wheeze. The susceptibility to HRV-induced bronchiolitis and wheezing seems to be linked to predisposition since it is often associated with atopic dermatitis, blood eosinophilia and family history of asthma/atrophy [9,10].

**Viral infections and asthma exacerbations**

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

**Viral infections and allergic sensitization**

Is it allergic sensitization that favors viral infection or is it viral infection that favors wheezing/asthma inception and exacerbation? Murine para-influenza LRTI models suggest that the viral respiratory infection can induce allergic predisposition upregulating the high-affinity IgE receptor on lung antigen presenting cells, producing Th2 inflammatory cell and inflammatory mediators and increased immune response to inhalant allergens [2,9]. The importance of the viral infection as the initial event (“the first hit”) to favor airway allergic inflammation may therefore involve: a) the disruption of the airway epithelial barrier with enhanced allergen exposure, related to the viral-induced injury, and b) the role of the innate immunity response to the virus in modulating the interaction between viral infection and inhalant allergen exposure [2]. On the opposite, viral infections may be favored by allergic sensitization since the Th2 bias, which is the characteristic of the immune responses against allergens in atopic individuals, may modify the host antimicrobial defenses and thus attenuate the ability to fight viral infections via immune deviation.

Viral LRTI may be a marker for atopic predisposition and not the cause of future wheezing and asthma. In the Childhood Origins of Asthma (COAST) study, allergic sensitization to aeroallergens was identified as a significant risk factor for viral induced wheeze but, having viral wheeze did not increase the risk of developing allergic sensitization [10]. It is probable that these 2 scenarios, either bronchiolitis as a cause or a marker for asthma theories, are not mutually exclusive.

**Conclusion**

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

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**IMPACT OF RHINITIS ON ASTHMA IN CHILDREN**

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Allergic rhinitis is one of the most common chronic diseases in children, with prevalences ranging from 6% in 3-yr olds to 25-24% in adolescents.1,2 Despite its high prevalence, surprisingly few studies have addressed the long-term treatment of the disease, or its impact on and relationship with asthma in children. It has long been recognized that asthma and allergic rhinitis frequently coexist, due to their similarities in anatomy, physiology and immunopathology. Conflicting results have been published on the relationship between allergic rhinitis on the one hand and morbidity of asthma in children on the other. Very few studies have assessed the impact of allergic rhinitis on asthma control.

In an Italian study comparing 200 children with allergic rhinitis to 150 normal control subjects, the rhinitis children had a mean FEV1%predicted of 89%, compared to 100% in normal controls.3 Conversely, in a series of 203 children with asthma from our centre, 157 (76%) had symptoms of allergic rhinitis, but only half of these children had been recognized and treated as such by a physician.4 Asthma control was considerably poorer in asthmatic children with coexisting allergic rhinitis than in those without allergic rhinitis: the odds ratio of having an asthma control questionnaire score in the uncontrolled range was 2.74 (95% CI 1.28-5.91, p=0.0081).5 The recommended long-term treatment for persistent allergic rhinitis is nasal corticosteroids, because these drugs effectively control nasal and systemic allergic rhinitis symptoms in the large majority of affected children. One year treatment with nasal corticosteroids is associated with a significant, but small (0.27±0.45 cm) reduction in height growth in children,6 similar to treatment with inhaled corticosteroids in children with asthma.

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**II. TOPIC SESSIONS**

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**IMPACT OF RHINITIS ON ASTHMA IN CHILDREN**

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ROLE OF FOOD ALLERGY IN CHILDHOOD RESPIRATORY SYMPTOMS AND DISEASES

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

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

Although there is firm evidence of a link between food allergy and asthma, food allergy is an important factor affecting asthma control only in a minority of children with asthma. Therefore, dietary restrictions are not necessary unless food allergy is confirmed by objective testing. For those children with food allergy as a precipitating cause of their co-existing asthma, asthma exacerbations tend to be of sudden onset. In highly sensitive individuals, symptoms may be precipitated by exposure to aerosolized food proteins (7-8). The exact mechanisms of how food allergens may precipitate asthma are not clear. It is possible that small amount of allergens may reach the airways during mastication and swallowing. The allergic proteins can also elicit an effect in the lower airways via a systemic inflammatory response similar to the response to pollens in allergic rhinitis and asthma (9).

In conclusion, for children presenting with poorly controlled asthma, evaluation of possible co-existing food allergy is needed. A detailed relevant history and objective testing such as skin-prick test or measurement of serum-specific IgE are necessary to determine if dietary restrictions are needed. For patients presenting with abrupt onset of severe bronchospasm along with other systemic symptoms, proper evaluation and treatment for possible anaphylaxis are warranted.

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Asthma is both under- and over-diagnosed, but there are no clear data suggesting that there is an asthma “epidemic”. In many countries, death from asthma has decreased over the past two decades due in part to better recognition and therapy. On the other hand, about a third of adults with physician diagnosed asthma are misdiagnosed. Incorrect diagnosis is more common in children, the elderly and obese adults who use emergency department resources for the treatment of dyspnea.

**Myth #4:** Chronic cough is usually due to asthma

Although there is a phenotype of asthma that has been referred to as cough variant asthma or cough dominant asthma (my preferred term), this appears to be associated with airway mucus hypersecretion and poor response to beta-agonist bronchodilators. Chronic cough as a sole symptom of childhood asthma is rare, representing less than 4% of children with cough that persists for more than three weeks. Furthermore, it has been demonstrated that neither inhaled salbutamol nor inhaled steroids benefit most children with chronic cough.

**Myth #5:** Dyspnea with exercise is usually due to asthma

Sear and colleagues studied 52 children with poorly controlled “exercise induced asthma” but found only eight of these (15.4%) had greater than a 10% decrease in FEV1 with exercise. These data are consistent with studies by Weinberger and colleagues showing that a much larger percentage of these children with exertional dyspnea are unexplained, have vocal cord dysfunction or habit cough, or no abnormalities to testing.

**Myth #6:** Rapid inhalation pulls medication deeper into the lungs

Optimal deposition of aerosols from a nebulizer or pressured metered dose inhaler (pMDI) requires slow inhalation followed by a breath hold. Rapid inhalation leads to impaction of the aerosol on the oral pharynx and swallowing of drug, rather than inhalation. Similarly a child that is crying has a very rapid inhalation and a long exhalation that dramatically decreases medication deposition in the airway.

**Myth #7:** Jet nebulization of salbutamol is more effective than pMDI delivery in the emergency department (A&E)

There have been many studies demonstrating that using a pMDI and valved holding chamber (VHC) to treat acute asthma in children, even those with acute life threatening asthma and hypoxemia, is at least as effective in providing relief and much faster and safer than administering salbutamol using a jet nebulizer. Six randomized controlled trials in nearly 500 children found that beta-agonist by pMDI and VHC are more effective than nebulized therapy for decreasing admission rate and symptoms score and lead to shorter stays in the emergency department.

**Myth #8:** When giving an aerosol to a small child, the dosage must be based on ideal body weight

Small children have smaller airway surface area and thus a clinician may surmise they need a lower dose of medication to achieve the same benefit. However, small children have a more rapid respiratory rate, lower tidal volume, and smaller airways leading to less aerosol getting to the lower respiratory tract which may be interpreted as a need for a greater amount of medication to be administered. Fortunately, studies have shown that these two factors balance out well and thus the dosage of medication to be administered to infants, children, adolescents, and adults should be the same when using either pMDI or dry powder inhaler.

**Myth #9:** When using a nebulizer small children should always inhale using a mask

Although children under the age of three years are often unable to form a seal on a mouthpiece and coordinate inhalation, most children over age 3 who are competent with drinking from a straw, can inhale medication by swallowing of drug, rather than inhalation. Similarly a child that is crying has a very rapid inhalation and a long exhalation that dramatically decreases medication deposition in the airway.

**Myth #10:** People with asthma should not have pets; and as a corollary, a crying child will pull aerosol deep in the lungs

Although it is possible to develop allergies to foreign proteins in the dander of some dog breeds are hypo-allergenic.
protective effect. All dogs, regardless of size or breed, shed skin and dander as foreign proteins and thus no breed of dog is “hypoaллерergic.”

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

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

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

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

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

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

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

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

Conclusion

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

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ASThma PHENOTYPING IN CHILDREN: CLINICAL APPLICATIONS AND IMPLICATIONS

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Summary

Asthma is a heterogeneous condition characterized by differences in clinical presentation, such as age of onset, natural history and severity of symptoms, and by its association with intermediate traits, including atopic sensitization and airway physiology. Using these observable characteristics, asthma can be disaggregated into a number of different phenotypes. This leaves a question about whether these descriptive phenotypes are true manifestations of distinct biological processes (endotypes) or whether they arise from stochastic variations in asthma presentation in person, place and time. If the former, they have the potential to contribute to understanding of pathways of asthma inception and asthma natural history, informing responses to treatment. These open the possibilities of primary prevention and tailored approaches to treatment or personalised medicine for asthma in children.

A substantial proportion of asthma has its onset during childhood. Therefore, longitudinal studies beginning at birth or during early childhood have made a major contribution to investigating factors in early life that influence asthma onset and natural history. It is generally acknowledged that asthma develops as a consequence of interactions between genetic susceptibility and environmental exposures and there is some evidence in support of this for specific pathways, e.g. endotoxin exposure and CD14 gene polymorphisms.1 However, despite considerable research firepower being directed towards identifying the causes of asthma, they remain largely unknown. It seems unlikely that any important risk factors have evaded detection, so definition of the end-point may be part of the explanation for the difficulties in detecting the drivers of the increase in asthma prevalence seen in most developed countries. If there are several asthma endotypes manifesting as phenotypic variation, it is likely that these will have individually specific gene-environment interactions underpinning them. Disaggregating asthma phenotypes may help to identify these previously hidden associations when asthma is considered as a unification of all of its component phenotypes and endotypes. Novel statistical approaches to longitudinal2,3 and multieategorical4-5 analysis of asthma-related outcomes have identified sub-types of asthma but, to date, there is little convincing evidence that any of these is differentially associated with putative novel risk factors for asthma.6,7 Therefore, although different clusters of symptom progression over time or of symptoms with other measurable outcomes can be delineated, this exercise has been rather limited in identifying new asthma endotypes.

One of the inherent difficulties in translating phenotypes derived from longitudinal epidemiological data into clinical practice is that, although these are modelled on prospectively collected data, they are by their nature post hoc analyses and cannot be constructed without knowledge of future outcomes. This difficulty is encapsulated in the concept of predicting which infants and young children who wheeze will have persistence or resolution of their symptoms by school-age; when asthma is usually clinically apparent. Approaches to this problem have included the construction of risk-prediction tools6-10 based largely on clinically observable characteristics but their clinical utility in predicting the outcome for the individual is questionable. As a high proportion of childhood asthma is associated with wheeze that begins in the pre-school years, the European Respiratory Society convened a task force that reported in 2008 on the definition and treatment of pre-school wheeze; classifying wheezing as episodic (viral) wheeze and multi-trigger wheeze; the latter more likely to acquire a diagnosis of asthma and possibly more likely to respond to anti-inflammatory treatment.11 However, it has become clear that these rather artificial divisions based on triggers do not map to distinct biological disease processes and they are not stable over time.12 Patients moving in both directions between groups as acknowledged in a review of the original task force report in 2014.13 Phenotype-directed treatment in this age group is still limited by considerable uncertainty about phenotypic classifications. Recently, an attempt has been made to reconcile epidemiological and clinical approaches to asthma phenotyping in early childhood. In the multicentre Protection against Allergy Study in Rural Environments (PASTURE), latent class modelling of longitudinal wheeze reports identified a similar pattern of phenotypes13 to those described earlier in ALSPA2 and PIAMA.3 The authors of this study also classified phenotypes using clinically-relevant descriptors. The LCA approach has high sensitivity and specificity for clinical outcomes and the combined approach identified a clinically-relevant subgroup with high symptom load and decreased lung function but who had not been diagnosed or treated for asthma. This suggests the LCA phenotypes had reasonable external validity but it is interesting to note that the wheezing histories of the clinical phenotypes were indistinguishable from each other during the first two years of life. Therefore, the predictive value of early wheezing...
history alone does not seem likely to be a useful indicator of future clinical disease phenotype.

There is clearly a need for early indicators of specific disease phenotype if the goal of tailoring treatment to individual pathophysiological processes (personalised medicine) is to be realised in this field. Atopic status may be one of these but the concept of the ‘atopic march’ has recently been called into question and atopy, in the same way as asthma, needs to be considered as more than a binary variable. However, using advanced statistical modelling, different patterns of atopic sensitisation show associations with different clinical asthma outcomes. The emerging possibility however is to use biomarkers of disease endotypes. There is good evidence that asthma has a high heritable component and a number of genetic variants (SNPs) have been identified in association with asthma, notably at the 17q21 locus near the ORMDL3/SGDMB gene. SNPs in this region are associated with wheeze that begins early and persists through childhood with a strong association with atopy and clinically diagnosed asthma. Knowledge of the influences of genetic variants on asthma inception is starting to challenge established observational epidemiological findings; for example, the relationship between early life antibiotic prescription and asthma can be explained through increased susceptibility to viral infection associated with impaired antiviral immunity and variants at the 17q21 locus. The ability to analyse complex interplay between genetic susceptibility and environmental exposures using advanced statistical and data mining techniques and incorporating other biomarkers, including epigenomic modifications due to environmental exposures, promises to usher in a new era of discovery that can reveal information about the endotypes underpinning asthma’s phenotypic heterogeneity. This is required to develop tractable interventions that can be tailored to individual groups of patients and which may alter the natural history of progression of early wheeze to asthma.

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PRESCHOOL WHEEZE AND WHEEZY INFANT: THE BEST PRACTICE

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

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

There are both anatomical and behavioral challenges

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

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

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

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

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

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AEROSOL THERAPY: NOVEL DEVICES AND DRUGS

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

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

Small volume liquid inhalers have also been introduced, the most prominent among these being the Respimat soft mist inhaler. This device is disposable, with the energy of aerosolization produced by spring compression. Because it takes more than one second to deliver the aerosol at a velocity of approximately 10 m/s, this soft mist is less likely to produce a staccato effect, can improve coordination, and gives a higher efficiency of drug delivery than other liquid inhalers. The dose chamber is small with a volume of 15 μL, limiting the amount of medication that can be given with each inhalation.

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

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

Dry powder inhalers (DPI) have also evolved. There are now DPIs, including the Tudorza Pressair, that give the user feedback on inhalation technique and delivery of medication. There are also active DPIs that have a low plume velocity. These include the Teva Microdose which is piezo driven, the Inspironatic (OPKO), and the Occoris (Team Consulting). These active DPIs disperse powder very much the same way as a pMDI and without the disadvantage of requiring an inspiratory disaggregating flow. Commercially-available engineered particles are also now in use such as the Pulmospheres used to deliver tobramycin DPI. This is a simple inhalation device but the particles themselves are spherical and thus have low surface energy making them easier to disaggregate; and are hollow and porous allowing more sustained delivery of medication. Other novel formulations under development include aerosols with enhanced excipient growth that enables very fine particles to bypass the upper airway but then deposit in specific areas of the lung as they grow in size.

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

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

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

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

Pulmonary hypertension is well treated by aerosol agents, most notably Iloprost which is a prostacyclin analog. Other agents with longer duration of action are also under study.
ASSURING ADHERENCE AND COMPLIANCE WITH AEROSOL THERAPY

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

Aerosol therapy is the mainstay of the management of asthma and cystic fibrosis (CF) in children. For both respiratory disorders, good adherence is associated with improved lung function and fewer respiratory exacerbations. For both respiratory disorders, good adherence is 21-68% lower compared to children who are less adherent.2

Assuring adherence

There are many additional aerosol applications being evaluated including administration of peptides such as growth hormone, and using magnetic targeted aerosol therapy to treat lung tumors. With further improvements in devices, interfaces, and novel drugs, it is very likely that we will see the lung as a portal for drug administration much more commonly in future years.

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S14 Abstract

The lungs are also a portal to the systemic circulation. The first use of an aerosol to treat a systemic disease was aerosolization of insulin in 1925 to treat diabetes. Because of inefficient aerosolization, this never became widely used until the introduction of Exubera by Pfizer, a decade ago. Unfortunately this did not find commercial success. Last year, Alferaza (MannKind) was approved by the FDA for the treatment of diabetes using a small disposable dry powder inhaler called the DreamBoat. There is also a vibrating pump nebulizer by Aerogen that is being used by Dance Pharmaceuticals to deliver aerosol insulin. It is hoped that these more convenient forms may improve the clinical uptake of this therapy.

The Future

There are many additional aerosol applications being evaluated including administration of peptides such as growth hormone, and using magnetic targeted aerosol therapy to treat lung tumors. With further improvements in devices, interfaces, and novel drugs, it is very likely that we will see the lung as a portal for drug administration much more commonly in future years.

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

Aerosol therapy is the mainstay of the management of asthma and cystic fibrosis (CF) in children. For both respiratory disorders, good adherence is associated with improved lung function and fewer respiratory exacerbations.1 In fact, the risk of an asthma exacerbation in children with good adherence is 21-68% lower compared to children who are less adherent.2

Unfortunately, adherence to inhalation medication in children with asthma or CF is sub-optimal and often less than 50%.1,2

There is a wide variation in adherence, both between and within individual patients as well as in time, from day-to-day and week-to-week.3 Also, a variety of adherence patterns and behaviors are seen.3 Some patients use their device more than prescribed, others don’t take any, some start well and subsequently show decreased adherence, others start poorly and then adherence improves.3

Barriers for adherence

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

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

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

Fourth, relationships (family and treatment team) are important for adherence. Children from unhappy families with conflicted relationships are at greater risk of poor adherence.3 The relationship with the CF team can be a motivator for adherence. Finally, psychological factors might be associated with adherence. In asthma, psychiatric co-morbidity is associated with worse medication adherence.5 However, in CF, current data are inconclusive. Optimistic acceptance and hopefulness, as well as worrying about the condition and anxiety disorders have been associated with greater adherence to CF treatment.1

Methods to assess adherence

Several methods can be used to assess adherence to inhalation medication. Subjective measures of adherence comprise patients’ self-reports, questionnaires, daily diaries and physician’s judgment.2 These methods all overestimate adherence due to social desirability bias and inaccurate recall.6 A problem for objective measures, such as pill counting, canister weighing and the use of prescription/dispensing/refill data, is “dumping”. This is the action by which patients try to conceal non-adherence by intentional emptying of the inhaler before study visits and, again, leads to overestimation of adherence. Electronic monitoring devices (EMDs) are the most objective method of adherence monitoring6 and are seen as the gold standard measure.2 EMDs are user-friendly, well accepted by patients, record the exact time that an inhaler is used and are able to detect dumping.6 On the down side, EMDs are costly and prone to software and equipment problems. In addition, use does not necessarily reflect (good) inhalation of medication. EMDs record the exact time that an inhaler is used and are able to detect dumping. This objective insight in the adherence to aerosol therapy can be used to increase treatment adherence as it gives the opportunity to physicians to identify problems and to discuss this with the patient.6 EMDs have become available for both metered dose inhalers (MDI) (e.g. DOSER, MDI Chronolog, MDILog and Smartinhaler), as well as for nebulizers (e.g. Nebulizer Chronolog, Akita and I-neb). The I-neb not only provides objective measurement of adherence, but also coaches the patient to improve inhaler technique by providing positive feedback signals. Positive feedback is given on each inhalation and at the completion of aerosol delivery. The Akita delivery system works in a similar way as the I-neb. Both nebulizers allow monitoring patient adherence to treatment, compliance with correct use and cleaning of the device. Health care providers can use this information to tailor their advice to overcome the patient’s specific barriers to non-adherence and to suit the needs of the individual patient.

Inhalation competence and contrivance

However, even if patients take medication daily, the delivery of drug into the lungs may fail due to an incorrect inhalation technique (competence) or knowing how to use the device effectively but choosing to use it in an inappropriate way (contrivance).7 A poor inhalation technique reduces the amount of deposited drug at the site of action and thus reduces the effects of medication. For this reason, patients need to be carefully instructed into how to use a device effectively and this needs to be repeated several times to ensure the inhalation is performed correctly. In addition, competence needs to be checked at every visit as it is shown that errors often recur within 4-6 weeks after initial training.7 For asthmatic children, it is known that competence related to inhalation therapy is poor. An incorrect inhalation technique is seen in up to 80% of the patients8 and lack of competence is described in all age groups.7 The level of
incorrect inhalation technique and type of mistakes differ per device, depending on the handling that need to be done. Repeated instructions are strongly effective for improvement of inhalation technique. However, even when repeated instructions were given, 10-20% of asthmatic patients still made mistakes. To the best of our knowledge, no studies have been published to date evaluating competence of inhalation medication in patients with CF.

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

How to improve adherence?

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

Summary

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

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Improvement in fitness (training in children and adolescents with asthma usually found an improvement in bronchial asthma, lung function, QoL and BHR, whereas it has long been discussed as to whether physical activity and training (QoL) and BHR be a possible protective factor against asthma development (OR 0.87 (95% CI: 0.77-0.99)) (8).

On the other hand, it has been shown beyond doubt that physical training and meta-analysis including 5 longitudinal and 34 cross-sectional studies showed that the longitudinal studies demonstrated physical activity to be a possible protective factor against asthma development (OR 0.87 (95% CI: 0.77-0.99)) (8).

Myth: Physical activity protects against asthma development

Controversy: Physical activity causes asthma development in athletes

It has been maintained that physical activity may protect against asthma development. However, this is difficult to document, as it requires long term follow-up studies. Rasmussen followed 757 asymptomatic children, aged 9.5 -11 years, for 10.5 years and examined their fitness by measuring maximum workload by cycle ergometer. He found that fitness at the first examination was inversely related to later development of physician-diagnosed asthma and that the risk for development of asthma during adolescence was reduced by 7% by an increase in the maximal workload of 1 W/kg. On further follow-up to 29 years, it was found that the tracking of physical fitness was high from 9 to 29 years, and that the risk of asthma development was reduced by 3% by an increase in maximal workload of 1 watt/ kg at 9 years of age (6). On the other hand, Berntsen reported that 13 year-old children with asthma were as fit as healthy children (7). A systematic review and meta-analysis including 5 longitudinal and 34 cross-sectional studies showed that the longitudinal studies demonstrated physical activity to be a possible protective factor against asthma development (9).

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

Controversy: Physical activity causes exercise-induced asthma

It has long been discussed as to whether physical activity and training improves bronchial asthma, lung function, QoL and BHR, whereas it has generally been acknowledged that physical training improves fitness in asthmatic children. Several systematic reviews and meta-analyses have been performed (10), and their conclusions mostly agree. The effect of physical training in children and adolescents with asthma usually found an improvement in fitness (V’O2max), maximum heart rate and QoL. Lung function was usually not affected, whereas recent reports tend to suggest an improvement in BHR (10).

On the other hand, asthma symptoms induced by heavy physical activity is frequently reported in asthmatic children, and the treatment of EIA is a major objective in most international asthma guidelines. These facts taken together underscore the importance of optimal asthma management in children with asthma to enable them to master EIA and participate actively in physical training activities.

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

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

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

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

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(LR=7.4 for asthma at age 6 years) and PIAMA \(^4\) (score \(\geq 20\) has LR=2.5 for asthma at age 7-8 years).

However, several important issues need to be understood regarding these asthma predictive rules before choosing the optimal approach. Among these five rules only the original API \(^\ast\) is relatively generalizable since it was developed in an unselected ethnically diverse birth cohort. The PIAMA \(^6\) and Isle of Wight \(^7\) include respiratory tract/recurrent chest infections among their many criteria which could misrepresent the reporting of episodes of recurrent wheezing. The PIAMA \(^6\) is more arduous to determine because the many criteria used have different weights. In addition, its generalizability may be reduced since it includes health beliefs and socioeconomic information that may vary between ethnicities. The Isle of Wight \(^7\) suffers from the lack of external validation. The unAPI \(^7\) was also developed in a high risk cohort. Similarly, the mAPI \(^7\) developed by expert opinion for a high-risk cohort was recently validated only in another high-risk birth cohort. \(^7\) In contrast; the original stringent API and the PIAMA prediction rules were validated in different populations.\(^8\)

However, the original stringent API \(^\ast\) is the only asthma prediction rule in which the third (impact) and fourth (implementation) steps of clinical prediction rules are presently being studied. When the original stringent API was compared and correlated with surrogate markers of airway inflammation, such as FeNO used as a minor criteria replacing eosinophil determination in the original API, it showed lower positive LR (1.199) for predictive asthma at age of 4.\(^9\) Recently, when comparing with the API (but replacing eosinophilia by specific IgE), the addition of volatile organic compounds and gene expression improved asthma diagnosis from 60 to 89%. It is well known that eosinophilia is a better predictor of remission of asthma than specific IgE or skin prick test. Finally, an implementation or application value of the original API for therapeutic strategies was recently published.\(^10\)

For clinical use, the original stringent API is simple, inexpensive, noninvasive, and has been well validated. Therefore, clinicians worldwide can use a positive original stringent API to identify at-risk children and educate parents on the importance of asthma maintenance therapy and treatment of flares. Its major strength is its good positive LR (the effect on post-test probability of disease improved significantly), but since its sensitivity is modest it cannot be used to rule out the development of asthma.

More studies are needed to explore the effect of asthma controller medications based on an infant/preschooler’s API status.

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

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

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

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

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

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12. S18 Abstract
   "NOVEL INSIGHTS INTO AIRWAY SMOOTH MUSCLE CONTRIBUTIONS TO ASTHMA: ROLES FOR IGE, IL-8 AND CFTR"

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

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

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

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

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

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

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THE POWER OF UNITY: BRINGING TOGETHER BIRTH COHORT DATA
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Pediatric Pulmonology
Summary
Over the last few decades, it has been increasingly recognised that events in early childhood development could manifest themselves through the lifecourse in the evolution and presentation of a number of non-communicable diseases. One productive approach to the investigation of the early origins of asthma, a relatively common disease that manifests during childhood in a high proportion of cases, has been the longitudinal, prospective cohort study. Several cohorts recruited prenatally or at birth have been assembled to investigate the influences during pregnancy and early life that are associated with asthma and wheezing illnesses in children. These have been very successful in identifying novel risk factors for childhood asthma using conventional observational epidemiology approaches. However, the associations are generally modest at best, not all have replicated and most of the published literature in this field consists of reports from single studies. The problems of cofounding, publication bias and reverse causation in the observational epidemiology literature have been well described. A further issue is that, due to the resource-intensive data collection methods employed in these studies, they are often resource-limited to recruiting limited numbers of participants, compromising statistical power to detect small effect sizes and interactions. Individual birth cohort studies are also inefficient for the study of rare diseases and those with long latencies. Therefore, the concept that at least some of the variance of COPD can be explained by early life influences requires either extrapolation of proxy measures, such as lung function variables, in childhood to adult disease or a different approach to study design that harnesses information from longitudinal studies that have covered different epochs of the lifecourse. Therefore, there are lots of drivers for amalgamating the wealth of data that is banked in cohort studies to maximise their potential for knowledge generation.

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

In the United Kingdom, there are several long-established, population-based, birth cohort studies that are either multidimensional and include respiratory outcomes or which have asthma, allergy and respiratory disease as their core outcomes. Each of these cohorts has particular aspects that makes it unique but all have common goals to discover the causes of asthma and related phenotypes. In 2005, Asthma UK recognised the potential of amalgamating data from these birth cohorts and funded the initial Study Team for Early Life Asthma Research (STELAR) Consortium, comprising the Asthma in Ashford Study, the Avon Longitudinal Study of Parents and Children (ALSPAC), the Isle of Wight Birth Cohort Study, the Manchester Asthma and Allergy Study (MAAS), and the Study of Eczema and Asthma To Observe the influence of Nutrition (SEATON). As these studies were at different stages of gestation, this network enabled the establishment of common objectives and operating protocols to ensure harmonisation of outcome measures at future clinic sweeps. Subsequently, the principal investigators of each cohort have agreed to share data and resources to create the Asthma eLab, a data repository for the unified dataset linked to computational facilities and a scientific social network to support collaborative research in a secure web-based environment. In this way eLab facilitates iterative interdisciplinary dialogue between clinicians, biostatisticians, geneticists and computer scientists to develop and process ideas. The development of a ‘Team Science’ approach backed by a large, harmonised data resource and advanced computational tools, such as machine learning approaches to identifying latent structures in complex data sets, promises to advance discovery and understanding of the early origins of asthma more rapidly and efficiently than any one cohort could manage alone.

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Respiratory disease is the predominant cause of illness, death and chronic disease in children globally. Childhood pneumonia is the predominant cause of death in children under 5 years of age outside the neonatal period. Asthma is the commonest non-communicable disease in children occurring in approximately 15% of adolescents worldwide. Although the Africa childhood population constitutes only around 18% of the global childhood population, the incidence of childhood pneumonia and death is disproportionately high, accounting for almost 40% of deaths worldwide. Further, the prevalence of asthma in African adolescents is higher than the reported global average. The impact of early respiratory illness on child health has not been well studied in African children despite the high prevalence of risk factors for severe disease and the high incidence of disease.

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

pregnancy and childbirth. 1000 mother-child pairs are then followed until children are at least 5 years of age. Biomedical, environmental, psychosocial, and demographic risk factors are longitudinally measured. Environmental exposures (carbon monoxide, particulate matter, dust microbiome, SO2/NO2 and volatile organic compounds) are measured using monitors placed at home visits during the antenatal period and 4-6 months after birth. Maternal and child urine samples are longitudinally collected for urinary cotinine as a biomarker of tobacco smoke exposure. Lung function [tidal breathing measures, multiple breath forced oscillator technique (FOT)] is measured in children at 6 weeks, annually and during LRTI episodes. Analysis of the infant follow-up indicates a high incidence of LRTI despite high immunization coverage and a high prevalence of risk factors associated with severe pneumonia. Microbiologic investigations including multiplex PCR measures are done longitudinally and at LRTI episodes to evaluate etiological pathogens. An intensive cohort is followed twice weekly for the first year of life during which clinical information, nasopharyngeal (NP) swabs and monthly stool samples are collected; data from NP samples preceding a LRTI should assist with attributing etiological diagnosis. The NP microbiome is also longitudinally studied to describe its composition in healthy children and to identify associations between patterns of nasopharyngeal colonization and the development of pneumonia or wheezing illness in children. The stool microbiome is longitudinally investigated to describe the composition and factors influencing this, as well as the association with respiratory illness. Other aspects include detailed evaluation of maternal mental and physical health and the impact on child health and infant brain imaging with evaluation of neurodevelopmental outcomes. A large biorepository has been created comprising several categories of biological specimens including blood, urine, respiratory specimens, stool and household dust microbiome specimens. This approach provides an innovative, longitudinal assessment of a range of clinical, molecular, environmental and socioeconomic variables impacting on child health and the evolution of chronic disease in a low and middle-income country setting. The DCHS is a unique African birth cohort study that uses sophisticated measures to comprehensively investigate the early life determinants of child health in an impoverished area of the world.

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ISSUES AROUND MANAGEMENT OF CHILDHOOD TB IN HIGH BURDEN COUNTRIES

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Childhood Tuberculosis is an enigma because despite being an important disease affecting children in high burden countries (HBCs), its exact magnitude is not known. WHO estimates that about half a million TB cases (0.53 million; 6% of global TB burden) were among children and about 74 000 children died from TB in 2012. This is in addition to the TB-related deaths in children infected with HIV. The burden of TB in children is likely to be higher since, in HBCs, around 10–20% of all TB cases occur in children. The mortality due to tuberculosis is also very high in these countries. Children are also susceptible to the dual epidemic of TB/HIV. HIV-infected children are at 20-times greater risk of TB disease than HIV-uninfected children and at much higher risk of TB-related death. There are
also no estimates of the burden of multi drug resistance or extremely drug resistance cases among children though these are likely to be significant.1,2 The absence of a reliable estimate stems from a lack of an accurate sensitive diagnostic test for TB in young children. The diagnosis of TB in children is often based on indirect clues such as presence of evidence of infection and suggestive radiological picture. This approach has potential for both under- and over-diagnosis. Furthermore, children with TB do not get clearly represented under a national TB control programme for several reasons. Difficulty in obtaining sputum and the paucibacillary nature of primary disease makes it difficult for any programme manager to get an easy diagnosis of TB among children, particularly at resource-challenged peripheral health facilities. The focus of TB control has been to break the chain of transmission by quickly diagnosing and treating infectious adults. As paediatric TB contributes little to the maintenance of TB epidemic, it has largely kept childhood TB on the fringe of TB control strategies in most countries. TB is also not adequately recognised as an important cause of mortality within the overall child survival framework which focuses on pneumonia, diarrhoea, malnutrition and neonatal diseases. The care of children with TB is, thus, lost between the adult-oriented TB control strategies and non TB-oriented child survival strategies disease. The challenge remains to better understand its contribution to the common causes of morbidity and mortality in young children, such as pneumonia, malnutrition, meningitis and HIV. Increasing evidence suggests that TB may be an important primary cause of illness or comorbidity in these contexts. It is only in recent times that focus of the global effort has shifted to zero deaths from TB and is now aiming to increase efforts for managing childhood TB as well. WHO and a few countries like India have developed separate guidelines specifically for childhood tuberculosis. Despite these encouraging steps, expectedly enough, most programme managers prefer to have paediatric TB case definitions and treatment guidelines as close to the standard TB care protocols (adult guidelines) as possible, so that there is no confusion while effecting delivery at peripheral health units. The marked heterogeneity in prevalence of disease, availability of funds and health infrastructure for TB control also make these guidelines quite varied in approach and detail.3-5

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

Treatment of childhood TB
Amongst the major challenges around treatment of TB in children are establishing the most appropriate dose of each drug; finding combined formulations which could ensure adherence and decrease risks of missing some of the drugs or doses; and, making treatment child-friendly. With the change in the recommendations of dosages for anti-TB drugs for paediatric use, there are not many formulations available which provide the three drugs (RHZ) in the correct proportion as a combination. The tedious and expensive process of regulatory clearances and the small market for these drugs damps any efforts by the pharmaceutical companies from evaluating and providing data for licensing of these formulations. The drug combination for treating TB will need to be different for different nations depending upon the rates of resistance to individual drugs in those settings. In many countries like India, high levels of resistance to INH has led to a situation where there is a need for a third companion drug (like Ethambutol) to rifampin and INH in the continuation phase to prevent likelihood of amplification of resistance to rifampin.

While the national programmes and guidelines are useful, an equally important area to be covered for quality treatment is involvement of private sector doctors who are often the first point of contact for a significant proportion of the patients. Targeted and innovative educative interventions are needed to update them and to effect a change to rational prescription behaviour. Countries like India and Bangladesh have worked in these directions. The issues and challenges related to childhood TB are immense and evolving. The paediatricians must persist with public health specialists for sustained effort to improve and innovate.

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PERINATALLY ACQUIRED TUBERCULOSIS - DIAGNOSTIC AND THERAPEUTIC APPROACH

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The HIV epidemic has seen a resurgence of tuberculosis (TB) in young women of childbearing age. In 2013, the World Health Organization (WHO) reported 3.3 million new cases of TB in women, resulting in 510 000 deaths,
of which 180,000 (35%) were in HIV co-infected women (1). Infants born to mothers with TB (TB-exposed newborns), with or without HIV, are at high risk of TB infection and disease. Congenital TB transmission occurs with hematogenous spread via the placenta or with aspiration or ingestion of infected amniotic fluid before or at birth. Postnatal TB develops shortly after birth, due to respiratory droplet spread from an infectious TB source case, most commonly the mother. As the exact time of TB infection is difficult to determine, and the clinical presentation and management of congenital TB (rare) and postnatal TB (more common) are similar, these two entities are now combined into perinatal TB.

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

Standard three/four-drug treatment with isoniazid, rifampin and pyrazinamide, with or without ethambutol, remains the drugs of choice as first-line TB drug regimens in infants. There is very limited information on the side effects of these drugs in neonates and infants. There are also very limited PK and safety data available in neonates and infants for first-line TB drugs, with none available for long-term use in second-line TB drugs settings. (10)

A mother with recently diagnosed or undiagnosed TB may pose an infectious risk not only to her own newborn but also to other newborns in the nursery. Heyns et al. reported on Kangaroo mother care (KMC) and the risk for transmission of TB. KMC has become the standard of care for low-risk preterm babies born in developing countries. He reported on an infant (sentinel case) who was admitted to the pediatric intensive care unit (PICU) with extensive pulmonary tuberculosis and tracked back the contact as the mother in KMC. [5] It has previously been shown that there is a 60-80% TB transmission risk for infants from a close smear-positive TB source case, and 30-40% from a smear-negative TB source case (6). HIV co-infection also contributes to a high infant mortality with a four-fold increase observed among infants born to TB/HIV-infected women in India (3). Schaaf et al. have shown a 24% mortality in those aged less than 3 months of age with culture-confirmed TB in a South African study (4).

Conclusion

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

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DIAGNOSIS AND TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

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The diagnosis of multidrug-resistant (MDR) tuberculosis (TB) in a child can either be confirmed or presumed. Confirmed disease occurs when M. tuberculosis is isolated from the child and is demonstrated to grow in the presence of isoniazid and rifampicin (phenotypic resistance) or to contain genes that are associated with resistance to both these drugs (genotypic resistance). A diagnosis of presumed MDR-TB can be made when the child is diagnosed with TB on the basis of symptoms, signs and radiology in combination with risk factors that might imply drug resistance. Such risk factors include the child being treated previously for TB or them being in contact with a source case that is known to have MDR-TB or one that has died, failed treatment or defaulted. In addition, if a child being treated for TB with first-line medications is failing treatment in spite of a well-adhered to regimen, it may be appropriate to also treat for MDR-TB.

Before starting treatment, it is important to obtain appropriate samples from the child. These might include expectorated sputum (if the child is old enough to co-operate), induced sputum, gastric aspiration, nasopharyngeal aspiration, cerebrospinal fluid or appropriate biopsies. Once a sample has been obtained it can either be evaluated directly with genotypic tests (GenXpert MTB/RIF or line probe assays) or can be cultured (using liquid-based media such as mycobacterial growth indicator (MGIT)) and then have drug susceptibility testing (DST) performed using either genotypic or phenotypic tests. Microscopic observation drug susceptibility (MODS) is a culture-based test that also

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evaluates for the presence of resistance to isoniazid and rifampicin.5 If the child is clinically suspected of having MDR-TB, treatment should be started whilst awaiting confirmation. WHO has placed the drugs used in the treatment of MDR-TB in five groups.4 Group 1 drugs are considered first-line with the remainder second-line. When designing a regimen to treat children with MDR-TB, the target should be to use at least four, but preferably five drugs, which are likely to have activity against the infecting organism. Decisions on which drugs to include in an MDR-TB treatment regimen should be guided by the DST pattern of the presumed source case. As they are the most potent drugs, with the fewest adverse effects, any first-line drugs to which the organism is still susceptible should be used. The next step is to add an injectable drug and then a fluoroquinolone. Further drugs from group four should then be added, including ethionamide (or prothionamide), cycloserine (or terizidone) and para-aminosalicylic acid (PAS). Finally, agents from group five can be added if required. Both clofazimine and linezolid have, in recent studies, demonstrated promising efficacy and should be considered useful drug options.5,6 Two newly licenced drugs, bedaquiline and delamanid, appear to have good efficacy against M. tuberculosis and may in the future have a more prominent role in the treatment of paediatric MDR-TB.

Children should be monitored for three reasons: to determine response to therapy; to identify adverse events early; and to promote adherence. Response to therapy includes clinical, microbiological and radiological monitoring and these should be evaluated at follow-up. Children should also be assessed at follow-up for symptoms and signs of adverse effects. Both ethionamide and PAS can cause hypothyroidism7 and the injectable drugs can cause renal impairment and hearing loss.8 Prior to the start of treatment, children should have a baseline assessment of thyroid function, renal function and have audiological and vision examinations. They should then have their hearing assessed as well as their renal and thyroid function during treatment. Adverse events should be managed early and aggressively to avoid permanent side effects or adherence compromise. At each consultation, adherence advice should take place; treatment supporters and counselling are also of benefit. If children are diagnosed early and treatment taken conscientiously, favourable treatment outcomes are achieved in greater than 80% of cases.9 Few studies have been conducted to evaluate the correct management of children who have been exposed to MDR-TB. Observational data suggest that six months of preventive therapy with a fluoroquinolone-based regimen is likely to be effective in preventing the development of TB disease. Guidelines are inconsistent.10 Three trials will soon be conducted to evaluate the management of MDR-TB child contacts.

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COMMUNITY ACQUIRED PNEUMONIA IN THE DEVELOPING WORLD

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

Magnitude of the problem and efforts to control it

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

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

This has led to the development a Global Action Plan for Pneumonia (GAPP) which focuses to promote the expansion and improvement in community case management, to reduce risk factors for disease, and works for the massive roll–out of vaccination against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae by countries through support from the GAVI Alliance. Diarrhoeal disease, the dethroned killer king, continues to be the second important cause of disease and death among children (600,000 diarrhoea deaths in 2012; of these 72% in under 2 years of age). The strategies to manage and decrease deaths due to these two major killers have much in common. Breast feeding, zinc supplementation, Immunisation, adequate and appropriate nutrition, better hand and personal hygiene are important preventive interventions to control both these diseases. Further, young children often have more than one morbidity and underlying malnutrition increases the risk of death from both pneumonia as well as diarrhoea. An early detection through expanded community case management and early referral continues to be advocated through Integrated management of neonatal and childhood illnesses in many high burden countries, including India. Internationally, WHO, UNICEF and other agencies have launched a Global Action Plan for Pneumonia and...
**Diarrhoea (GAPPD).** The subsequent discussion critically analyses the various components of this strategy.2

**Challenges posed by prevalent strategies and course correction**

**Diagnosis and case management**

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

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

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

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

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

WHO recently revised recommendations on the basis of evidence from studies comparing antibiotic treatment for pneumonia. The newer guidelines now advise domiciliary oral antibiotics for children with pneumonia who have fast breathing and/or lower chest indrawing. It is only the children with severe disease (SpO₂ <90% or inability to feed, altered sensorium or severe respiratory distress) who are advised admission for antibiotic and oxygen. Pulse oximetry, the “standard of care” for detecting, treating and monitoring hypoxaemia in higher income countries is not routinely available in health facilities of resource-challenged countries as it is moderately expensive. Further, a shorter 3–day regime is advocated for non-severe cases. It is pertinent to point out that the evidence for the efficacy for shortened regime comes from studies using the clinical definition which has been criticised for its inability to distinguish bacterial from viral pneumonia or from children with wheezing. A recent study from Pakistan reported radiological evidence of pneumonia in only 14% of children with WHO-defined non-severe pneumonia.8,9 Pulmonary tuberculosis is increasingly recognised as a cause of acute pneumonia especially in children in tuberculosis-endemic countries. The difficulty of diagnosis as well as rational therapy is not restricted to community case management algorithm alone. Clinical data are often imprecise, and microbiological data is not only less often available but is also challenging to interpret. Additionally, chest radiographs, often used in the larger health facilities or in the private sector, have several difficulties e.g. they lag behind clinical presentation, lack ability to completely differentiate bacterial from viral aetiology, even when simultaneously taking into account several clinical factors—including hypoxia, history of fever, focal decreased breath sounds, and the absence of wheezing. There is a tendency to treat all hospitalised children with newer 3rd generation antibiotics or co-amoxylav or vancomycin without adherence to the principle of antibiotic therapy. In this direction, efforts to develop guidelines for first and higher level referral facilities in both public and private sectors is needed. Country-specific guidelines such as those prepared by the Indian Academy of Paediatrics for rational therapy of all respiratory illnesses is a welcome step in this direction.

**Preventive strategies**

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

**Social determinants**

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

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DEVELOPED WORLD: IMPACT OF PNEUMOCOCCAL CONJUGATED VACCINE ON CHILDHOOD PNEUMONIA

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

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

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

An analysis from 2010 reviewing hospitalizations in the US (1997-2006), spanning the period around the introduction of PCV7, revealed that rates of CAP decreased for infants <1 year of age but increased for children >5 years; systemic complications (acute respiratory failure, sepsis, ECOM) decreased only for infants <1 year of age; however, local complications (empyema, lung abscess, necrotizing pneumonia) increased for all age groups. There is evidence that since PCV7 covers only 7 of more than 92 pneumococcal serotypes, with the introduction of the vaccination; non-vaccine types (NVT) have increased among asymptomatic carriers in a process dubbed “serotype replacement”. This increase in NVT consequently resulted in little or no net change in the bacterial carriage prevalence and may have reduced the benefits of vaccination. There is indeed evidence that the observed increase in invasive pneumococcal disease (IPD) was associated with such replacement, and IPD was often caused by pneumococcal types that were infrequently observed in the population prior to PCV7. A review of these observations addresses the surveillance biases that might affect these findings. It also contends that the magnitude of serotype replacement in disease can be partially attributed to a combination of lower invasiveness of the replacing serotypes, biases in the pre-vaccine carriage data (unmasking), and biases in the disease surveillance systems that could underestimate the true amount of replacement. The authors conclude that absence of prospective longitudinal studies designed to analyze these trends and connections, renders the statements of causality difficult, and emphasize the key role for future surveillance studies.

PCV13, which increased the conjugated vaccine from 7 to 13 serotypes, was licensed in the US and largely replaced PCV7 as of 2010. Studies from around the globe appear to all support a marked effect of reduction of morbidity, including IPD, and mortality associated with this vaccination. A study from Massachusetts reveals that PCV13 reduced the prevalence of colonization with PCV13 serotypes among children 6–23 months old, but its efficacy was not shown among older children.6

Impressive effects are reported on reduction of morbidity. Two summary reports from the CDC (2013-2014).5 conclude that substantial direct and indirect effects are evident after 3 years of use. PCV13 appears highly effective at preventing IPD among children who receive the vaccine. Specifically; 89% effectiveness of >1 dose PCV13 vs. PCV13-type IPD; 88% reduction in PCV5-type IPD among children, leading to an estimated >20,000 cases of IPD and >2,000 deaths prevented.

Data from Israel spanning 2004 to 2013 were reported from an ongoing nationwide, prospective, population-based, active surveillance study7 and included all IPD episodes (Streptococcus pneumoniae isolated from blood and/or cerebrospinal fluid). The study showed that following initiation of a PCV national vaccination plan, a rapid and substantial 2-step IPD reduction was observed in children <5 years. The serotype-specific rate reduction reflected the sequential introduction of PCV7/PCV13. From Norway a prompt effect of replacing PCV7 with PCV13 on the epidemiology of IPD disease was also reported.7

It appears that the transition from PCV7 to PCV13 is indeed amplifying the effect of reduction of infections related to pneumococcal disease. Long-term surveillance will reveal the possible impact of replacement in this vaccinated population, but studies to date are suggesting that the pernicious burden of pneumococcal disease is being substantially reduced in childhood by the current vaccination regimen.

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Ventilator associated pneumonia (VAP) generally refers to pneumonia that arises more than 48–72 hours after endotracheal intubation. It is the second most common hospital-acquired infection among pediatric and neonatal intensive care unit patients. (1) It is often difficult to define the exact incidence of VAP, because there may be an overlap with other lower respiratory tract infections, such as infectious tracheobronchitis in mechanically ventilated patients. The exact incidence varies widely depending on the case definition of pneumonia and the population being evaluated. (2,3) For example, the incidence of VAP may be up to two times higher in patients diagnosed by qualitative or semi-quantitative sputum cultures compared with quantitative cultures of lower respiratory tract secretions. The risk of VAP is highest early in the course of hospital stay, and it is estimated to be 3%/day during the first 5 days of ventilation, 2%/day during Days 5 to 10 of ventilation, and 1%/day after this. Because most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation. The intubation process itself contributes to the risk of infection, and when patients with acute respiratory failure are managed with noninvasive ventilation, nosocomial pneumonia is less common. In pediatric populations, the published data are unmatched for severity of illness and univariate but suggest that pediatric patients with VAP may have excess mortality and length of PICU and NICU stay. A cross-sectional cohort study done by Kusahara et al. revealed a significant association between the occurrence of VAP and the use of a nasoenteral tube, intermittent administration of nutritional formula, emergency reintubation, use of vasoactive drugs, duration of mechanical ventilation, and length of stay in both the PICU and the hospital. Logistic regression analysis indicated that use of vasoactive drugs, presence of a nasoenteral tube, and PICU length of stay were independent risk factors for VAP in infants and children. (4)

Diagnosis
In 2014 in the U.S., the Centers for Disease Control and the National Healthcare Safety Network (NHSN) made extensive revisions of the definition of VAP for surveillance purposes. (5) Although the impact and relevance of these new definitions are unclear for pediatric units, the new terminology includes the broad term ventilator associated events (VAE), with three defined subcategories or tiers: 1) ventilator associated condition (VAC), a sustained episode of respiratory deterioration, both non-infectious and infectious in origin, 2) infectious ventilator associated conditions (IVAC), which aims to capture events related to infection, and finally 3) ventilator associated pneumonias (VAP), which attempts to capture new both probable and possible infection related events with purulent respiratory secretions and/or positive respiratory culture with probable cases dependent upon rigorous standards of quantitative or semiquantitative thresholds for pathogen growth. Previous clinical criteria for the diagnosis of VAP included two or more abnormal chest radiographs with at least one of the following signs: new or progressive and persistent infiltrate, consolidation, caviation, and/or pneumatoceles (in infants ≤ 1 year of age). A few studies have examined the sensitivity and specificity of lower airway sampling in PICU patients and found the sensitivity and specificity of BAL (10^4 CFU/ml) to be 50 to 72% and 80 to 88%, respectively. Diagnostic testing is ordered for two purposes: to define whether a patient has pneumonia as the explanation for a constellation of new signs and symptoms and to determine the etiologic pathogen when pneumonia is present. For patients diagnosed with ARDS, suspicion of pneumonia should be high and the presence of only one of the three clinical criteria described should lead to more diagnostic testing. A high index of suspicion should also be present in patients who have unexplained hemodynamic instability or deterioration of blood gases during mechanical ventilation. In the absence of any of these findings, no further investigations are required. The incidence of colonization in hospitalized patients in general and even more in patients requiring endotracheal intubation is high. Antibiotic treatment of simple colonization is strongly discouraged. Routine monitoring of tracheal aspirate cultures to anticipate the etiology of a subsequent pneumonia has also been found to be misleading in a significant percentage of cases.

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

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

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

Future directions
The application of the new VAE definitions to adult units is occurring currently and has generated considerable debate. Although most studies do show that there is an adverse outcome for patients with VAEs, the value of reporting rates of VAP as a measure of quality-based payment is being debated. In an editorial comment to a recent prospective study, Niederman and Nair noted that there are not enough data to endorse the measurement of VACs as a reflection of quality of care, particularly because most episodes of a VAC are not VAP, and we do not have a prevention strategy that is able to prevent both. The new definitions of VAC and VAP will apply to pediatric units is unclear and will undoubtedly produce significant research and QI efforts for pediatric units in the U.S. in the future. A viable definition and risk stratification system incorporating preventable and nonpreventable risk factors for pediatric VAP would assist intensivists in the refinement of pediatric-specific VAP prevention bundles.

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S28 Abstract

AIRWAY INFLAMMATION IN CF AND THERAPEUTIC TARGETS

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Lung disease in cystic fibrosis (CF) occurs as a consequence of a cascade of events initiated by CF transmembrane conductance regulator (CFTR) dysfunction. It leads to failure of chloride secretion and sodium hyperabsorption at the apical airway surface causing dehydration of the fluid layer and impaired mucociliary clearance. The desiccated mucus obstructs the airways and prevents elimination of bacteria from the lung, allowing chronic infection to become established. The resultant neutrophilic inflammation causes progressive damage to the airways. The vicious cycle of intense neutrophilic inflammation, oxidative stress and continuous infection contributes to irreversible airway destruction and fibrosis.

Lung disease begins very early in life and some changes to the airways may even occur prenatal. The presence of inflammation and bacterial infection was demonstrated soon after diagnosis, in infants diagnosed by newborn screening. Inflammatory markers were found in high concentrations in bronchoalveolar lavage (BAL) fluid, even in infants with normal lung function and without apparent bacterial colonization. Once established, airway inflammation may be associated with decreased lung function and significant structural damage, including bronchiectasis and poorer nutritional status.

Data derived from primary murine tracheal cell suggest that following P. aeruginosa infection, inflammatory mediators are concentrated in the thin dehydrated periciliary fluid layer of CF airway epithelial cells resulting in high chemokine concentration gradients across the epithelium and an exaggerated inflammatory response. Greater hospitalization rates, growth impairment and reduction of lung function are seen in CF patients as a consequence of respiratory viral infections, predisposing the patient’s airway to bacterial infections and earlier acquisition of P. aeruginosa.

Fungi infections, mainly Aspergillus, may lead to an inflammatory response in the airways, playing a role in the pathogenesis of CF lung disease. Assessing airway inflammation in CF is essential for initiating early treatment. Forced expiratory volume in 1 second (FEV₁) is a non-invasive and reproducible test and is considered the gold standard for monitoring disease progression; however, it shows a poor correlation with inflammation. Other tests e.g., multiple breath washout, sputum cultures, exhaled breath condensate, and BAL can help in assessing airway inflammation. High resolution computed tomography (HRCT), a sensitive tool to detect early structural changes, cannot distinguish between old scars and active inflammation. Positron emission tomography-CT (PET-CT) can directly measure neutrophilic activity and detect inflammation, however, it involves high radiation levels.

Anti-inflammatory agents in CF have been the subject of intense investigation. Corticosteroids and non-steroidal anti-inflammatory drugs have shown some benefit, but considerable side effects limit their use. High-dose ibuprofen was shown to significantly slow the rate of decline in FEV₁ especially for patients <13 years of age, however, the use is limited specially because it has potential gastrointestinal and renal side effects. Azithromycin, used as an immuno-modulating agent for both patients with and without P. aeruginosa colonization, was shown to significantly reduce the number of respiratory exacerbations and the rate in decline of lung function, and to improve quality of life in patients colonized with P. aeruginosa and S. aureus.

Early diagnosis, aggressive therapy, and continuous monitoring of the inflammation in the airways are required in order to avoid deterioration of lung function and improve survival of patients with CF.

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Typical pneumonia, usually caused by *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*, is characterized by acute onset of fever and constitutional symptoms, prominent response in inflammatory markers and alveolar, often lobar, infiltrate on chest radiograph. Pneumonia with less acute onset, less fever and milder constitutional symptoms is called atypical pneumonia. The infiltrate on chest radiograph is less prominent without alveolar solid consolidations. In the 1960’s, an association was found, first in the military, between atypical pneumonia and serological responses to *Mycoplasma pneumoniae* in respiratory samples. This association was confirmed in 1970’s and 1980’s. In children treated at home for chest infection, PCR was positive for *M. pneumoniae* or *C. pneumoniae* in 7% and for *M. pneumoniae* in 7% by PCR and/or serology. The figure for *C. pneumoniae* etiology was found in 11% by PCR and/or serology. The figure for *C. pneumoniae* etiology was found in 11% by PCR and/or serology.

**Diagnosis**

Diagnostic tests for CAP include chest radiography, serological tests, and polymerase chain reaction (PCR) based tests. Chest radiography is performed to rule out severe complications such as pleural effusion, pneumonia, or pneumothorax. Serological tests include the enzyme immunoassay (EIA) which measures IgM and IgG antibodies separately, and the test is rather specific but non-sensitive. Antibody responses are often slow, and the response is not necessarily to be seen in paired sera taken at two to three weeks intervals. *C. pneumoniae* infection may lead to chronic latent infections or subclinical serological responses triggered e.g. by viral infections, and of course, to false activations of latent infection with clinical symptoms. These characteristics explain the high number of mixed infections in children with CAP caused by *C. pneumoniae* in serology-based studies.

In an American study in children hospitalized for CAP, *M. pneumoniae* was found by EIA or PCR in 14%, and *C. pneumoniae* by MIF or PCR in 9%, and half of the cases were mixed infections with other viruses or bacteria. Either *M. pneumoniae* or *C. pneumoniae* were identified in 22% of the cases. In children treated at home for CAP, PCR was positive for *M. pneumoniae* in 7% and for *C. pneumoniae* in 6%, as reported earlier by the same research group. According to the American Clinical Practice guidelines, children with signs and symptoms suspicious for *M. pneumoniae* should be tested to help antibiotic selection, but diagnostic testing for *C. pneumoniae* is not recommended, mainly due to the lack of a reliable and readily available test. The updated British Thoracic Society guidelines on diagnosis and treatment of pediatric CAP do not recommend routine microbiological testing in ambulatory patients, but recommend acute and convalescent serology for *M. pneumoniae* and *C. pneumoniae* in children treated for severe or complicated CAP in hospital.

**Treatment**

Both American and British guidelines recommend that CAP in children can be diagnosed without chest radiography or any laboratory measurements. The treatment should always cover *S. pneumoniae*, since most severe complications after CAP are connected to pneumococcal pneumonia. In addition, the finding of a virus or an atypical bacterium in respiratory specimen does not rule out pneumococcal infection. Both guidelines recommend that macrodides should be prescribed, in addition to penicillin, amoxicillin or another beta-lactam, if *Mycoplasma* etiology of CAP is suspected. Despite this recommendation, current evidence is insufficient to support these guidelines.
support or refute the effectiveness of macrolides or other antibiotics in children with Mycoplasma CAP. Seventeen studies were included in a recent systematic review including five in a meta-analysis, and the pooled risk difference although favoring treatment was only 0.12 and statistically non-significant. According to the American guidelines, antibiotics are not routinely required to preschool-aged children with CAP, and amoxicillin is the first-line oral therapy for children with CAP suspected to be of bacterial origin. Macrolides should be prescribed for school-aged children with findings compatible with CAP caused by atypical bacteria. According to the British guidelines, all children with CAP except those less than two years of age presenting with mild symptoms, should be treated with antibiotics, and oral amoxicillin is the first choice. Macrolides should be added if either M. pneumoniae or C. pneumoniae is suspected, if the clinical presentation is very severe, or if there is no response to first-line antibiotics.

The suspicion of Mycoplasma or Chlamydia etiology is usually based on the clinical picture of CAP. No doubt, M. pneumoniae and C. pneumoniae cause CAP in children, and although spontaneous resolution is more likely the rule rather than the exception, there also are severe cases which need treatment with antibiotics effective to atypical bacteria. However, there is no existing clinical or laboratory-based algorithm to discern the cause of pneumonia in children. This means that certain overtreatment with antibiotics, and with macrolides combined with beta-lactams in particular, is justified in pediatric CAP.

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NEWBORN SCREENING IN EUROPE: METHODS AND OUTCOMES

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

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

Generally, the choice of a protocol is a “balancing act”, whereby avoidance of negative outcomes (e.g. carrier detection, parental distress) and detection of inconclusive cases, is weighed against timeliness of diagnosis and CFNBS costs [1,2]. Thus when genetic testing is not utilised, there is a marked increase of false positive results with a negative psychological impact on the family and health care services reflected by the need to assure follow-up and testing [1,2]. On the other hand, DNA testing increasingly detects carriers, thereby requiring genetic counselling which strained genetic services have a difficulty to provide in a timely manner.

It also “produces” infants with an inconclusive diagnosis where long-term clinical monitoring is necessary. In the United States, mainly due to legal and health care insurance-related reasons, infants with an unclear diagnosis following CFNBS are designated as having the “CFTR related metabolic syndrome” (CRMS) [1,2]. However, in Europe there is consensus in favour of avoiding definitive diagnosis thus the term “CF Screen Positive Inconclusive Diagnosis” (CF-SPID)” is advocated [1,2]. Established CFNBS problems now currently increasingly deals with issues related to the communication between professionals and patients, mainly aimed at avoiding misconceptions and minimising parental distress. Therefore, in the Internet information era, there is a need to provide accurate and up to date CFNBS portals to counter often outdated or misleading online information [1,2].

Although all CFNBS schemes utilise two steps (or “tiers”) comprising: a) initial measurement of immunoreactive trypsinogen (IRT) on a dried blood spot sample (i.e. the “Guthrie card”) and b) IRT test for confirmation or exclusion of CF diagnosis, they differ with regards to the intermediate tiers aimed at improving the specificity of the IRT testing. Intermediate tiers are performed either a) on the original- or less frequently on the b) newly sampled blood spot which represents a logistics challenge. The latter “resampling option” is utilised at approximately 3 weeks of age when IRT levels non-specific for CF have markedly decreased. Since the initial IRT cut-off has a significant effect on NBS performance with regard to both sensitivity and specificity, optimisation of its cut-off levels is crucial (usually more than 99th percentile) and should be continually monitored. Decrease of IRT cut-offs does not influence screening sensitivity, but negatively affects specificity which cannot be efficiently mitigated by an intermediate tier. The IRT cut-off value is also closely related to the day of sampling, which is in most European countries set up to three days, while in others even up to eight days after birth. Some CFNBS programmes utilise a floating cut-off to account for analytical and/or seasonal variability. Analytical issues include retesting in atypical levels, assay calibration or elucidation of blood spot contamination with stools. False negative cases should be investigated to clarify whether the issue is of biological or analytical origin. IRT could also be measured from the second blood spot for reasons specified above [1,2].

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

In order to limit the disadvantages of DNA testing in CFNBS, another biomarker, pancreatitis associated protein (PAP), could be measured in the...
original blood spot [7]. There is increasing evidence that IRT/PAP schemes have acceptable sensitivities [7] and generate less CFSPID cases. However, their positive aspects are offset by higher need for sweat testing to exclude/confirm diagnosis of CF in PAP-positive instances. As with IRT testing, alternative PAP schemes include additional tiers aimed at increasing their sensitivity (e.g. EGA), but limit their positive aspects [7].

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

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

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

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

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

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

**PULMONARY ASPERGILLOSIS IN CHILDREN**

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

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

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

ABPA is a hypersensitivity reaction to aspergillus antigens, mostly A. fumigatus. Patients usually present with wheezing, expectation of brown mucus plugs, pleuritic chest pain, and fever, and the diagnosis is confirmed by radiologic and serologic testing. It is typically seen in patients with long-standing asthma, but also occurs in up to 15% of patients with CF.

In CF, due to overlap of symptoms, the diagnosis of ABPA is sometimes delayed or even missed, and might result in irreversible pulmonary damage. Treatment of ABPA in CF consists of either oral steroids or IV pulses of methylprednisolone or oralizumab combined with oral antifungal therapy (itraconazol or voriconazol) for a long time period.

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

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Long term morbidities and AHI after T&A

The group of children with persistent AHI >1 are important to follow as they were shown to have decreased baroreflex sensitivity and increased BP variability and likely higher risk for hypertension. The gradual but significant increase in AHI to over 5 per hour over 3 years post-T&A is also important as AHI >5 in children was shown to be associated with significant higher BP and decrease in grey matter volume over the prefrontal and temporal regions. Higher blood pressure, decreased baroreflex sensitivity, increased BP variability and grey matter density deficit constitute the long term morbidities that were attributed to the unresolved OSA which, given time, may well become adult OSA.

Child-Adult OSA

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

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

Conclusion

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

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**DIAGNOSIS OF OBSTRUCTIVE SLEEP DISORDERED BREATHING IN CHILDREN**

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

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

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

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

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

Tsai et al. performed a retrospective study on 148 Taiwanese children aged 3 to 12 years (30% obese). They reported that the oxygen desaturation index (≥4% decrease in SpO2 per hour of sleep) was highly correlated with the AHI (r = 0.89). Overall, an oxygen desaturation index cut-off of 2.05 had a positive predictive value of 98% for OSAS. Moreover, they were able to predict mild, moderate and severe OSA with a relatively high sensitivity (77.7 to 89.1%) and specificity (86 to 89.9%), suggesting that oxygen desaturation index is a good predictor of OSA severity (5). Validation in other settings is needed.

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

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

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

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

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

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

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

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FOLLOW-UP AFTER PRETERM BIRTH/BPD
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Pediatric Pulmonology
The effects of these minor decrements in lung function are not well described. Airway disease can be split into components (Table), and the contributions of each may differ between generations of BPD survivors. This is really important when reviewing studies talking about ‘asthma risk’; essential to know what it is the authors meant by asthma. In terms of change in clinical practice, today’s adult survivors were largely ventilated at slow rates with high airway pressures, whereas survivors coming through will be more likely to have had antenatal corticosteroids, more likely to have been given surfactant, and more likely to be ventilated at fast rates with lower mean airway pressures. The nature of the disease may change further with the recent changes in neonatal resuscitation and even more conservative ventilation strategies. Furthermore, the possibilities of coincident disease, and complications of whatever caused prematurity in the first place, must not be forgotten.

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

What is the nature of lung disease? Large airway disease should not be forgotten, especially since it may be surgically correctable. Especially in ‘new’ BPD, alveolar simplification leads to a reduced area for gas exchange and loss of alveolar tethering points and hence airway obstruction. ‘Old’ BPD in particular is characterised by increased airway smooth muscle. However, there is no evidence of eosinophilic or other airway inflammation, and hence no justification for the prescription of inhaled corticosteroids, unless there is no evidence of eosinophilic or other airway inflammation, and hence no justification for the prescription of inhaled corticosteroids, unless there is evidence that spirometry may deteriorate in the first year of life. In the longer term, there is some evidence of catch up growth in terms of airflow obstruction and neo-alveolarisation. However, whether there will be an accelerated rate of decline in lung function, and premature airflow obstruction, remains to be seen. In general, young adults have relatively subtle abnormalities of lung function and exercise performance, but increased respiratory morbidity. The chief importance of these abnormalities is their effects when the lung ages, which has yet to be determined.

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

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

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| Component | Pathophysiology | Relevance to BPD |
|-----------|----------------|------------------|
| Fixed airflow obstruction | Intraluminal – iatrogenic granuloma, vocal cord palsy, acquired subglottic cysts | Potentially new and old |
| | Luminal – failure of normal development | ?Both |
| | Extraluminal – loss of alveolar tethering | Both, especially new BPD |
| Variable airflow obstruction | Intraluminal – mucus production | Possible, especially old BPD |
| | Luminal – bronchospasm | Bronchospasm especially old BPD |
| | Extraluminal – loss of alveolar tethering | Both, especially new BPD |
| Airway inflammation | Neutrophilic | No evidence in either new or old BPD |
| | Eosinophilic | Both |
| | | None |
| Airway infection | Bacterial | Acute infection only as far as is known |
| | Viral | |

LONG-TERM CARDIOPULMONARY CONSEQUENCES OF CHILDHOOD MALIGNANCIES AND THEIR TREATMENT

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Introduction

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

Effects of primary malignancy.

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

Effects of opportunistic pulmonary infections.

During cancer therapy, patients are prone to a variety of secondary infections from both common and chest wall, pulmonary metastases from solid tumors, and secondary treatment on cardiopulmonary function, including exercise.

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

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

Effects of cancer surgery.

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

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

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

Late effects of chemotherapy on cardiopulmonary function

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

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

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

Effects of human stem cell (HSCT) transplantation.

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

Areas for current and future research.

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

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PERINATALLY ACQUIRED TUBERCULOSIS - DIAGNOSTIC AND THERAPEUTIC APPROACH

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The HIV epidemic has seen a resurgence of tuberculosis (TB) in young women of childbearing age. In 2013, the World Health Organization (WHO) reported 3.3 million new cases of TB in women, resulting in 510 000 deaths, of which 180 000 (35%) were in HIV co-infected women (1).

(1) World Health Organization. Global Tuberculosis Report, 2014. Geneva, Switzerland: WHO, 2014.

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At Boston Children’s Hospital, between 2006 and 2013, there was a 46% decrease in the overall use of CT. The cause of this decline is speculative but presumably relates to the heightened concern for reducing radiation exposure (ALARA concept) and an attempt to respond to societal concerns about the rising costs of medical care.

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

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

There are several steps or “rules” that, if followed, will enhance an observer’s ability to appreciate abnormalities on CXR. 1) When possible, look at the image BEFORE learning the history. This will decrease pretest bias and increase the likelihood of seeing things unrelated to the issue in question. 2) Be confident in your ability to read a CXR and the CXR’s ability to reveal the abnormalities. Studies have shown that the level of radiologists’ confidence in reading mammograms is directly correlated with the accuracy of their interpretations. 3) Be detail oriented. Just because something “does not belong there”, do not ignore it. 4) If you have a concern, act on it. This may be a repeat CXR. It does not always need to be a CT or MRI. A high percentage of CXR are obtained for nonspecific signs and symptoms. This often relates to some combination of cough, fever, wheeze. Do not be lulled into assuming it is just another case of bronchiolitis. Always be alert for the unexpected vascular ring, lucent foreign body, IOL, occult trauma, etc. Keep in mind that persistent, stable peribronchial thickening is the first radiographic manifestation of cystic fibrosis and not just reactive airways disease/asthma.

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

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

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

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

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

MECHANISMS LEADING TO PULMONARY EDEMA
All diseases that cause pulmonary edema do so by only one of two processes. The most frequent process is increased transvascular pressure gradient that causes augmented fluid movement out of the microvasculature. Two examples...
are congestive heart failure (CHF) where there is an abnormally high intravascular pressure with fluid being squeezed out of the vessels, and re-expansion pulmonary edema where markedly negative interstitial pressures “suck” the fluid out of the blood vessels. The second process is where the lung’s blood vessels, highly permeable to solutes, abnormally leak, and intravascular fluid easily permeates into the lung’s interstitium and airspaces. The clinical correlate being the acute lung injury (ALI) - “adult” respiratory distress syndrome (ARDS). Often diseases have both processes present simultaneously. The table lists some of the pulmonary diseases that are associated with pulmonary edema with the relative contribution of these two processes shown semi-quantitatively by the number of + signs. The underlying mechanisms are discussed in greater detail elsewhere.1

**MECHANISMS FOR AIRSPACE FLUID CLEARANCE**

Alveolar fluid clearance (AFC) arises from the lung’s distal lung epithelia (DLE) actively transporting Na\(^+\) with Cl\(^-\) and water following. Humans have AFC rates of ~25%/h. To transport Na\(^+\) with Cl\(^-\) and water following, cells must have Na\(^+\) permeant ion channels on the apical membrane, Na\(^+/\)K\(^-\)/ATPase in the basolateral membrane and intercellular tight junctions. Under normal conditions, the activity of Na\(^+\) permeant ion channels on the apical membrane represents the rate limiting step in lung epithelial Na\(^+\) transport. Inadequate or abnormal active Na\(^+\) transport by the respiratory epithelium has been shown to play a pathogenic role in the initiation of two lung disorders characterized by airspace edema. The newborn lung is filled with a protein-poor fluid that was secreted by the fetal epithelium. Although this fluid is not, strictly speaking, pulmonary edema, this airspace fluid must be cleared by the epithelia’s active transepithelial Na\(^+\) transport. As reviewed elsewhere, premature born infants frequently have immature epithelial Na\(^+\) transport and the resultant impairment of the clearance of this fetal lung liquid, combined with immaturity of the surfactant system, are the two factors that initiate the neonatal respiratory distress syndrome. High altitude pulmonary edema is initiated by an excessive increase in pulmonary microvasculature pressure with an initial non-inflammatory leakage of fluid across the alveolar-capillary membrane that is followed by a secondary inflammatory reaction promoting an increase in permeability. Since human respiratory epithelial Na\(^+\) transport decreases in response to the decreased PO\(_2\) at high altitude and salmeterol, that both alters vascular tone and increases Na\(^+\) transport, diminishes the frequency of high altitude pulmonary edema, it is currently believed that abnormal or defective lung epithelial Na\(^+\) transport may be involved in the pathogenesis of high altitude pulmonary edema. The ability to clear pulmonary edema correlates with patient survival and clinical parameters, such as length of ventilation and O\(_2\) requirements, regardless if the patients have CHF- or ARDS-induced pulmonary edema. Further details are available in a recent review.6

**Correction of Hypoxemia**

The patient’s arterial oxygen saturation should be returned to normal levels as soon as possible. For mild and predominately interstitial pulmonary edema, an increase in the F\(_{O2}\) will be very effective as it compensates for the low ventilation to perfusion (V/Q) ratios (< V/Q < 1) arising from airway dysfunction secondary to excess fluid within the bronchovascular sheaths and reflex vagal stimulation. When there is significant airspace pulmonary edema with much of the hypoxemia being secondary to shunt, by definition is V/Q = 0, then a physician must increase transpulmonary pressures and mean airway pressures to hold the lung at a higher volume and recruit lung units thereby decreasing the amount of shunt. This can be achieved through a variety of approaches, most commonly and effectively by increasing the positive end expiratory pressure. Increasing peak inspiratory pressure and prolonging the inspiratory time and duration of the inspiratory plateau will further increase mean airway pressures.

**Reduction of the rate of fluid filtration**

The rate of fluid filtration into the lung should be decreased and treating the disorder that is responsible for the pulmonary edema is the first priority. For example in CHF one would: i) improve cardiac contractility; ii) reduce preload; iii) relieve anxiety and its associated increased sympathetic nervous system activity (e.g. morphine) thereby reducing both preload and afterload for the heart; iv) decrease blood volume and left atrial pressure while increasing plasma colloid osmotic pressures (e.g. administration of diuretics); v) decrease systemic or pulmonary vascular pressures or both using vasodilators and vi) reduce excessive salt and water intake. These therapeutic maneuvers will reduce the microvascular pressures in the lung regardless if the edema arises from hemodynamic or increased vascular permeability to water and solutes. Diuretics, such as furosemide, can improve the patient’s status within a few minutes and prior to the diuresis. Indeed, diuretics are even beneficial in pulmonary edema in anuric patients. This effect arises from furosemide’s beneficial effect on vascular tone with a concomitant increase in the systemic venous capacitance. Diuresis helps manage body salt and water volumes but is directly responsible for only trivial amounts of fluid removal from the lung. Since the lung represents only 1 per cent of the total body weight, even a 3 liter diuresis would only remove 30 ml from the lungs, with the remaining fluid coming from the remainder of the body. This 30ml is trivial compared to the liters of fluid present in the airspaces of adult patients with florid alveolar edema. In high permeability pulmonary edema our goal is to return the permeability of the alveolar capillary membrane back to normal levels. Regrettably, although many studies have been performed, there is no reliable proven way to directly modulate alveolar-capillary membrane permeability. Of course, therapy of the underlying cause, such as sepsis, is beneficial.

**Minimization of Treated Related Lung Damage**

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

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

Intact fluid clearance from the lung’s airspaces has been associated with survival, shorter periods of assisted ventilation and lower F\(_{O2}\) regardless if the patients have CHF- or ARDS-induced pulmonary edema. Although it has been known for decades that exogenous catecholamines significantly augment airspace fluid clearance (e.g. \(\beta\)) in animal models of pulmonary edema, recent randomized controlled trials have demonstrated that neither inhaled \(\beta\) nor intravenous \(\beta\) agonists improve the clinical outcomes of patients with pulmonary edema. It is unknown if the alveolar epithelium in these patients has become unresponsive to beta agonists, whether alternative approaches are required or that the currently used lung-protective strategies
are sufficiently protective to mask any benefit from an increase in alveolar fluid clearance.

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PCD GENETICS: A COMPLEX PUZZLE
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Primary ciliary dyskinesia (PCD) is a rare, congenital disorder, caused by abnormalities in the structure and/or function of the motile cilium.

Patients with PCD present with chronic and recurrent upper and lower respiratory tract infections, situs inversus in almost half of the cases and an increased incidence of male infertility [1].

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

The genetic origin of PCD is very heterogeneous. It is a mainly inherited in an autosomal recessive manner, although X-linked and autosomal dominant inheritance have rarely been described. Most often the disorder is isolated, but can be seen as part of a broader genetic syndrome, such as retinitis pigmentosa (RPGR) or orofaciodigital syndrome (OFD). Motile cilia are very complex organelles, consisting of more than 250 proteins. Cross-section of a normal ciliary shaft (axoneme) shows 9 pairs of microtubules, surrounding a central pair of microtubules (9+2 structure). ODAs and IDAs protrude from the microtubules: ODAs contain ATP-binding domains and form the motor units of the cilia. Nixin links interconnect the peripheral microtubules and radial spokes connect the peripheral pairs to the central pair. The axoneme is anchored to the cytoplasm by the basal body, a specialized centriolar structure.

In theory, alterations in the function of each of these 250 proteins can cause PCD. Until now, mutations in more than 30 genes have been detected to cause PCD and with this information around 60% of the cases can be solved genetically.

Several approaches can be used to search for new genes in PCD or other genetically heterogenous disorders [3]: genetic screening of experimental models with abnormal phenotype (i.e. Chlamydomonas, Xenopus, ..) is a solid approach because cilia are well-conserved organelles and was able to identify the first PCD-causing gene, DANI1. Homozygosity mapping in large families with PCD could identify several other genes. Analysis of transcriptomes or cilia proteomes from healthy control and patient samples is a more recently introduced technique that provides extensive information on the structure and function of cilia. Of course, the advent of massive parallel sequencing has allowed rapid detection of new genes that are involved in ciliary structure and function.

There is a clear correlation between the ultrastructural abnormalities and the mutated genes.

Mutations in genes encoding several ODA components are identified as PCD-causing if affected by detrimental mutations: DNAH5, DNAH1, DNAI2, DNAI1, TXNDC3. Mutations in these genes cause partial or complete absence of the ODA on electron microscopy. Most of the cilia are completely immotile. DNAH1 is also a component of the ODA. Mutations in DNAH1 have been described, but without TEM abnormalities. The cilia typically have a hyperkinetic, stiff beat pattern. In our cohort, more than 30% of the patients have PCD with normal ultrastructure. Using a whole exome sequencing approach, we were able to detect biallelic mutations in DNAH1 in 17/25 screened families of patients with PCD and normal ultrastructure[4]. In this way, the diagnosis of PCD with normal ultrastructure could be confirmed.

Mutations in the radial spoke head genes RSPH1, RSPH4A and RSPH9 cause absence or displacement of the central pair in a subset of the cilia. These have conserved motility, but the beating is not effective. Patients with mutations in these genes do not have situs abnormalities, as the nodal cilia (important for lateralization during embryogenesis) lack a central pair. Mutations in another component of the central pair, HYDIN, also cause PCD without situs inversus. However, ultrastructural evaluation of the cilia is normal in patients with HYDIN mutations, as it is too small to see on TEM.

Recently, mutations in several genes that are responsible for the cytoplasmic or axonemal assembly of ciliary proteins have been described: DNAF1 (LLRC50), DNAF2 (KTU), DNAF3, DNAF4 (DIXC1), CCDC103, HEATR2, LRRC6, ZMYND10, SPAG1 and C1orf59. These genes encode cytoplasmic proteins that are responsible for binding or assembly of the ODA and/or IDA components before intraflagellar transport to the axoneme. Consequently, the motor proteins are absent in the ciliary shaft but mislocalized in the cytoplasm.

CCDC151, CCDC114 and ARMC4 are components of the ODA-docking complex. Patients with mutations in these genes have ODA deficiency. CCDC164 and CCDC65 are components of the dynein regulating complex (DRC) and cause absence of the nixin links if mutated. These defects cause very subtle abnormalities in structure and function of the cilia, and can easily be missed. CCDC39 and CCDC40 are also assembly factors, but are responsible for the attachment of IDA to the dynein regulating complex. Mutations in these genes cause an absence of IDA and disorganization of the microtubules.

Patients with sensory ciliopathies like retinitis pigmentosa (caused by biallelic mutations in RPGR) or orofaciodigital syndrome (caused by biallelic mutations in OFD1) rarely have motile cilia dysfunction with symptoms of PCD.

Very recently, 2 genes were described, involved in a PCD-related disorder of mucociliary clearance characterized by a reduced generation of multiple motile cilium (RGC), previously reported as ciliary aplasia. The respiratory epithelium of these patients has only one or two (instead of >200) motile cilia per cell. Using cell culture techniques, the innate nature of this disorder has been shown. In collaboration with several other centers, we identified mutations in CCNO and MCI1AS in patients with RGC disorder[5, 6]. Both proteins are responsible for inducing ciliogenesis: CCNO is a cytoplasmic protein that induces centriole amplification and docking to the cell membrane. MCI1AS is a nuclear protein that acts upstream of CCNO and also induces FOXJ-1 induced expression of motile proteins. Therefore,

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

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

At this moment, around 60%-65% of PCD cases can be solved genetically, with DNAH5, DNAH11 and DAPKH1 being mutated most frequently[7]. It is expected that the rapid evolution of ciliary genetics will continue and that several new genes will be identified in the near future.

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INTERSTITIAL LUNG DISEASES
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Childhood interstitial lung diseases (ILD) represent a large spectrum of individually rare diffuse parenchymal lung diseases (DPLD), prevalent in children of all ages. Due to recent emphasis on orphan diseases, much progress has been made on the etiologies, pathomechanisms, diagnosis, treatment and overall management of such diseases. Since many children are treated by pediatricians, general practitioners, general and specialized childreñs hospitals, it is important to differentiate conditions from the many other children with frequent upper and lower respiratory tract symptoms, driven by recurrent infections or allergies, as ILD may be readily overlooked or patients lost among the other patients. Of great importance, novel classification systems have been suggested which hold more novel entities. In the group of developmental disorders (A1), larger patient series have been detailed, including filamin A deficiency and FOXF1 deficiency. Progress has been made in the group of children with chronic tachypnoe of infancy (A3), allowing differentiation in usual and aberrant cases. Larger series of children with surfactant dysfunction disorders (A4) have shown genotype-phenotype correlations for ABCA3, but not for SFPTC mutations. New identities have been described for alveolar proteinosis including genetic diseases and together with elegant novel therapeutic options like macrophage transplantation in model systems. Among the novel genetic diseases which have an ILD as central part of their clinical spectrum are STING and integrin a3 mutations. Tools for the collection of prospective data on all these rare entities are available and will be demonstrated during and after the presentation.

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

The original definition of bronchiectasis is pathological showing normal airway histology destruction with inflammation; however, since bronchiectasis is a structural phenomenon, the best non invasive method to diagnose it is by chest CT that demonstrates dilated airways with thickened wall. However, there is a complex relationship between the severity of radiological disease and that of the clinical syndrome. Furthermore, it is difficult to assess the severity of the disease. Patients may have severe diffuse bronchiectasis with minimal changes in pulmonary function. Bronchiectasis might be localized with purulent secretions or multilobar. A common clinical finding among patients with bronchiectasis is the chronic productive cough.

The causes of bronchiectasis in children are variable. Exclusion of pancreatic sufficient CF is important. These patients may have borderline or normal sweat chloride values, rare CFTR mutations and CFTR sequencing is often required to rule out CFTR-associated disease. Other causes are primary ciliary dyskinesia, immunodeficiency, foreign body aspiration and recurrent food or gastric aspiration, connective tissue disorders, allergic bronchopulmonary aspergillosis as well as other miscellaneous conditions. The diagnostic work-up should include, in addition to sweat test, CFTR function by nasal potential difference and, if not available, CFTR mutation analysis or CFTR sequencing including MLPA. PCD can be ruled out by nasal NO screening and electron microscopy. However, cases of PCD with normal EM appearance or normal nasal NO have been reported. Bronchoscopy should be performed to exclude foreign body aspiration or congenital anomaly that predisposes for bronchiectasis as well as pH monitoring and upper GI series to rule out GERD. The immune work-up in a child that only has bronchiectasis is expensive and, most of the time, is negative. Therefore at this stage a full coding regions sequencing can be performed and may reveal mutations in immune regulating genes.

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

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

The current evidence-based medicine level on NIV in the pediatric critical care setting will be analyzed from its highest level to the lowest one.

**Systematic reviews and meta-analyses**

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

**Randomized controlled trials**

Two hundred and twenty-five randomized controlled trials (RCT) were found if COPD patients are excluded. Again, data in pediatrics are disappointing. Generally speaking, it can be said that the use of initial NIV setting) is supported by a single RCT in pediatric intensive care unit (PICU) patients with acute respiratory failure. Twenty-five patients per group were included. Inclusion criteria for Yanez’s study were: respiratory failure criteria with fraction of inspired oxygen (FiO₂) > 95%; Ti ≤ 0.25; SpO₂ > 94% (5):484-489.

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

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

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

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

Almost all of the largest pediatric studies published have studied a mixed population (iNIV, nRNIV, eNIV), making it difficult to identify reliable predictive factors of failure. Nevertheless, several cohort studies with large samples (n> 100 patients) have identified predictive factors of failure that can be summarized as a tripod: lack of decrease in work of breathing (WOB), a younger age, and hypoxemia, measured in different ways (SpO₂/FiO₂ (SF) ratio, acute respiratory distress syndrome (ARDS) diagnosis, higher FiO₂).

There are also several studies evaluating NIV in specific diseases (bronchiolitis, pneumonia, neurogenic diseases, etc.) and situations (transport, postoperative cardiac patients, postoperative scoliosis, postoperative hepatic transplant, etc.) favoring the use of NIV.

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

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

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

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

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PATIENT-VENTILATOR INTERACTIONS DURING NASAL VENTILATION: A LARYNGEAL PERSPECTIVE

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

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

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

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

Active inspiratory laryngeal closure during NIV in lambs

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

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

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

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

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

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

Inspiratory active laryngeal closure in nPSV cannot be prevented by decreasing the inspiratory pressure rise time (unpublished data).
Clinical importance of inspiratory active laryngeal closure observed in lambs during nPSV

The occurrence frequency of inspiratory active laryngeal closure during nPSV in lambs with respiratory diseases is still unknown. Given that all our experiments were performed in healthy, full-term lambs, the observed active laryngeal closure may be a protective reflex mechanism against forced, unnecessary lung inflation at positive pressure. Hence, although the results previously obtained by Rodenstein’s team show that active inspiratory laryngeal closure can be present in humans during NIV, its clinical importance remains to be clarified.

In summary, active inspiratory laryngeal closure can be observed in certain NIV modes. Although the clinical importance of this patient-ventilator asynchrony remains to be clarified, it may be especially relevant in knowing that mild to moderate hypercapnia, as well as the use of nPSV, can prevent such laryngeal interference with the ventilator in NIV.

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UPDATE ON PULMONARY COMPLICATIONS OF ORGAN AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

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

Pulmonary complications of solid organ transplantation

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

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

Pediatric Pulmonology
Pulmonary complications of bone marrow and hematopoietic stem cell (HSCT) transplantation. Pulmonary complications of HSCT include numerous infectious complications, which vary in etiology according to the time of transplant and engraftment. (2) Non-infectious complications include mucositis, pulmonary edema, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, and pulmonary-renal veno-occlusive disease. Late non-infectious complications post HSCT include bronchiolitis obliterans (BO) syndrome, and cryptogenic organizing pneumonia (formerly bronchiolitis obliterans-organizing pneumonia (BOOP)). (4-6) Lung function changes post HSCT. A number of studies have examined lung function changes post HSCT, and the important role of pre-transplant lung function has been convincingly demonstrated. (5-8) Lung function prior to transplant provides a basis for comparison to post-transplant studies, but studies from our institution and others also suggest that lung function studies prior to transplant can help predict future risk of pulmonary complications as well as mortality post transplant. Lower pre transplant FEF25-75% was associated with a greater risk of all pulmonary complications and lower FVC and FEV1 were associated with lower overall survival post HSCT. Lower Lung Function Scores (a summation of FEV1 and DLCO) also predicted a higher risk of post transplant respiratory failure.(5-7) Strategies to alter transplant regimens for patients with low baseline lung function have not yet been performed to determine if these complications can be reduced or prevented. Longitudinal studies in HSCT patients suggest that the risk of decline in lung function is partially reversible for most but continues long past the transplant in a significant population. (7,8)

Advances in chronic lung allograft dysfunction (CLAD) and bronchiolitis obliterans (BO) syndrome. Chronic lung allograft dysfunction (CLAD) is a general term used to describe a sustained loss of lung allograft function, and includes the well-defined bronchiolitis obliterans (BO) syndrome as well as less well standardized phenotypes such as restrictive physiology, diffuse alveolar damage, and pleuroparenchymal fibroelastosis. (1,3) Serial monitoring of lung function helps detect early FFT changes that prompt additional evaluations; known risk factors for development of BO in the lung transplant population include primary graft dysfunction, acute cellular rejection, lymphocytic bronchiolitis, humoral rejection, GER, infections, and evidence of BAL neutrophilia.(3) In lung transplant patients, transbronchial lung biopsy (TBB) can be used to monitor for early evidence of rejection and lead to increased immunosuppression. Recently TBB has been shown to have value even in younger lung and heart-lung transplant patients, although there are significant technical issues with the small biopsy forceps available for pediatric bronchoscopes. This difficulty may be helped by a new generation of ultrathin bronchoscopes with a larger (2 mm) operating channel for large TBB samples. (9) TBB has a low yield for small airway tissue sufficient to diagnose BO, thus high resolution CT on inspiration and expiration has become the major diagnostic tool for pediatric patients with suspected BO. Chronic azithromycin has been used in a number of BO patients, with the best evidence for benefit being in a subset of patients with suspected BO. (10) For patients with advanced BO post transplantation, the only therapy available is lung transplantation. In lung transplant patients who develop BO, the outcome after a second lung transplant is not as good as with a first transplant, and the risk of redeveloping recurrent BO is higher compared to the group requiring a second lung transplant for other causes. (1,3) A small number of lung transplants have been performed in HSCT patients developing advanced BO, and the results of one small series suggest that survival is similar to matched controls with CF endstage lung disease. (10)

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HOW TO PUBLISH YOUR PAPER

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Introduction. Publish or perish is likely to be true for the academic for the foreseeable future. However, before trying to publish, it is a good idea to have something worth writing. You need a question which interests and excites you – because if it does not, no-one else will be interested or excited. And you need to be able to answer the only two worthwhile questions about any research project - So what? and, What for? The purpose of this presentation is to try to guide the reader away from the common traps which so often wreck a paper before it is started. A common trap is the failure to distinguish between changes that are statistically significant, and may give important hints about disease mechanisms, and changes that are useful in the clinical management of the patient – a much more stringent test, requiring minimal overlap between groups. Absence of use as a clinical test does not disqualify the paper – but overcalling the significance of your findings certainly will. Furthermore, a cross-sectional study (A and B are associated) will NEVER tell you about causation, and do not try to pretend it does. A may cause B, B may cause A, C may cause A and B, or it is all coincidence – to sort out these possibilities a longitudinal study (does A precede B) or even better an intervention (if I stop A I also stop B) is required.

Finally, consider which journal you are aiming at – always aim high (you never know, they may ask your mother to review your paper), but not ridiculously high – a case report will never make Nature, no matter how much you like it. Chose a journal that publishes your sort of work (e.g. the New England Journal of Medicine never publishes animal work, so do not send your mouse model data there); and style your manuscript so it fits the...
Journal. Keep to the word count – you may think you write like Tolstoy, but the editor will not agree, and may return overlapping manuscripts unreferenced. Finally, nothingpeeves an editor more than a manuscript obviously in the style of someone else’s Journal, and likely previously rejected from it.

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

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

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

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

The Discussion – what it means. Do not repeat the introduction, and do not extrapolate wildly beyond your study population. The tyro may find it useful to structure this section using five headings (Table). .

Special issues: Case reports. When doctors meet, they always talk about interesting cases, but Editors hate to publish them, because they are not cited. There must be a take-home message: SO WHAT! is even more important. This is not answered by a report of the 17th example of a rarity in your country, or an association between two rare conditions which will likely never happen again. Go for the literature, or the first report of a rarity in your country, or an association with no biological plausibility or validation elsewhere, for example in animal or cell line studies; no validation in a second population, or the so-called replication in fact pinpoints different SNPs in the same gene.

So the editor has asked you to revise your manuscript! You are probably outraged that anyone could possibly want your perfect paper changed in any way. But they do! Swallow your pride and your bile, and say you are grateful, even if you are not; and thank the reviewers for the helpful comments (even if you think they were idioms; remember they are probably good friends of the editor.). Prepare a point by point response, saying what you have done; what you have inserted; and where you have inserted it. Make the reviewers life easy.

Summary. Good luck, it’s worth keeping on trying. Finally, ten top traps (courtesy Vic Chernick) to avoid:

1. You did not read the instructions
2. You have a major conflict of interest
3. The manuscript was not checked for typos; if the writing is careless, the editors will think the rest of the work was too

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

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

Further reading
1. Chernick V. How to get your paper rejected. Pediatr Pulmonology 2008; 43: 220-3.
2. Stratton IM, Neil A. How to ensure your paper is rejected by the statistical reviewer. Diabetic Medicine 2004; 22: 371-3.
3. Sterk PJ, Rabe KF. The joy of writing a paper. Breathe 2008; 4: 225-32.
4. Hoppin FG. How I review an original scientific article. Am J Respir Crit Care Med 2002; 166: 1019-23.

Table: headings to give structure to the Discussion

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

HOW TO GET YOUR PAPER REJECTED, PART 2

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

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

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

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

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

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

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

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

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

8. Study design and statistics. Clinical studies especially need the input of scientists schooled in proper study design and the appropriate statistical analysis. Pediatric Pulmonology uses multiple biostatisticians each of whom has very extensive experience with pediatric clinical trials. One of the most frequent mistakes is the failure to perform a power analysis to determine how many control and treatment subjects are needed to find a predetermined measurable and (justified) relevant clinical effect.

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

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

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

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

Possibilities

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

3. Reread the manuscript several years ago from Wiley demonstrated that if your manuscript is resubmitted to a journal that has rejected it, the rejection rate is large is a problem that calls for fixing.” This is not a scientific approach.

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

References

1. Chernick V. How to get your paper rejected. Pediatr Pulmonol 2008; 43 (3):220-223.
2. Hoppin FG Jr. How I review an original scientific article. Am J Respir Crit Care Med 2002; 166:1019-1023.

III. FINALIST’S ORAL COMMUNICATIONS

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

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