days. Of children on mechanical ventilation, 1 attended school, 2 were weaned, and 21 experienced improvement in muscle strength. No fatal or serious complications were observed while children were on home mechanical ventilation. Mean cost of daily ICU admission was $912 ± 1028, while the mean daily cost of home mechanical ventilation was $6.86 ± 4.95 ($p < 0.001).

Conclusions: Home mechanical ventilation is more cost-effective compared to ICU admission for only mechanical-assisted ventilation.

J. INVESTIGATION AND DIAGNOSTIC TESTS

#J28 - LUNG CLEARANCE INDEX (LCI) IN PATIENTS WITH BRONCHIOLITIS OBLITERANS AND CYSTIC FIBROSIS (CF) PATIENTS.
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Introduction: Lung clearance index (LCI) is a simple clinical marker which provides a global measurement of ventilation inhomogeneity. It has been used to monitor early pulmonary changes and as a treatment efficacy endpoint in cystic fibrosis (CF). Bronchiolitis obliterans (BO) is a form of chronic obstructive lung disease following an insult to the lower respiratory tract, mainly adenovirus. To date, there are no published studies evaluating LCI in BO not related to bone marrow transplantation.

Aim: To evaluate LCI in patients with BO; to compare LCI of BO patients to that of CF patients and to parameters of lung function tests.

Methods: The study was approved by local IRB. Patients with CF and patients with BO were included. Data regarding history and diagnosis were recorded. LCI was measured and compared to spirometry.

Results: Twenty-six CF patients (50% males) were compared to 20 BO patients (65% males). Their mean age was similar, 15.9 ± 7.5 and 15.1 ± 8.3 years, respectively; p = 0.72. BMI was also similar between the two groups (18.8 ± 3.6 vs. 19.3 ± 5.3, p = 0.77). Seventeen patients with CF were pancreatic insufficient (65%), and five had CF-related diabetes (19%). LCI percent predicted (%) was slightly higher in the BO group, but did not reach statistical significance (190.4 ± 63.5 vs. 164.9 ± 39.4, p = 0.1). FRC LCI % was higher in the BO group, indicating air trapping (92.5 ± 35.9 vs. 71.3 ± 18, p = 0.014). FEV1% and FEF 25–75% were significantly lower in the BO group (60.5 ± 17.8 vs. 72.7 ± 20.7, p = 0.041 and 42.8 ± 22.8 vs. 66.4 ± 37.4, p = 0.017, respectively). In both groups, LCI was inversely correlated with percent predicted FVC, FEV1 and FEF 25–75. Linear regression found that LCI correlated better with FEV1% and FEF 25–75% in BO compared to CF patients.

Conclusions: Similarly to CF, LCI provides a sensitive and useful estimation of ventilation inhomogeneity in BO patients. Further prospective studies including larger number of patients with BO, comparing LCI with clinical disability, pulmonary function tests and airway trapping degree assessed by plethysmography and CT scores are needed.

#J29 - TIDAL BREATHING ANALYSIS AS A TOOL FOR ASTHMA DIAGNOSIS IN CHILDREN AGED SIX MONTHS TO FIVE YEARS
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Background: Asthma is difficult to establish in children below 5 years old using spirometry. There is limited data on infant pulmonary function testing due to their inability to follow instructions. Tidal breathing analysis (TBA) can provide useful information regarding lung function in infants and young children, as it is effort-independent.

Objectives: The aim was to determine if baseline and post-bronchodilator ratios of the time and volume until peak expiratory flow to the total...
expiratory time and volume, (tPEF/tE and VPEF/VE) can distinguish asthmatics from normal children.

Methods: This is a cross-sectional study wherein 146 children ages 6 months to 5 years old completed TBA before and 15 minutes after administration of 250 µg of salbutamol via nebulization. Children 3 years old and below who did not cooperate were given sedation with oral diphenhydramine (1 mg/kg dose). The tPEF/tE and VPEF/VE were compared between the controls and asthmatics.

Results: In subjects below 2 years old, the baseline tPEF/tEs of asthmatics and non-asthmatics were 29.6 ± 13.8 and 22.0 ± 6.6 (p-value 0.046), respectively. The area under the curve (AUC) was 0.649 (95% CI: 0.305 to 0.993) at tPEF/tE of 32.250, with a sensitivity and specificity of 50% and 97%, respectively. The baseline VPEF/VEs of asthmatics and non-asthmatics were 32.7 ± 12.4 and 26.0 ± 4.9 (p-value 0.031), respectively. AUC was 0.661 (95% CI: 0.302–1.000) at VPEF/VE of 34.500, with a sensitivity and specificity of 50% and 97%, respectively. In subjects 2 to 5 years old, the baseline tPEF/tEs of asthmatics and non-asthmatics were 35.3 ± 14.7 and 35.0 ± 13.1 (p-value 0.903), respectively. The baseline VPEF/VEs were 37.0 ± 12.3 and 36.7 ± 10.7 (p-value 0.911), respectively. After salbutamol nebulization, the tPEF/tEs of asthmatics and non-asthmatics in all ages were 30.9 ± 13.7 and 27.9 ± 10.8 (p-value 0.172), respectively. The VPEF/VEs were 34.1 ± 11.4 and 30.9 ± 9.0 (p-value 0.078), respectively.

Conclusion: Baseline tPEF/tE and VPEF/VE could distinguish asthmatics from non-asthmatics in children below 2 years old. Baseline tPEF/tE and VPEF/VE in children 2 to 5 years old and post-bronchodilator tPEF/tE and VPEF/VE in all ages could not distinguish asthmatics from non-asthmatics after nebulization with 250 µg of salbutamol.

#J44 - THE IMPACT OF NEW REFERENCE EQUATIONS (GLI 2012) ON SPIROMETRY INTERPRETATION IN CHILDREN AND ADOLESCENT

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Introduction: Spirometry is relevant to diagnosis, classification of severity and prognosis of respiratory diseases. The use of the new, all-age (3–95 years), multi-ethnic reference equations published by the Global Lung Function Initiative in 2012 (GLI) is recommended for spirometry interpretation by the major respiratory international societies, reducing key-point deviations, especially in the transition into adult care medicine. Aim: This study intends to determine the clinical impact of switching to the GLI equations in a pediatric lung function laboratory on interpretation and classification of spirometry results.

Methods: Analysis of 1444 spirometry records/children [60% boys, 9% black, average age 11.05 ± 3.36 years] performed in 2013; main diagnosis: asthma, cystic fibrosis, other chronic obstructive pulmonary diseases and neuromuscular diseases. Z-scores and %predicted for FEV1, FVC and FEV1/FVC were calculated using Zapletal and GLI equations and compared. Abnormally low FEV1 and FVC were defined if below the lower limit of normal (LLN), airway obstruction if FEV1/FVC < LLN and a “restrictive pattern” in spirometry if FEV1/FVC ≥ LLN + FVC < LLN. The severity of obstruction was classified based on %predicted FEV1 (ATS/ERS). The calculations were performed using Excel and a specific software provided by the GLI working group (www.lungfunction.org/) and the statistics analysis (t and χ2-tests) using SPSS v.22.

Results: The z-score values for FEV1 and FVC were significantly lower with the GLI vs. Zapletal equations: –0.28 ±1.36 vs. 0.05 ±0.94 and –0.06 ±1.29 vs. 0.01 ±0.98 respectively. The rates for abnormally low values were higher with the GLI vs. Zapletal equations: FEV1 < LLN 13.5% vs. 4.7%, FVC < LLN 8.9% vs. 4.6% and FEV1/FVC < LLN 14.2% vs. 5.0%, as well as both the rates for airway obstruction 12.1% vs. 4.1% and restrictive pattern 6.8% vs. 3.7%. All differences were statistically significant (p < 0.001). The differences in spirometric indices (Zapletal-GLI) were greater for FEV1 (and FEV1/FVC) in children <6 years and ≥14 years [boys 0.64 (and 0.63) and 0.71 (and 0.40); girls 0.58 (and 0.81) and 0.68 (and 0.64) respectively, all p < 0.05]. In the classification for severity, 58 patients changed degree of severity with the GLI equations [50 (86%) worsened], however, the difference was not significant. When the analysis was restricted to white children aged ≥6 years (n = 1208), the population validated in the Zapletal equations, the differences remained. Discussion/Conclusion: As suggested in the literature, the introduction of the GLI equations has a significant impact on spirometry interpretation in pediatric clinical care, increasing the results below the lower limit of normal for gender, age and height. If it will influence management and treatment, such introduction will have to be assessed.

#J80 - DIAGNOSTIC TESTS FOR PCD: STRENGTHS AND WEAKNESSES

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Pediatric Pulmonology
Aim: To evaluate the efficiency of diagnostic tests in patients with a clinical suspicion of PCD.

Patients and methods: Included in the study were patients with a high clinical suspicion for PCD based on the ERS Task Force Consensus Statement for the diagnosis and treatment of PCD. A detailed review was conducted for all suspected patients including measurement of nasal nitric oxide (nNO) levels, ciliary electron microscopy analysis and whole exome sequencing (WES). Confirmed PCD diagnosis was defined as (1) the presence of typical clinical characteristics and a recognized ciliary ultrastructural defect on EM and/or the presence of two pathogenic mutations in a known PCD causing gene.

Results: Fifty-four patients were included in the study, 24 (44%) male. In 37 (67%) patients, a family history of consanguinity was reported. Fifty-one (94%) had bronchiectasis on chest CT, 16 (30%) had heterotaxy and 13 (24%) had a history of neonatal respiratory morbidity. nNO levels were evaluated in 49 (89%) patients, ciliary EM analysis was performed in 52 (95%) and genetic analysis was completed in 38 (69%) patients.

In 43 (80%) patients, a diagnosis of PCD was confirmed, in 10 (18%) patients a final diagnosis could not be reached and in one patient an alternative diagnosis was made.

All patients with a confirmed diagnosis of PCD in which nNO levels were evaluated had an abnormally low result (<100 ppb) (38 out of 38 evaluated patients). A ciliary ultrastructural defect was demonstrated in 63% of patients with a confirmed PCD diagnosis in whom EM was performed. The genetic analysis identified pathogenic mutations in 28 of 31 (90%) patients with a confirmed diagnosis of PCD and established an alternative diagnosis in one patient. Twelve of the 28 (32%) patients with a molecular confirmed diagnosis had a normal reported ciliary ultrastructure on EM.

Conclusion: Classical clinical features of PCD coupled with low nNO levels carry a high yield for the diagnosis of PCD. Ciliary ultrastructure EM analysis cannot be a gold standard since it can be normal in about one third of the patients. Our results suggest that in patients suspected to have PCD who have low nNO levels, a WES might be the next diagnostic step rather than ciliary EM analysis.

**#J101 - LOCALIZATION OF TRACHEOESOPHAGEAL FISTULA USING BRONCHOSCOPY AND SHORT JETS OF LOW PRESSURE OXYGEN**

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**Background:**

Tracheoesophageal fistula (TEF) is a common congenital anomaly of the respiratory tract. Diagnosis of isolated TEF is challenging. The traditional method requires contrast studies. The fistulous tract may be missed in these studies. Bronchoscopy can be a reliable alternative, although it is easy to overlook a TEF at bronchoscopy. The opening of an isolated TEF is usually small and located on the posterior wall of the trachea at the level of the thoracic inlet within a fold of the mucosa.

**Objectives:**

We aimed to examine the safety and efficacy of a low pressure oxygen jets technique while performing a flexible bronchoscopy, for H type TEF or fistula reopening after surgery repair.

**Methods:**

We retrospectively described 11 patients, followed between the years 2006–2014 in the Schneider Children’s Medical Center in Israel. All of the patients had TEF and a complete TEF surgery repair. We compared the imaging that contributed to the diagnosis versus the results of the bronchoscopy. All bronchoscopies were performed with an Olympus bronchoscope, viewing the fistula origin with and without using jets of oxygen through a Suction valve MAJ-207 with 2 L/min flow.

**Results:**

Of the 11 patients with mean age of 1.62 ± 0.12 years, 7 (63%) were girls, 10 (91%) were examined for reopening of the fistula examination and 1 for new investigation of suspected H type fistula. All had Upper Gastrointestinal (GI) imaging investigation prior to bronchoscopy. Eight (73%) patients were found to have an open fistula. Of these, 3 (33%) had positive imaging results with Upper-GI study and 1 (12.5%) negative results even on bronchoscopy. Although 4 (50%) of the patients appeared to have a closed fistula at first during the usual bronchoscopy without oxygen small jets, the other 4 (50%) were found to have an open fistula after using small jets of oxygen technique. There were no complications during the procedure.

**Conclusions:**

Bronchoscopy is a reliable method for diagnosis of TEFs, however if the TEF opening is small, it is easy to overlook. Small jets of oxygen can be a reliable and safe method for the diagnosis of TEFs, especially for a recurrence and reopening of a fistula after surgery repair. Larger studies are needed to further investigate the safety and efficacy of the small jets technique.

**#J94 - MILK REINTRODUCTION IN CHILDREN WITH COW’S MILK ALLERGY**

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The acquisition of tolerance in Cow’s milk allergy (CMA) is achieved in more than 90% of cases by three years of age. This tolerance is tested by the oral challenge test which is not always safe and has to be done in hospital. We propose to analyze the results of the milk reintroduction test, mainly the ones with failure.

**Methods:** Thirty-one children with CMA were included in this study during the period between 2007 and 2015, in the department B of the Infantile Medicine of Tunis Children Hospital.

**Results:** The diagnosis of CMA was made at the mean age of 2.16 months (15 days–6 months). Twenty-three patients had an IgE-mediated CMA, and had a non-IgE-mediated allergy. All patients were treated by free cow’s milk protein diet. Cow’s milk was introduced at home in 58% and failed in 44%. Oral challenge test was performed in hospital in 29 cases. Specific IgE levels were decreased over time in 4/5 cases before oral challenge test. Cow’s milk skin testing was performed in 79.3% and was negative in 95.6%. The mean age of the first oral challenge test was 2.11 years (8 months–11 years). The oral challenge test was successful in 24 cases. The mean age of tolerance acquisition was 1.86 years (8 months–6.5 years). In five patients, the reintroduction failed. Three patients had persistent cow’s milk allergy. Cow’s milk reintroduction was possible in two patients. Oral challenge test was performed another time with success in one patient and tolerance for cooked milk was achieved for another. On follow-up, four patients developed asthma.

**Conclusion:** Oral challenge test may provoke severe allergic reactions. Specific IgE antibodies and skin prick test may guide the right time for milk reintroduction.
All samples were stored at ~80°C and tested at Viroclinics Biosciences (Rotterdam, Netherlands). Quantitative RT-PCR and viral cultures were performed. Spearman test for correlation analysis between the methods was performed. Viral load was assessed for correlation with clinical parameters. Results: One hundred samples were collected from 13 infants (mean age 5.7). Twelve patients were RSV-A positive and one was RSV-B positive. Correlations were found between UTM and VCM (0.92, P value < 0.001), and between nasal swab and nasal wash (0.62, P value = 0.02), with higher signals in nasal wash vs. swab. No correlation was found between viral load and length of O2 requirement or length of stay.

Conclusion: RSV viral load was comparable between nasal wash and swab. No differences were observed between different transport media. No correlation was found between viral load and disease severity. Limited sample size warrants further large scale analysis.

K. THERAPEUTIC PROCEDURES

#K26 - STUDY OF EXTERNAL STENTING IN TRACHEO-BRONCHOMALACIA

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Introduction: Deciding the treatment and management of tracheo-bronchomalacia may become a burden in many cases. We have used vascular grafts as external stents to surgically treat tracheo-bronchomalacia. We report the treatment outcome and pulmonary function of external stenting. Patients and methods: Fifty patients, 81 lesions (42 tracheal, 28 left main bronchial, 11 right main bronchial) with tracheo-bronchomalacia treated with external stents were studied. A gore-tex vascular ring graft was used as external stents, and pulmonary function tests and chest CT were performed before and after surgery; bronchoscopy was performed before, during, and after surgery. A bronchoscope manufactured by Machida with an external diameter of 2 mm and a bronchoscope manufactured by Pentax with an external diameter of 2.4 mm were used. Pulmonary function was measured using a pulmonary function measuring device, ARFEL1, manufactured by Aivision.

Results: Forty-six out of 50 patients (92.0%) survived to discharge, and 4 patients (8.0%) died during hospital stay. Patency of airway was confirmed in 70 out of 81 lesions (86.4%) under bronchoscopy and chest CT. Pulmonary function tests showed no change in static compliance (Crs) before and after surgery, 1.26 ± 0.59 (ml/cmH2O/kg) to 1.26 ± 0.60 (ml/cmH2O/kg), but airway resistance (Rrs) decreased significantly from 669 ± 434 (kg cmH2O/l/sec) to 520 ± 267 (kg cmH2O/l/sec) before and after surgery. Complications were experienced in 8 out of 50 cases (16%): mediastinitis in 3, tracheal necrosis in 1, chylothorax in 1, and stenosis in the later period in 3. External stenting was performed extensively in the case with tracheal necrosis, and interception of the feeding vessel of the trachea was thought to be the reason. No complications led directly to mortality.

Discussion: External stents seems to be effective in the treatment against tracheo-bronchomalacia. It is difficult to determine the condition of airway patency from the surgical field, thus intraoperative bronchoscopy is thought to be necessary when performing this operation. Bronchoscopy, chest CT, and pulmonary function tests were useful in assessing the effectiveness of external stenting. External stents are left inside the body, hence further studies are thought to be needed to assess the influence of external stents in future airway development.

#K59 - INVESTIGATION OF THE EFFICACY OF BIPHASIC CUIRASS VENTILATION FOR CHILDREN HOSPITALIZED WITH A MODERATE BRONCHIAL ASTHMA ATTACK

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Introduction: Biphase cuirass ventilation (BCV) is an external ventilator with five respiratory modes, one of which, the continuous negative mode (CN mode), assists breathing physiologically by simply making internal negative pressure adjustments within a cuirass, which is a plastic shell over the thorax. Furthermore, the secretion clearance mode (SC mode) also helps to clear sputum. We have seen that the combination of CN and SC modes can deliver rapid and effective relief for moderate exacerbations of bronchial asthma (BA), characterized by limited airflow due to contraction of bronchial smooth muscle, swelling of respiratory mucosa, and increased secretions. Therefore, we investigated the efficacy of BCV for moderate BA attacks. Methods: The cohort study consisted of 14 patients (10 boys and 4 girls; median age: 79 months) admitted to our hospital between January 1 2014 and October 31 2015 for moderate BA attacks and subsequently treated with BCV as an add-on to conventional BA therapy (Group A). The results of these patients were compared to those of a control group consisting of 15 patients (9 boys and 6 girls; median age: 82 months) hospitalized for moderate BA attacks before the hospital had introduced the use of BCV (Group B). The following variables were also compared between these two groups: the changes in HR, RR, and SpO2 before and the day after initial therapy; details of BA therapy; and length of hospitalization. The results were statistically analyzed using the Mann-Whitney U test. BA therapy was conducted according to the Japanese Pediatric Guidelines 2012 for Treatment and Management of Asthma. The respirator used in this study was an RTX® (United Hayek Medical, London, United Kingdom), which was used first in CN mode for 1 to 2 hours, followed by SC mode to clear sputum. The above procedure was done twice per day. Results: The BCV group showed a significant improvement in both HR (Group A: 26.2 ± 14.0/min, Group B: 13.9 ± 13.5/min; P = 0.014) and RR (Group A: 13.3 ± 10.5/min, Group B: 6.4 ± 7.9/min; P = 0.047). There was no significant improvement in SpO2 values (P = 0.93). The number of days on oxygen was significantly shorter in the BCV group (Group A: 2.9 ± 1.3 days, Group B: 5.2 ± 1.8 days; P = 0.005). There was no significant intergroup difference in the number of days on steroids (P = 0.07) and the administration of continuous isoproterenol inhalation (P = 0.25). Length of hospitalization was significantly shorter in the BCV group (Group A: 5.7 ± 1.7 days, Group B: 7 ± 1.4 days; P = 0.04). Discussion: BCV as an add-on to conventional therapy for pediatric BA attacks enabled significant stabilization of the patients’ cardiorespiratory condition from the day after commencement. Furthermore, BCV reduced the length of hospitalization and oxygen administration and proved useful from a health economic perspective. Conclusion: BCV is effective for moderate BA attacks.

#K73 - ALTITUDE TESTING FOR CHILDREN: WHO ARE AT RISK FOR HYPOXIA AT HIGH ALTITUDE?

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Background: At high altitude, the lower air pressure decreases the available oxygen. Hence hypoxia occurs at high altitude causing pulmonary and cerebral symptoms. Our Pulmonary Laboratory provides high altitude simulation testing to determine who might need oxygen at high altitude. Most of the referrals are children diagnosed with chronic lung disease or complex medical conditions. These are children who plan to travel by air. The altitude test helps parents determine if oxygen is needed for air travel. Meticulous arrangements need to be made with the airline and respiratory vendor in advance to have the special model of oxygen unit on board.

Objectives: To identify who are the patients at risk for hypoxia at altitude. Method: Retrospective review of high altitude simulation (FiO2 = 16%) test reports from the Pulmonary Laboratory at Children’s Hospital Los Angeles from 1/1/2000 to 9/30/2015. Demographic and clinical variables were studied. Setting and participants: All children who had been referred to the Pulmonary Laboratory for altitude testing were the primary focus of the study.
Results: 153 altitude studies were evaluated. Ninety-eight (64%) of the studies demonstrated SpO2 < 95% at simulated altitude. Gender, median or mean years at study age, gestational age and BMI percentile were similar. No specific patient characteristic predicted hypoxemia at simulated altitude. Demographics profile

<table>
<thead>
<tr>
<th></th>
<th>SpO2 &gt; 95%</th>
<th>SpO2 &lt; 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, % (n)</td>
<td>58 (32)</td>
<td>61 (60)</td>
</tr>
<tr>
<td>Study age, median years (IQR)</td>
<td>4.4 (1.4, 7.3)</td>
<td>2.7 (1.4, 6.7)</td>
</tr>
<tr>
<td>Study age, mean years (SD)</td>
<td>5.3 +/- 4.61</td>
<td>4.8 +/- 4.8</td>
</tr>
<tr>
<td>Gestational age, median weeks (IQR)</td>
<td>40 (29, 49)</td>
<td>37 (27, 40)</td>
</tr>
<tr>
<td>BMI percentile (IQR)</td>
<td>22 (3.2, 50)</td>
<td>16 (2, 53)</td>
</tr>
</tbody>
</table>

Of those who had a baseline oxygen requirement at the time of the altitude simulation test, 79% required O2 at simulated altitude. The Pearson Test p = 0.004. Most of these children needed oxygen therapy during sleep at home. SpO2 at simulated altitude of 8000 ft (FiO2 = 0.16) by diagnosis and O2 requirement

### Diagnosis, n

<table>
<thead>
<tr>
<th></th>
<th>SpO2 &gt; 95%</th>
<th>SpO2 &lt; 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease, 61</td>
<td>32%</td>
<td>68%</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia, 4</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Complex disease, 40</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Hypo-plastic lung, 2</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Neuromuscular disease, 4</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Pulmonary hypertension, 11</td>
<td>27%</td>
<td>73%</td>
</tr>
<tr>
<td>Miscellaneous, 31</td>
<td>39%</td>
<td>61%</td>
</tr>
<tr>
<td>O2 Requirement at discharge, n = 87</td>
<td>31%</td>
<td>69%</td>
</tr>
<tr>
<td>Baseline O2 requirement, n = 74</td>
<td>21%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Conclusion: Three-fifths of the patients referred required supplementary oxygen during flight. There were no specific patient characteristics associated with risk factors for hypoxia at altitude except for those with a baseline O2 requirement at the time of altitude testing.

### L. CELLULAR AND MOLECULAR BIOLOGY

#### #L99 - IL-4 AND IL-13 SECRETING TYPE 2 INNATE LYMPHOID CELLS ARE PRESENT IN HUMAN CORD BLOOD

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Background: Type 2 innate lymphoid cells (ILC2s) are a novel cell population thought to be involved in the pathogenesis of allergy and severe asthma. ILC2s secrete IL4, IL5 and IL13 and have been found in BAL, sputum and blood from children with severe asthma. Although they are present in cord blood, their function and cytokine secretion pattern in early life is unknown.

Methods: Cord blood was collected from seven elective term cesarean section deliveries. Peripheral mononuclear cells were isolated and further stimulated with phorbol 12-myristate 13-acetate (PMA), ionomycin and brefeldin. Innate lymphoid cells were identified by absence of staining for cell surface markers found on lymphocytes using a lineage (Lin) cocktail (CD3, CD14, CD19, CD20, CD34 and CD36). Markers specific for type 2 ILCs included extracellular stimuli (CD45, CD127, CRTH2, CD161), the type 2 transcription factor (GATA3) and interleukins typically secreted by type 2 cells. Cells were analyzed by flow cytometry and data analyzed with FlowJo version 10.1r5 software.

Results: We identified a population of CD45 + Lin-(negative) cells (3.45% SD:1.45 of live CD45+ lymphocytes). Within this population 1.13% SD:1.35 were positive for specific ILC2 markers (CD127 + CRTH2 + CD161 + GATA3+). Compared to girls, boys had more ILC2s (1.79% SD:1.51 vs. 0.25% SD:0.13 of CD45+ Lin-cells). About one sixth of ILC2s (CD127 + CRTH2 + CD161 + GATA3+) (17.6% SD:9.1) were positive for IL13 while only 2.6% SD: 3.5 were positive for IL4 with no difference in cytokine secretion between boys and girls.

Conclusions: This is the first description of IL4 and IL13-producing ILC2s in cord blood. Cord blood ILC2s showed a greater capacity of producing IL13 rather than IL4. In addition, cord blood from boys had more ILC2s than girls, which is in keeping with previous reports of an increased Th2 response in boys compared to girls.

### M. PEDIATRIC PULMONOLOGY IN DEVELOPING COUNTRIES

#### #M24 - ACCESS TO THERAPY IMPROVES LUNG FUNCTION IN ASTHMATIC CHILDREN IN A LOW-MEDIUM INCOME COUNTRY

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Background: Asthma is a well-known and researched condition, but few of these studies are done in low- and middle-income countries.

Aims and objectives: To assess the level of asthma control and the evolution of asthma control over time. Secondly, to explore whether demographics, type of asthma medication, co-morbidities or exacerbations impacted asthma control.

Material and Methods: Data were collected from a pediatric pulmonologist-led asthma clinic retrospectively over a 5-year period. Assessments for levels of asthma control were based on objective and parental/child symptom reports over the past 3 months. Associations between different time points of lung function parameters were investigated using Pearson correlation coefficients.

Results: Data were available for 189 children with 62% males. Asthma control was acceptable in only 44.9% of patients with the majority (81.0%) on low dose inhaled corticosteroids. When assessing for correlations at different time points for FEV1% predicted; there was a positive correlation between lung functions and duration on asthma therapy; p < 0.05. Exacerbations episodes and uncontrolled asthma had a negative impact on FEV1% predicted; p < 0.05.

Conclusion: The level of asthma control in the current study was lower than that described in the literature. Longer duration on asthma therapy was associated with improved pulmonary functions.

#### #M66 - THE EFFICACY OF NEBULIZED HYPERTONIC SALINE (3%) AMONG CHILDREN WITH MODERATE TO SEVERE BRONCHIOBITIS – A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

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Bronchiolitis is a viral respiratory tract infection characterized by acute inflammation, edema and necrosis of epithelial cells lining the small airways which leads to increased mucus production and bronchospasm. Supportive care remains to be the cornerstone in the management of bronchiolitis and...
this includes oxygen supplementation and hydration. Controversies exist regarding the available treatment in acute bronchiolitis. Recent evidence has demonstrated advantages of the use of inhaled hypertonic saline (HS) in improving clinical scores and shortening the duration of hospitalization. The purpose of this study is to determine whether nebulized 3% HS has a significant effect in shortening the length of hospital stay and in improving clinical severity scores in patients admitted for bronchiolitis. Patients who were diagnosed with moderate to severe bronchiolitis (Modified Woods Clinical Asthma Score of ≥5 on admission) were invited to participate in this study. The study period was from March to October 2015. The sample size was computed using the Open Epi software with a confidence level of 90% and odds ratio of 5. The patients were assigned a MWCAS score on admission and at specified hour intervals until they were fit for discharge. Standard of care in the form of oxygen supplementation and intravenous fluids was given. The patients were randomly assigned to two groups and received either 0.9% normal saline (NS) or 3% HS via oxygen-driven nebulization every 4 hours. 3% HS was prepared by the pharmacist using pure sodium chloride dissolved in distilled water. The investigator, patient and health care providers were blinded from the study. The primary outcome was the length of hospital stay (LOS) expressed in hours. A total of fifty (51) patients were enrolled. Of these, 9 subjects were dropped out due to pneumonia. In an intention-to-treat basis, using a one-tailed two-sample t-test and level of significance alpha of 0.05, the NS group had a mean LOS of 75 hours (SD 33.42) while the HS group had a mean LOS of 56 hours (SD 21.53). The difference in LOS between the two treatment groups was 11.89 hours which was noted to be statistically significant (p value 0.01). Hypertonic saline (3%) is superior over 0.9% saline solution in improving clinical severity scores and in shortening the length of hospital stay in patients admitted for moderate to severe bronchiolitis. No adverse events were noted, hence, it is considered safe for use even in the vulnerable pediatric age group. The raw materials are relatively cheap and readily available, therefore, it can be easily prepared and may be used as an effective adjunct therapy in the hospital setting. There is paucity of data on local studies. We recommend that larger scale studies with bigger study populations be done in order to validate the results of this study and build an extensive database which may be used in future studies.

Results
Forty-two children received home ventilation between 1994 and October 2013 (figure 1). Median age at initiation of home ventilation was 3.5 years (range 0.3 – 17.6) and median time between initiation of ventilation to first hospital discharge was 79 days (IQR 37 to 179). The most common indication was congenital neuromuscular disease (24, 59%). In 33 children (79%), ventilation was initiated during emergency ICU admission. Tracheostomy-assisted ventilation was the most common interface (36, 86%); 6 (14%) were initiated on mask-assisted ventilation, mostly after 2010. Unemployment, substance abuse and incomplete school education were reported in 15 (36%), 10 (24%) and 21 (50%) of caregivers respectively; 8 (19%) families lived in informal dwellings and 9 (21%) had no indoor water or sanitation facilities. Twenty children (48%) were still on home ventilation in October 2013; 7 (16%) were weaned off ventilation and 15 (36%) died. Death was unexpected and equipment-related in 2 (13%) patients; other deaths were related to the underlying condition.

Figure 1. Flowchart study population

Conclusion
Pediatric home ventilation in South Africa is feasible despite difficult socioeconomic circumstances. Survival outcome was comparable to high income countries. However, successful home ventilation requires high level of psychosocial support and interventions.

Going forward:
Mask-assisted (MAV) and polysomnography have become more accessible and affordable in the past few years. Neuromuscular patients are being initiated earlier on MAV. Follow up analysis documenting similar outcomes is being planned. Data that document improved survival, fewer admissions and fewer complications will be useful to convince health authorities to support and budget for pediatric home ventilation programs in South Africa.

#M78 - HOME VENTILATION IN SOUTH AFRICAN CHILDREN: FEASIBILITY, OUTCOME AND SOCIOECONOMIC INFLUENCES

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2. Paediatric Pulmonology, Red Cross War Memorial Children’s Hospital and University of Cape Town — Cape Town, South Africa
3. Division of Paediatric Critical Care, Red Cross War Memorial Children’s Hospital; Department of Paediatrics and Child Health; University of Cape Town — Cape Town, South Africa
4. Paediatric Pulmonology, Red Cross War Memorial Children’s Hospital; Department of Paediatrics and Child Health; University of Cape Town — Cape Town, South Africa

Background
The feasibility of pediatric home ventilation in low income settings is unknown. Poor socioeconomic circumstances and poverty are common in such settings and perceived to be barriers to successful home ventilation. Pediatric home ventilation has escalated rapidly in high income countries but is underreported and underfunded in low-middle countries.

Methods
A retrospective chart review was undertaken covering the past 20 years of the Breatheasy programme at the Red Cross War Memorial Children’s Hospital in Cape Town, South Africa, a low-middle income country without polysomnography or home-based nursing care services. Data collection included demographics, socioeconomic aspects, and clinical information and survival outcomes.

#M86 - UNEXPECTED FINDINGS IN AN OPEN LUNG BΙOΣΥΠΙΟΥ IN A MIDDLE-INCOME COUNTRY

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2. Anatomical Pathology, Stellenbosch University — Cape Town, South Africa
3. Cardiothoracic Surgery, Stellenbosch University — Cape Town, South Africa

Introduction
South Africa is a middle-income country (MIC) with a large young population and a high incidence of HIV and tuberculosis. In these circumstances, infectious causes of diffuse lung disease (DLD) more likely overshadow non-infectious causes. This hypothesis has not been tested in a MIC. Open lung biopsy (OLB) is the gold standard for diagnosing DLD when non-invasive diagnostic techniques fail to establish a definitive diagnosis.

Pediatric Pulmonology
Aim: The aim of this study is to determine the diagnostic yield of OLB in children with undiagnosed DLD and compare the findings in HIV-infected to those in HIV-uninfected children.

Method: This retrospective descriptive study was performed in the Tygerberg Children’s Hospital, a tertiary care hospital in the Western Cape, South Africa, serving approximately 2 million people (HIV prevalence = 15%; TB incidence = 400/100000 children per annum).

Included were all children (1 month to 13 years) requiring an OLB from January 2004 to June 2014. The cases were identified from databases of the PICU, pulmonology unit and pathology reports. Included were 2 groups of children: Group 1 being ward patients with oxygen dependent DLD, Group 2 being infants and children ventilated for hypoxic pneumonia, not responding to therapy. In both groups OLB was performed via a mini-thoracotomy under general anesthesia if a diagnosis remained uncertain after extensive investigation including CT chest.

Results: The study included 51 children, median age 6.3 months, median mass of 6.3 kg, with 61% severely malnourished. Of the 86% children tested for HIV, 30% were HIV-infected, 58% HIV-uninfected and 12% HIV-exposed at birth but remained uninfected. Eight of the 13 HIV-infected children were receiving antiretroviral treatment.

The diagnostic yield of OLB was 86% (n = 44) which was significantly higher in HIV-infected compared to HIV-uninfected children (77% vs. 48%) (p = 0.01)).

Pneumonia was the commonest diagnosis (n = 25) (57%) with common agents being viral (28%), cytomegalic virus (CMV) (20%), Pneumocystis jiroveci (PJP) (12%), and a combination of CMV and PJP (12%). In the HIV-infected and HIV-exposed children, an infectious agent was more common than in HIV negative children. (83% vs. 44%) (p = 0.01)). There was no difference in diagnosis between group 1 and Group 2. Previous undiagnosed TB (n = 5) (10%) occurred equally in HIV-infected and uninfected children.

Non-infectious causes of DLD (n = 5) (10%) were: Idiopathic pulmonary hemosiderosis (n = 2), Congenital lymphangiectasis (n = 1), Sarcoidosis (n = 1) and Langerhans cell histiocytosis (n = 1). Complications occurred in 12%; equally in the HIV-infected and uninfected children.

No mortality was associated with OLB. Conclusion: OLB had a diagnostic yield of 86% in MIC proving to be an extremely useful diagnostic tool in HIV infected and uninfected children and diagnosed unsuspected TB and non-infectious DLD in 22%. OLB should be more widely implemented in MIC.

#M115 - POST-INFECTIOUS BRONCHIOLITIS OBLITERANS: DIAGNOSTIC AND THERAPEUTIC DIFFICULTIES IN TUNISIAN CHILDREN

Hamouda S.1, Belladi I.1, Khalsi F.1, Ben Romdhane M., Tinsa F., Boussetta K.1, Child Department B, Bechir Hamza Children’s Hospital – Tunis, Tunisia

Introduction: Post-infectious bronchiolitis obliterans (BO) is a rare but serious condition. It is often misdiagnosed and its management is not codified. We report four cases of pediatric BO. Methods: In our retrospective study, patient data were collected from medical records in 2015. Clinical, paraclinical and outcome data of the disease were analyzed for each child. Results: The mean age of our four patients was 20 months. They presented an initial severe viral pneumonia, due to the influenza virus in two cases and continued to demonstrate severe obstructive respiratory events which did not respond to bronchodilators. They were oxygeno-dependent. Further investigations (sweat test, immune explorations and echocardiography) were normal. Chest CT scan showed a mosaic perfusion in all cases. The diagnosis of post-viral BO was made. The treatment consisted of high-dose corticosteroids, azithromycin and long-term oxygen therapy. An improvement was observed in two cases. One patient continued to have serious exacerbations and another chronic respiratory failure. Conclusion: Although the diagnosis of post-viral BO in children is well defined, it remains difficult in the absence of virus isolation. The therapeutic resources are insufficient to overcome severe obstructive exacerbations.

#M116 - PULMONARY ALVEOLAR PROTEINOSIS: A DOUBLE ROLE FOR THE BRONCHOALVEOLAR LAVAGE IN A RARE DISEASE IN TUNISIA

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1. Child Department B, Bechir Hamza Children’s Hospital – Tunis, Tunisia
2. Department of Anesthesia and Intensive Care, Bechir Hamza Children’s Hospital – TUNIS, Tunisia
3. Intensive Care Department, Bechir Hamza Children’s Hospital – TUNIS, Tunisia

Introduction: Pulmonary alveolar proteinosis (PAP) is a rare lung disease in children. The bronchoalveolar lavage (BAL) has a diagnostic and a therapeutic role. We describe its benefits in two pediatric PAP cases managed in the Children’s Hospital of Tunis.

Methods: In our retrospective study, patient data were collected from medical records in 2015. Clinical, paraclinical and outcome data of the disease were analyzed for each patient.
RESULTS: The first patient was three months old and presented with oxygen-dependent persistent pneumonia. The second patient was nine months old and presented with recurrent respiratory tract infections in the second case. Thoracic imaging revealed diffuse alveolar and interstitial lesions. BAL showed PAP. The etiological investigation was negative, suggesting a primitive origin in the two cases. On follow-up, the first patient was cured after four therapeutic BAL. Eight therapeutic BAL were performed in the second patient. At the age of four years, she has a failure to thrive and is dependent on oxygen. Her chest CT scan lesions are stable.

Conclusion: The only effective treatment for PAP remains the therapeutic BAL, an invasive procedure requiring close multidisciplinary collaboration.

#M118 - OBSTRUCTIVE SLEEP APNEA SYNDROME REVEALED BY NEUROLOGICAL COMPLICATIONS IN TUNISIAN CHILDREN

Hamouda S., Khalsi F., Belhadi I., Ben Romdhane M., Tinsa F., Boussetta K.
Child Department B, Bechir Hamza Children’s Hospital – Tunis, Tunisia

Introduction: Obstructive sleep apnea syndrome (OSAS) is characterized by an irregular sleep snoring with breathing pauses responsible for sleep architecture changes shown in polysomnography. Its neurological manifestations include behavioral disorders and academic difficulties. We report in two pediatric cases, a rare revelation of this syndrome: axonic seizure.

Methods: In our retrospective study, patient data were collected from medical records in 2015. Clinical, paraclinical and outcome data of the disease were analyzed for each child.

Results: Our two patients were six years old and 20 months old. The first presented a generalized seizure while sleeping. The second had a hypotonic seizure and coma during two days. Chronic snoring history was found in both cases. Polysomnographic recordings showed a high apnea-hypopnea index. Echocardiography was normal. A tonsillectomy was performed and the outcome was favorable with weight gain, better sleep quality and cognitive behavior.

Conclusion: Although common, OSAS remains unknown. Its screening must be systematic in children with sleep snoring to avoid its complications.

#M121 - PULMONARY TUBERCULOSIS IN TUNISIAN INFANTS: A CONTINUOUS CHALLENGE

Hamouda S., Belhadi I., Khalsi F., Ben Romdhane M., Tinsa F., Boussetta K.
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Introduction: Pulmonary tuberculosis (TBC) is rare in infants and its diagnosis is difficult. We study its special features through five observations.

Methods: In our retrospective study, patient data were collected from medical records in 2015. Clinical, paraclinical and outcome data of the disease were analyzed for each infant.

Results: Our five patients, aged seven months on average (3–18 months), were hospitalized for chronic cough and fever in 4 cases, and for lameness associated with cervical lymphadenopathy in one case. Adult index case was reported in two cases. The imaging revealed a severe pulmonary TBC in one case, pulmonary and mediastinal TBC in three cases (including a tumor-like shape), and disseminated TBC in one case (including tuberculous lymphadenitis, arthritis, osteomyelitis and meningitis). The average diagnostic delay was two months (28 days – 11 months). The tuberculin skin test and gastric aspirate were positive in one case. Bronchoscopy showed caseum in one case. Epitheloid cell granuloma was found in two cases. On follow-up, one patient has hearing sequelae, and another has diffuse bronchiectasis.

Conclusion: Screening and early diagnosis of TBC are needed in children especially in infants to prevent lesion dissemination.

#M127 - POST-INFECTIONOUS BRONCHIOLITIS OBLITERANS: A REVIEW OF TWO CASES.

Tinsa F., Khalsi F., Hamouda S., Belhadi I., Ben Romdhane M., Brini I., Boussetta K.

CONCLUSION:

- The only effective treatment for PAP remains the therapeutic BAL, an invasive procedure requiring close multidisciplinary collaboration.

- Obstructive sleep apnea syndrome (OSAS) is characterized by irregular sleep snoring with breathing pauses responsible for sleep architecture changes shown in polysomnography.

- Neurological manifestations of OSAS include behavioral disorders and academic difficulties.

- In our experience, OSAS was revealed by a rare neurological manifestation: axonic seizure.

- Two pediatric cases were studied, with favorable outcomes in terms of weight gain, sleep quality, and cognitive behavior.

- Pulmonary tuberculosis (TBC) is rare in infants, and diagnosis is difficult due to its gradual presentation.

- In our study, five infants were hospitalized for chronic cough and fever, with disseminated TBC in three cases and tuberculosis lymphadenitis in another.

- The average diagnostic delay was two months.

- Bronchoscopy showed caseum in one case, and epitheloid cell granuloma in two cases.

- The only effective treatment for TBC in infants remains the therapeutic BAL.

N. MISCELLANEOUS

#N43 - RECURRENCE IN ACUTE RESPIRATORY FAILURE IN CHILDHOOD

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Tracheomalacia consists in a failing shape of the tracheal cartilaginous support. Reasonably, this condition has been found in almost 30% of cases who underwent a bronchoscopic procedure. Moreover diagnosis is achieved only incidentally in case of mild presentation and lacking usual signs and symptoms. Chiari malformation (CM) is a congenital or acquired herniation of the cerebellum through the foramen magnum (small posterior fossa condition). Different forms are described on the basis of length extension: Type 1 CM is indicated as the isolated protrusion of the cerebellar tonsils of 5 mm or more. Although this condition in many cases is asymptomatic, it can determine headaches, ocular and oto-neurologic disturbances, lower cranial nerve signs, ataxia or spasticity; onset occurs usually in the third decade of life, inheritance recurs in 10–15% of cases.

Clinical description

We describe a 20-month male baby born prematurely (30th wk) from twin birth who required mechanical ventilation for some days from birth in addition to exogenous surfactant administration before he was finally discharged, eight weeks after, in healthy condition. After only a few months, there appeared wheezing, recurrent vomiting, disturbed sleep, respiratory difficulties with increasing frequency and needing many hospital visits culminating, at the age of 11 months, to pediatric reanimation unit because...
of severe RDS and PNX. On this occasion, the patient underwent bronchoscopy, after curare, which resulted negative. A new episode of acute and severe RDS followed after a few months: a new bronchoscopy, in a spontaneous breathing setting, revealed severe tracheal lumen occlusion (90% or more) along the entire tracheal tract. Tracheostomy restored healthy spontaneous breathing. Subsequently, recurrent vomiting, continuous sleep disorders (until 27 hr of central apneas), downward displacement below 16 mm of cerebellar tonsils (at MNR), all of these problems, consistent with type 1 CM, necessitated surgical enlargement of the foramen magnum. After this sole measure, complete and quick regression of the entire symptoms was observed. The twin, healthy until 20 months of life, also presented a totally silent mild (less to 3 mm) herniation of cerebellar tonsils.

Discussion and Conclusions

The above-described clinical case raises interest for certain original aspects. The rare association between rare diseases in a premature twin newborn resulted in determining the origin of a severe RDS. The illness story is characterized by a very early onset of Type 1 CM despite of common reports and, at the same time, for the familiar recurrence of Type 1 CM. In fact, mentioned in this case regarding both twins. Tracheomalacia, maybe itself a complication of prematurity, is a cause of acute life-threatening that reported, in this case regarding both twins. Tracheomalacia, maybe itself a complication of prematurity, is a cause of acute life-threatening that necessitates only spontaneous maturation of cartilaginous rings allowing normal respiration in spite of any treatment and for which diagnosis is apparently very simple and, when necessary, require the same resulting treatment.

#N50 - RARE BRONCHO-PULMONARY CHANGE IN THE COURSE OF SEVERE PERSISTENT RDS IN A PRETERM NEWBORN.

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For a correct respiratory management, the most important step during neonatal ventilation, particularly in preterm babies, is weaning and tube removal in order to minimize complications. Because useful tests in the attempt to indicate readiness for extubation are scant, this field remains a case of trial and error. Extubation failure occurs in almost one third of attempts before a successful accomplished event. Sometimes it occurs despite resolution of primary ills due to prematurity and primitive surfactant deficiency. In these cases, a significant key role may be played by unrecognized additional conditions that can explain warning of respiratory pattern and unsuccessfully extubation. Many pulmonary diseases, such as primary unresolved diseases and broncho-pulmonary dysplasia, reasonably represent major causes of extubation failure.

Case Report

We describe the clinical case of a 32 wks female preterm who received intubation and surfactant administration at birth because of a severe RDS. She was then assisted for few days by SIMV ventilation before extubation. Routine echocardiography examination revealed a slight significant PDA and wide ostium secundum patency. At 38th day of life, the patient needed again to be intubated and moreover received surfactant due to a rapidly deteriorated respiratory profile and severe RDS with a wide opacity at the right lung with mediastinal retraction and thus, at chest CT, large atelectasis involving the same district; a coexisting less extensive atelectasis affected the left lung. The entire radiologic observation, explained as a complicated pneumonia, was treated with Meropenem and Amikacin (BAL-positivity for Serratia pn). Cyclic lung selective instillations with Poractant-alpha (Pulmozyme) were given as rescue-support. A following bronchoscopy resulted as doubtful regarding an extrinsic compression on the left main stem bronchus and the unresponsive RDS exhorted us to perform a chest Anglo-CT that finally diagnosed intralobar pulmonary sequestration associated with left-sided bronchial isomerism.

Conclusions

Intralobar pulmonary sequestration represents an uncommon congenital anomaly (0.2–6.4 % of cases) including a non-functional and dysplastic lung area non-communicating with the tracheo-bronchial tree and, at the same time, receiving blood supply by systemic circulation. When symptomatic, this condition can explain recurrent infections in the sequester segment. Early resection of the sequestration seems as a preferred and elective treatment. Bronchial isomerism, on the other hand, is a condition more difficult to explain but almost never causes symptoms. Many types of bronchial isomerism have been described. In the simple isolated form, the bronchial anatomy on the right side reflects a mirror image of the left side. In this case, a rare association of two uncommon congenital anomalies led to a difficult case management, fulfilling wide fields of interests (neonatologists; bronchoscopists; radiologists; pediatric surgeons).

#N77 - PEDIATRIC FLEXIBLE BRONCHOSCOPY IN EGYPT: 3-YEAR EXPERIENCE

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BACKGROUND: Flexible airway bronchoscopy is an accepted and frequently performed procedure in the evaluation of children with known or suspected airway and lung parenchymal disorders.

METHODS: Between 2012 and 2015, a retrospective analysis of 134 flexible bronchoscopies was performed in the Children’s Hospital, Cairo University, with regard to demographic profile, clinical and radiological presentation and diagnostic indication. The results were analyzed on the basis of bronchoscopy inspection, conclusion and future recommendations.

RESULTS: Of 134 patients undergoing bronchoscopy, 38% had foreign body (FB) in the airways although only 7.5% of patients had recalled a previous history of FB aspiration (15.6% in the upper airways, 52% in the right side, 31.3% in the left side), 14.1% had upper airway abnormality, 26.8% had post inflammatory changes, 56.7% had right-sided abnormality, 55.2% had left-sided abnormality, bronchoalveolar lavage (BAL) was performed in 30.6% of patients, FB was successfully removed in 15.6% of patients and further cardiothoracic intervention was needed in 29.8% of patients.

CONCLUSION: Flexible bronchoscopy is effective for diagnostic and sometimes therapeutic purposes of problems in the upper and lower respiratory airways in children, with a high success rate.

KEY WORDS: flexible bronchoscopy, foreign body

#N92 - PREVALENCE OF ACIDIC GASTROESOPHAGEAL REFLUX IN INFANTS AND YOUNG CHILDREN WITH RESPIRATORY MANIFESTATIONS REQUIRING HOSPITAL ADMISSION

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Introduction

Gastroesophageal reflux disease (GERD) remains one of the most common diagnoses made by pediatricians. Most cases of pediatric gastroesophageal reflux are diagnosed based on the clinical presentation. Conservative measures can be started empirically. However, if the presentation is atypical or if therapeutic response is minimal, further evaluation is warranted.

Objectives: To evaluate the frequency of acid (AR) and weakly acid reflux (WAR) among children presenting with recurrent or persistent respiratory symptoms (choking, wheeze, cough) and requiring hospital admission using combined pH/MII measurement.

Patients and methods

Sixty children with suspicion of GER presenting with combination of different symptoms: unexplained cough, wheezing and choking and requiring hospital admission in the Pediatric Hospital, Cairo University, underwent 24 hours combined pH/MII measurement using Sandhill Technologies.

Results

Patients were divided into 3 groups according to their age: 43 patients (58%) from 1-12 mo, 12 (20%) from 13-36 mo, and 5 (8.3%) aged more than 37 mo. 45% presented with respiratory manifestations and 53.3% with both respiratory and GIT manifestations showing cough in 93.3%, choking in 86.7% and wheezes in 75%.

Pediatric Pulmonology
A total of 4846 GER episodes were detected. 1776 (36.6%) were acidic and 2902 (59.8%) weakly acidic and only 209 (4.3%) were weakly alkaline. In the whole study group, the median number of weakly acid reflux events per patient was 39 (55.7%) which was higher than that of acid reflux events 24.5 (35%).

When children were divided in the three age groups, a progressive decrease in the weakly acid reflux-to-acid reflux occurrence was detected with increasing children age being (65% to 31%) in infants, while (45% to 51%) in toddlers and (28% to 70%) in older children.

Conclusion
Most of the presenting respiratory manifestations requiring hospital admission were mainly associated with acidic and weakly acidic reflux episodes.
In spite of the increased percentage of the weakly acidic reflux to acidic reflux, a progressive decrease in this ratio was detected with increasing children age.

#N111 - CONTINUOUS TACHYPNEA AS A RARE SYMPTOM IN AN INFANT WITH MOEBIUS SYNDROME

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INTRODUCTION
Moebius syndrome is a rare condition that is classically defined as a combination of congenital non-progressive facial and abducens nerve palsy. The clinical phenotype of Moebius sequence can be associated with increased and extended cranial nerve, oropharyngeal and musculoskeletal involvement.
The etiology is controversial and is believed to be due to disruption of the primitive vascular supply of the cranial nerve nuclei during embryological development.

AIM:
To recognize continuous tachypnea as a rare symptom in patients with Moebius sequence.

METHODS:
A case of a 4-month-old girl diagnosed with Moebius syndrome with continuous severe tachypnea is described.

RESULTS:
A girl was born term and presented with unilateral facial and abducens nerve palsy, bilateral club feet, axial hypotonia, hypoplasia of the mandible and palatoschisis. She developed respiratory failure shortly after birth with a need for mechanical ventilation. A tracheostomy was performed at the age of 1 month because of persisting respiratory distress and severe supraglottic edema. Brain MRI did not show any abnormalities. At the age of 3 months, she was admitted at a rehabilitation centre. During the whole stay, there was continuous severe shallow tachypnea (respiratory rates between 100 and 150 per minute), with paleness and sweating, but with normal blood gas values. After 1 month, she was transferred to the pediatric intensive care unit for mechanical ventilation because of progressive respiratory insufficiency with hypercapnia due to a respiratory tract infection. After the acute phase, chronic bilevel positive pressure ventilation was initiated because of persistent tachypnea. After initiation of chronic ventilation, tachypnea is intermittently present without signs of increased effort.

DISCUSSION:
It is known that pacemaking function of the respiratory center can be increased in patients suffering from medullary lesions (more specifically nucleus solitarius), if the ventrolateral respiratory group of the respiratory center is spared. We suggest that in patients with Moebius sequence, not only involvement of the cranial nerves but extension to broader regions can be seen, which can explain continuous tachypnea in this case.

CONCLUSION:
Continuous tachypnea can be a rare cause of Moebius syndrome. It can be explained by involvement of the respiratory centre. This can be an indication for home ventilation.
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