ABSTRACT

Topic Sessions

The Impact of the Environment on Respiratory Outcome

#1. Indoor Pollution in LMICs

Manuel E. Soto-Martínez

Pediatric Pulmonologist – Clinical Epidemiologist Respiratory Department, Hospital Nacional de Niños (National Children's Hospital), San José, Costa Rica
Email: msotom@hnn.sa.cr or quiquesoto@gmail.com

Introduction

According to WHO, air pollution, including indoor and outdoor sources, is the biggest environmental cause of death worldwide; contributing to more than 3 million premature deaths every year. The impact is more in the vulnerable and the poor, where major environmental risk factors have been demonstrated. Women and children living in LMICs have the highest exposure to household air pollution, especially from indoor biomass fuel combustion. Globally, nearly 3 billion people use biomass fuels such as coal, wood, dung or crop residues for domestic energy production (either cooking, heating or lighting) in homes with no chimney ventilation of smoke [1]. Exposure to toxic amounts of combustion-related pollutants has been associated with various respiratory diseases, including lower respiratory infections (LRTI) in children. Interestingly, the use of biomass fuels varies by location, culture and socioeconomic status, determining both exposure and resulting health risks.

The effect of indoor air pollution (IAP) on children's respiratory health in developed countries is much less extreme and varies from those observed in poorer homes in the developing world. However, there is increasing evidence that other sources of IAP (e.g. tobacco smoke exposure) contributes to respiratory disease in children in industrialized countries. Gauderman et al. showed adverse effects of air pollution on lung development in children 10 to 18 years old leading to clinically significant deficits in attained FEV1 as they reached adulthood [2].

Indoor vs. Outdoor Pollution

IAP is of equal or greater impact to human health than outdoor pollution. It is associated with many health effects, including acute and chronic respiratory and systemic disorders (particularly cardiovascular). The main reasons: the amount of time people (especially women and children) spend indoors, the wide and range of household emission sources, and the increased concentration of some toxic pollutants indoors compared with outdoors. For many pollutants (e.g. biological pollutants, formaldehyde and other volatile organic compounds), the

concentration is higher indoors than outdoors. Other important sources of indoor pollutants are tobacco smoke exposure, household cleansers, mold and mildew, burning incense, chemicals from aromatic candles and mosquito coils. However, a limiting factor is that information about indoor pollution is more difficult to collect than outdoor pollution. Pollutant concentrations must be measured separately in different houses, and it has been assumed that observations made over a short space of time (or even on a single occasion) represent habitual exposure.

The diseases caused by IAP impose great economic costs on public health. It's been calculated that people spend more than 80% of their time indoors, either, at home, school and the office. Children on average, spend over 16 hours inside at home. Also, pregnant women spend most of their time inside at home and, therefore, IAP exposures may also be critical during the pre-natal period.

Worldwide, environmental pollution is not appreciated, and in most places not quantified as a cause of disease. However, given that lung disease is a leading cause of morbidity and mortality globally, the effect of air pollution on lung health is of great interest [3]. Multiple early life factors can adversely affect lung function and future respiratory health. Recently, Gray et al. studied a group of infants enrolled in the South African birth cohort to assess the determinants of early lung function in African infants. They found that factors such as maternal smoking, maternal alcohol and household benzene is associated with altered early lung function [4].

In addition, an increased interest in ultrafine particles has been rising due to their specific physico-chemical characteristics. These particles are commonly known as nanoparticles (<0.1 μm), and due to their small size they are commonly underestimated in many pollution measurements [5].

Exposure to Tobacco Smoke

Tobacco smoke is a primary indoor pollutant in developed and developing countries. The evidence for increased respiratory morbidity from second-hand tobacco smoke, particularly in children, is consistent. Although a decreasing frequency of daily smokers has been reported during the last three decades in developed countries, in LMICs countries it remains high. Data worldwide reveal high prevalence of smoking in most LMICs, in particular, in the Asian countries (67.3% in China, 54.4% in India and 73.1% in Vietnam). Smoking indoors is an established source of particulate matter (PM), nicotine, carbon monoxide (CO), benzene and other toxic compounds.

According to Etzel [6], tobacco smoke is the number one cause of preventable morbidity and mortality. Unfortunately, children exposed to passive smoking have 57% more lower respiratory illnesses than children without smoker, being higher if the mother is the smoker (70%). In addition, maternal smoking also encourages children to smoke, potentially worsening their health. Also, children who live in homes with smokers are 50% more likely to become smokers themselves.

Maternal smoking during pregnancy continues to be a large public health problem, as exposure to tobacco smoke often begins prenatally resulting in decreased lung function at birth, reduced levels of immunity, increased hospitalization for LRTI, and an increased prevalence of childhood wheeze and asthma [7]. A study, estimated that 40% of young children worldwide, were exposed to cigarette smoke at home, and that this contributed to 28% of under-5 mortality in children [8]. This becomes important, as exposure to passive smoking increases the risk of severe pneumonia in children, and is an independent risk factor of poor outcome. A recent systematic review found a significantly increased risk of pneumonia-related death (OR 1.5 IC 95% 1.2-1.9) among young children with cigarette smoke exposure [3]. In another study, Do et al. reported that 81% of children hospitalized in a city in Vietnam for pneumonia had household cigarette smoke exposure [9].

Oxides of Nitrogen

Nitrogen dioxide (NO_2) is an important component for both indoor and outdoor air pollution. Indoor sources of NO_2 include gas-fueled cookers, fires and water heaters; paraffin heaters also emit NO_2 , and small amounts occur in tobacco smoke. Research suggests NO_2 contributes to respiratory symptoms in children, particularly asthmatic children. Other studies suggested a 20% increased risk of LRTI in children exposed to long-term NO_2 . Yet, exposure to NO_2 varies depending on the proximity of children to the source, and this is a major difficulty in determining the health impacts and as it is difficult to measure personal exposure.

Particulate Matter: Smoke and Other Particles

Socioeconomic status is a major predictor of exposure to IAP, as levels of indoor particulate matter in developing countries far exceed those in developed countries. The less expensive fuel options are generally the less efficient, produce more smoke and may cause more complications. Epidemiological studies have shown that approximately 75% of global exposure to PM is attributed to indoor exposures in developing countries, two thirds occurring in rural areas, mainly from household biomass fuel combustion. This type of pollution results in substantial carbon loading of alveolar macrophages, and is a risk factor of childhood pneumonia.

The increased levels of emissions indoors are associated with an open or poorly ventilated stove, typical of most developing countries. These fuels are usually burned in open fires for cooking, heating and lighting in or near the home environment. In Guatemala, a parallel randomized controlled trial (the RESPIRE study) showed a significant reduction in severe pneumonia in children heavily exposed to wood smoke from

cooking, after a chimney stove intervention was placed to reduce IAP [10]. Additionally, Heinzerling et al. reported that delayed installation of a chimney stove intervention is associated with poorer lung growth than immediate stove installation [11].

Biological Pollutants

These include indoor particles whose importance for health is out of proportion to their concentration. These include bacteria, viruses, animal dander, house dust, mites, cockroaches, pollen and mould spores. Many of these biological contaminants are small enough to be inhaled. Their importance to human health arises because of the increased prevalence of allergic respiratory disease in children and young adults. Sensitization is a key factor for the development of allergy, and to be sensitized the individual must be exposed to a particular allergen. In Costa Rica, Ly et al. showed in a multivariate analysis that parental report of mold/mildew in the child's home ($p = 0.04$), and a positive IgE response to Der p 1 ($p = 0.008$) were significantly associated with airway hyperreactivity in children with asthma [12].

Fungal spores are another potential cause of symptoms in allergic patients. Also, the occurrence of acute pulmonary hemorrhage in infants exposed to toxigenic moulds is another example of the infant's vulnerability to an environmental hazard [6].

Formaldehyde

The role of formaldehyde in lower respiratory symptoms and asthma in children is controversial. However, several studies have reported associations between formaldehyde concentrations in homes and schools with asthma, asthma severity, allergy and airway inflammation in children. The principal source of formaldehyde in the homes are insulating materials, construction materials, chipboard, plywood, water-based paints, fabrics, cleaning agents and disinfectants. Tobacco smoke can also make a major contribution, and other sources include heating and cooking.

Volatile Organic Compounds (VOC)

VOCs are organic chemicals that easily vaporize at room temperature and can be found in homes. Associations between measure of exposure and poor respiratory health have been observed in infants, preschool and school-aged children. Their sources include building materials, furnishing, furniture, adhesives, cleaning agents, cosmetics, the water supply, tobacco smoke and fuel combustion.

Conclusion

In summary, indoor pollution is a serious problem in LMICs; but its importance in developed countries should not be underestimated. Pollution-related acute and chronic diseases are becoming more common, particularly in children in LMICs who are proportionately more exposed to environmental pollutants. Global efforts to promote improved programs of pollution control are needed. For instance, specific interventions such as effective cooking solutions (as the use of improved fuels, cookstoves), or heaters, and improved ventilation can improve human health. Unfortunately, despite its enormous human and economic cost, environmental pollution has been largely overlooked.

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#2. Prenatal Exposure to Pollutants and Lung Disease

Judith A. Voynow, Edwin L. Kendig Jr.

Correspondence: Judith A. Voynow Professor of Pediatric Pulmonary Medicine, Children's Hospital of Richmond at VCU, Richmond, VA, USA
Email: judith.voynow@vcuhealth.org

Air pollutants constitute one of the greatest health threats to vulnerable populations including infants and children. The major sources of pollutants are indoor exposures to environmental tobacco smoke (ETS) and combustion of biomass fuels, and outdoor exposures to combustion products from traffic and industry including fuel production. Air pollutants comprise a heterogeneous mix of ozone, carbon monoxide (CO), nitrogen dioxide (NO₂), sulphur dioxide (SO₂), polycyclic aromatic hydrocarbons (PAH), lead and other heavy metals,

and fine particulate matter less than 10 microns in diameter (PM₁₀) or less than 2.5 microns (PM_{2.5}). Particulate matter is released by motor vehicles, particularly diesel engines, and consists of organic substances, nitrates, sulfates, elemental carbon, semiquinones and metals. Ozone is generated by ultraviolet light interaction with nitrogen oxides and volatile organic compounds. Exposure to pollutants varies with locale and season. However, with the accelerated industrialization of developing nations, there are more urban centers with toxic levels of air pollutants. In 2016, the World Health Organization estimates that 6.5 million deaths (11.6% of global deaths) per year are due to indoor and outdoor air pollution. South-East Asia and the Western Pacific have the greatest burden of air pollution and are the regions with the greatest morbidity and mortality associated with air pollution.

Air pollution exposures during pregnancy can have a major impact on fetal development and the respiratory health of the child. During pregnancy, there are physiological changes such as increased respiratory rate and minute ventilation, and increased fat accumulation that promote increased uptake and concentration of pollutants in the body. During pregnancy, oxygen demand is increased; but with higher concentration of circulating CO, there is less oxygen carrying capacity, and a risk of decreased oxygen delivery to the fetus. Fetal hypoxia can blunt alveolar development and promote primary pulmonary hypertension. Some pollutants can cross the placental barrier such as nicotine, while others may induce inflammation or alter growth factor pathways. For example, PM₁₀ and NO₂ prenatal exposures throughout pregnancy, induce changes in fetal cord blood biomarkers with high fms-like tyrosine kinase1 and decreased placental growth factor consistent with an anti-angiogenic state and possibly placental dysfunction.

Several systematic reviews have identified some associations between prenatal pollutant exposures and the impact on birth weight, preterm delivery and respiratory disease. There is a significant association between maternal exposure to CO, NO₂, PM_{2.5} and PM₁₀ and low birth weight, and maternal exposure to SO₂ and PM₁₀ and preterm delivery. Both lower birth weight and premature birth increase the risk for decreased pulmonary function tests and increased respiratory symptoms. Maternal exposure to CO, NO₂, PM_{2.5} and PM₁₀ are associated with airflow obstruction in children starting at age 5 weeks and persisting to 6-11 years. Maternal exposures to NO₂, PM_{2.5}, PM₁₀, and PAH are associated with increased risk for wheezing, cough, and lower respiratory tract infection.

With improvements in quantitation, localization and timing of pollutant exposures, there is an opportunity for more refined outcome analyses. One epidemiological study, the Boston Birth Cohort, followed 736 full-term infants and demonstrated that maternal exposure to PM_{2.5} at a specific time period during gestation, 16-25 weeks, increased the risk for asthma in boys, but not girls, at age 6 years. This study demonstrates that there are gestational windows of susceptibility for altered lung development resulting in risk for asthma and there may be offspring host factors that mitigate this risk.

Maternal smoking during pregnancy is a large public health problem with rates varying from 5-40% worldwide. There is strong epidemiological data that prenatal exposure, not postnatal exposure is a risk

factor for wheezing and asthma in offspring. Maternal smoking during pregnancy is a major cause of low birth weight and premature delivery; both factors predispose to increased risk of airflow obstruction. The impact on airflow obstruction is long-lasting and observed into adulthood. Nicotine crosses the placental barrier and is detected in neonatal cord blood. Thus, nicotine may negatively affect lung development. There is evidence that maternal smoking during pregnancy induces cord blood DNA methylation. In the Norwegian Mother and Child Cohort study, DNA methylation at 26 CpGs affects ten genes with important detoxification and development functions, including AHRR, the aryl hydrocarbon receptor repressor, CYP1A1, a P450 xenobiotic metabolizing enzyme, and GFI1, Growth Factor Independent 1 Transcription Repressor. Importantly, the DNA methylation pattern was confirmed in a separate validation study supporting a conserved epigenetic impact due to maternal smoking. Importantly, in addition to efforts to encourage cessation of smoking, there may be therapeutic approaches to mitigate the effect of maternal smoking on the offspring. A recent placebo controlled, randomized, double blinded, prospective trial administered Vitamin C to smoking, pregnant women to determine whether increased maternal levels of Vitamin C prevented airflow obstruction in offspring. Vitamin C administration did improve tidal lung function measures in newborn infants compared to the control infants. This intervention is currently being investigated in a larger study to determine whether Vitamin C has long-lasting effects on protecting lung function in offspring of mothers who smoke.

There are several complex challenges that need to be overcome to make progress in studying the mechanisms of how prenatal air pollutant and tobacco smoke exposure affect offspring. First, pregnant women may be exposed to mixtures of pollutants with varying concentrations, timing and duration. New models incorporating measurements from monitoring devices such as the satellite-derived aerosol optical depth spectroradiometry have improved the spatiotemporal accuracy of determining pollution exposure. However, the complexity of multiple pollutants still complicates the ability to model exposures or to attribute outcomes to specific constituents. Second, many host factors including socioeconomic status, maternal stress, and the maternal genome, microbiome and metabolome interact with pollutant exposures and together create the maternal "exposome". All these factors impact fetal development. Finally, it is difficult to separate antenatal pollutant exposures from exposures during infancy or childhood to determine the relative impact on lung disease in the child. Alveolar development continues through adolescence and therefore interactions between host factors and the child's exposures to pollutants and ETS may continue to impact lung development, risk for asthma and lower respiratory tract infections. However, this potential for new lung parenchymal growth and lung repair also provides an opportunity to mitigate early injury.

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#3. The Role of the Environment in Severe Bronchiolitis.

Fernando P. Polack

Professor, Department of Pediatrics at Vanderbilt University Scientific Director of the INFANT Foundation in Buenos Aires, Argentina
Email: fernando.p.polack@Vanderbilt.Edu

It is not clear why disease severity differs among healthy, full-term infants with RSV LRTI; however, virus titers, inflammation, and Th2 bias are proposed explanations. While TLR4 is associated with these disease phenotypes, the role of this receptor in respiratory syncytial

virus (RSV) pathogenesis is controversial. In this presentation, we will discuss the interaction between TLR4 and environmental factors in RSV disease and define the immune mediators associated with severe illness. Two independent populations of infants with RSV bronchiolitis revealed that the severity of RSV infection is determined by the TLR4 genotype of the individual and by environmental exposure to LPS. RSV-infected infants with severe disease exhibited a high GATA3/T-bet ratio, which manifested as a high IL-4/IFN- γ ratio in respiratory secretions. The IL-4/IFN- γ ratio present in infants with severe RSV is indicative of Th2 polarization. Murine models of RSV infection confirmed that LPS exposure, Tlr4 genotype, and Th2 polarization influence disease phenotypes. Together, our results identify environmental and genetic factors that influence RSV pathogenesis and reveal that a high IL-4/IFN- γ ratio is associated with severe disease.

Treatment of Severe Asthma

#1. Markers of Severity in Difficult-To-Treat Asthma

Andrew Bush

Imperial College and Royal Brompton Hospital, London, UK
Email: A.Bush@rbht.nhs.uk

The WHO definition of severe asthma [1] comprises three categories, each carrying different public health messages and challenges: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3) treatment-resistant severe asthma. Untreated severe asthma comprises children in areas where there is insufficient access to asthma care, and will not be discussed further, since the solution largely lies outside the hands of pediatricians. They should note the dramatic benefits of making simple, low cost treatments widely available; and the developed world needs to remember that for the vast majority of children, simple remedies properly used are all that is needed. However, it should be noted that there are few if any studies from low and middle income settings of markers for a severe outcome in a setting where adequate treatment is not available. Conventionally, severe therapy resistant asthma (STRA), or treatment-resistant severe asthma is defined as either (a) the need for high dose treatment to control the disease, or (b) either or both of uncontrolled symptoms and acute attacks despite high dose treatment (see Table) after reversible factors have been addressed [2]. The defining level of treatment in children is beclomethasone equivalent 800 mcg/day plus long acting β -2 agonist and leukotriene receptor antagonist, or at least failed trials of these agents.

Table: Conventional criteria for diagnosing uncontrolled asthma.
FEV₁ = first second forced expired volume

- Uncontrolled symptom >3/week use of short-acting β -2agonist and/or asthma control test <19/25
- >2 asthma attacks per year treated with oral prednisolone
- >1 severe attack, defined as needing hospitalization, intensive care or ventilation

- Persistent airflow limitation (FEV₁>2 Z-scores below the mean after systemic steroid trial plus short-acting β -2 agonist, or same level of FEV₁ after withhold of short and long-acting β -2 agonist

However, although those with STRA have bad outcomes, in the UK National Review of Asthma Deaths (NRAD), around 70% of those who died did not meet criteria for 'severe' asthma, despite death being rather a severe outcome. [<http://www.respiratoryfutures.org.uk/media/1531/why-asthma-still-kills-full-report.pdf>]! So markers of severity should be considered in all asthmatics. A proposed framework for airway disease comprises airway disease, extra-pulmonary co-morbidity, and lifestyle/environmental factors, considering clinical traits, treatment (especially what is treatable), and the expected benefits of treatment. I would also add physician behavior, which had significant effects in NRAD. Since we KNOW that most children with asthma are readily treated if low dose inhaled corticosteroids (ICS) are regularly and properly administered, the focus should initially be outside the airway, rather than uncritically adding more and more therapies. The subject has been comprehensively reviewed elsewhere [3]; this abstract is necessarily selective

A. Extrapulmonary Markers of Severity

1. **Food allergy:** This is commoner than anticipated in children ventilated for asthma in the Pediatric Intensive Care Unit (PICU), though whether causative or a fellow traveler is unclear [4]. The differentiation of acute asthma from acute anaphylaxis pathologically may be difficult
2. **Severe atopy:** As with food allergy, it is unclear whether this is causative or a marker of STRA. Either way, children with multiple aeroallergen sensitization with big skin prick test wheals and/or high specific IgE are a high risk group
3. **Severe asthma with fungal sensitization (SAFS):** There is no generally agreed pediatric definition; pragmatically, ours is STRA (any pattern) with sensitization (SPT or sIgE) to any fungus. Since allergic bronchopulmonary aspergillosis is rarely if ever seen in children with asthma, we do not include in the definition an IgE<1000, as do the adults. We have shown that children with SAFS have worse inflammation for a given level of treatment, thus putting them at greater risk of severe asthma [5].
4. **Obesity:** There is evidence that asthma complicated by obesity is pathologically different from non-obese asthma, and is associated with steroid resistance and a greater likelihood of admission to PICU. Certainly obesity is potentially a treatable trait

B. Environment/Lifestyle Markers of Severity

1. **Non-adherence:** This is probably the single most important cause of asthma attacks and a severe outcome, manifest by underuse of ICS and over-use of short-acting β -2 agonists (SABA). SABA over-use should be readily identifiable from dispensing records. Detection of ICS underuse is more

difficult; questionnaires are ineffective in our hands, prescription uptake does not equate to inhalation, and electronic monitoring merely means the device has been activated. This is an area where smart technology is needed. Also, identifying non-adherence is one thing; remedying it is quite another.

2. **Patterns of seeking health care:** Repeated attendance at emergency departments, and failure to attend regular reviews, is another concerning feature, likely a marker of a chaotic family life and therefore poor supervision of treatment as well.
3. **Environmental exposures:** Allergen exposure in those sensitized is associated with steroid resistance, and with a viral infection, a high risk of an asthma attack [6]. Passive smoking is also associated with steroid resistance [7].

C. Physician Behavior and Asthma Severity

1. **Asthma plans:** Failure to have a plan for dealing with attacks was another adverse marker in NRAD. Asthma plans have been shown to be effective, and should be carefully reviewed after an acute attack to determine if it was followed, and whether it should be modified.

D. Airway Markers of Severity

1. **Previous severe asthma attacks:** The roots of these mainly lie outside the airway, but it is quite clear that severe attacks are the major risk factor for another severe attack and death from asthma, as well as in the long term being associated with an accelerated decline in lung function. A severe attack should be a 'never event' and should prompt the most detailed re-assessment of asthma management of the child
2. **Persistent airway eosinophilia:** In adult studies at least this is a marker of risk of acute attacks, and there is certainly biological plausibility that uncontrolled eosinophilic inflammation contributes to severe exacerbations. Whether this is TH2 driven in children is dubious. Neither we [8] nor SARP [9] were able to demonstrate that this was due to the classical TH2 cytokines IL4, IL5. These two studies mean that anti-type 2 monoclonal antibodies should not be used uncritically; we need trials in children, and should not extrapolate from adult studies
3. **Absence of airway eosinophilia:** We have no add-on therapies for this phenotype, although possibly azithromycin may help; the absence of treatment options makes this a vulnerable group, for which more studies are needed
4. **Absence of intra-epithelial neutrophils:** Airway neutrophilia in BAL or in the submucosa is not a feature of pediatric STRA. We have recently shown that the presence of intra-epithelial neutrophils is associated with less severe asthma, quite different from what was shown in adults [10]; pediatric STRA is a different disease

TAKE HOME MESSAGE The most important way of reducing poor asthma control and reducing asthma attacks is NOT increasing airway treatment or deploying the latest monoclonal but by getting the basics right, including adherence and environmental exposure, and having an effective management plan for attacks. High risk patients are those who have had a severe attack, overuse SABA, and underuse ICS. It is always best to **KISS – Keep It Simple Stupid**, however experienced you are! And patients and pediatricians should never take asthma lightly – it is still a killing disease.

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Asthma and Allergies

#1. Allergic Rhinitis

Adnan Custovic

Department of Paediatrics, Imperial College, London, UK

Corresponding author: Adnan Custovic MD PhD, Clinical Professor of Paediatric Allergy, Imperial College London, Department of Paediatrics, St Mary's Campus Medical School, London W2 1 PG, UK Tel: +44 20 7594 3274, Email: a.custovic@imperial.ac.uk

Allergic rhinitis is one of the most common chronic diseases in childhood. The International Study of Asthma and Allergies in Childhood reported an average prevalence rhinitis of 8.5% among 6-7-year-old children, and 14.6% for 13-14 year-old children¹. The burden of allergic rhinitis to individual patients and the society is often underestimated, and there is a general lack of data on the risk factors and phenotypes of rhinitis in childhood and adolescence².

Diagnosis of Allergic Rhinitis

The diagnosis of allergic rhinitis is based upon clinical history, including type, duration and frequency of symptoms and exacerbating factors². Most children and teenagers with rhinitis experience upper respiratory symptoms including nasal blockage, itching, watery rhinorrhea and sneezing, but some may present atypically with cough or snoring. It is worth noting that despite often troublesome symptoms, rhinitis is often ignored, and only a minority of symptomatic children have appropriate diagnosis and management plans³. Examination of nose is essential in the diagnosis of rhinitis, and should always been carried out².

Atopic sensitization can be ascertained using skin prick tests or measurement of allergen-specific serum IgE. However, both these tests can be positive in the absence of any symptoms, and positive skin test or IgE does not confirm the expression of rhinitis symptoms upon allergen exposure. In allergen-driven rhinitis, symptoms have to be seen in association with allergen exposure². The data which demonstrated that quantification of atopic sensitization by using the titer of sIgE antibodies or the size of skin prick test wheals increases the specificity of these tests in relation to the presence and severity of rhinitis⁴ have in recent years changed the way we interpret the results of IgE and skin tests, with a move from dichotomization (positive/negative test) to quantification (IgE titer and skin test wheal size)². Measuring sensitization to allergen components (component-resolved diagnostics) may more be informative than standard tests using whole allergen extracts. However, the potential value of component resolved diagnosis in the diagnosis of rhinitis needs to be established before it can be considered for the routine use in clinical practice².

Other investigations may be required to evaluate other possible diagnoses (e.g. measurement of nasal mucociliary clearance, nasal nitric oxide, nasal endoscopy, acoustic rhinometry etc.).

Management

Management strategy for allergic rhinitis should include avoidance of relevant allergens when possible². Oral and intranasal antihistamines and intranasal corticosteroids are the first-line treatment of allergic rhinitis, with intranasal corticosteroids having the greatest efficacy. Add-on treatments may include oral leukotriene receptor antagonist and intranasal cromoglycate². In patients with allergic rhinitis over the age of five years who are inadequately controlled using standard pharmacological treatment, allergen-specific immunotherapy can be helpful and should be considered.

Allergic Rhinitis and Asthma Presence and Severity

Amongst school-age children, allergic rhinitis frequently co-exists with asthma³, and it often precedes asthma development⁵. There is a mounting body of evidence that patients with both asthma and rhinitis have more severe lower respiratory symptoms compared to those with asthma alone. For example, amongst adult patients with asthma, those with comorbid rhino-sinusitis have considerably poorer quality of life, and chronic rhinitis is an important co-morbidity of severe asthma⁶. Similarly, in children with asthma, allergic rhinitis has an adverse impact on asthma control⁷; in addition, children and adolescents with moderate/severe asthma who are treated with inhaled corticosteroids and have concurrent allergic have increased use of emergency care services compared to patients without rhinitis⁸. Among children with asthma recruited from the hospital asthma clinic, the presence of allergic rhinitis has been shown to have a significant adverse effect on asthma control, even when asthma was considered adequately controlled⁷. In a population-based study, we have demonstrated that amongst children with asthma, the presence of rhinitis has significant adverse effect on asthma severity⁹. Among asthmatic children, those with rhinitis had more frequent wheeze attacks (2.4-fold increase in risk), more severe attacks of wheezing associated with speech limitations (3.4-fold increase in risk), more frequent visits to the family doctor (9.5-fold increase in risk) and greater school absenteeism because of asthma (9-fold increase in risk)⁹.

Can Treatment of Allergic Rhinitis Improve Asthma Control?

In a study from the Netherlands, treatment of allergic rhinitis with intranasal corticosteroid reduced the adverse effect of rhinitis on asthma severity and control⁷. Similarly, in our study described above, adjusting for the use of antihistamines did not change the association between rhinitis and asthma severity, but adjusting for the use of intranasal corticosteroid resulted in a small, but consistent reduction in risk⁹. These observations are consistent with findings in a retrospective cohort of older children and adults, which showed that among patients with both asthma and rhinitis, those who were treated for allergic rhinitis were significantly less likely to visit emergency departments or be hospitalized than those who were not treated¹⁰. The results of the above studies suggest (but do not prove) that amongst children with both asthma and rhinitis, appropriate treatment of rhinitis with intranasal corticosteroids may improve asthma control. The definitive answer can only be obtained in appropriately designed randomized controlled trials; however, there are as yet no such long-term trials in children. It is however of note that a 4-week study among

children with mild/moderate asthma and intermittent allergic rhinitis has shown that intranasal corticosteroid may improve exercise-induced bronchospasm¹¹. In contrast, a double-blind randomized cross-over trial amongst adults with asthma and persistent allergic rhinitis did not demonstrate any steroid sparing effect of adding intranasal corticosteroid to low dose inhaled corticosteroids on lower airway outcomes¹². Recent meta-analysis of 18 studies assessing the effect of intranasal corticosteroid on asthma outcomes in patients with allergic and comorbid asthma concluded that intranasal corticosteroid may improve some lower airway outcomes, but that further studies are needed to confirm the role of intranasal corticosteroid sprays as therapy for asthma outcomes¹³.

In conclusion, allergic rhinitis is common, and is an important comorbidity of childhood asthma. All children with asthma should be assessed for the presence of rhinitis, and appropriately treated to alleviate both upper and lower respiratory symptoms.

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#2. Is Asthma over Diagnosed?

Dr Louise Fleming

National Heart and Lung Institute & Royal Brompton Hospital London, UK
Email: l.fleming@imperial.ac.uk

Asthma is the most frequently diagnosed chronic condition in childhood. Globally it is estimated that 334 million people have asthma¹. Given the frequency with which an asthma diagnosis is made, on the face of it, it would appear that diagnosing asthma is easy. However, most asthma diagnoses are made on the basis of symptom reporting and there is little objective evidence to support the diagnosis of asthma. This leads to both over and under diagnosis of asthma and delay in a definitive diagnosis. There is no other condition in children in which treatment is started in so many with so little objective evidence. Whilst symptom reporting is clearly the starting point which suggests the possibility of asthma, symptoms are insufficient on their own to confirm a diagnosis. Symptoms are non specific and some, such as cough, a feature of normal childhood viral infections. Parent-reported wheeze could mean any respiratory noise from the upper or lower airways; some cultures do not even have a word for wheeze and yet great weight is put on this item in both clinical practice and epidemiological studies.

Objective Tests for Asthma

There is no single gold standard test for asthma and the positive and negative predictive values of each test are far from optimal. However, that is not to say that NO tests should be undertaken, rather that testing is carried out in those with a suggestive history in a logical fashion to demonstrate one or more of the key features that characterize asthma as a chronic inflammatory disease with variable airflow obstruction and airway hyperresponsiveness². Objective testing includes measurement of peak flow, peak flow variability, spirometry, demonstration of reversibility of airflow obstruction, exhaled nitric oxide (FeNO), induced sputum or tests of airway hyper-responsiveness (such as methacholine or histamine challenge). Some of these tests may only be available in specialist centers; however the ability to measure peak flow, assess variability across a 2- to 4-week period and record the response to short acting beta agonists (SABA) should be available at all levels of care and measurement of FENO is likely to become increasingly available. The absence of variable airflow obstruction AND inflammation should really call into question the diagnosis. A trial of treatment may be helpful in some cases, provided that there is clearly documented evidence of response and deterioration on stopping.

Accuracy of Diagnosis

In a retrospective review of over 650 Dutch children diagnosed with asthma, the diagnosis was only confirmed in 16% (diagnosis was confirmed by presence of documented recurrent wheeze and dyspnea and demonstration of reversible airflow obstruction by spirometry and if needed additional tests such as histamine challenge)³. Twenty-three percent had probable asthma but no confirmatory test; 54% were deemed as over-diagnosed. The remainder had never been diagnosed with asthma and were prescribed an inhaler for another (unknown) reason. A Canadian study recruited 102 children with a diagnosis of asthma and 52 controls and carried out objective testing⁴. A diagnosis of asthma was confirmed by clinician assessment plus either reversible bronchoconstriction or a positive methacholine challenge. Forty-five percent of cases were overdiagnosed and 10% of symptomatic controls were underdiagnosed. However, it should be emphasized that these studies were cross-sectional and as previously stated there is no single gold standard test for asthma. It may have been that the diagnosis was correct when made and the child had grown out of their symptoms or given the variability of asthma assessment on a single day is unlikely to be sufficient to exclude a diagnosis in the context of suggestive symptoms. Nonetheless, these studies highlight how infrequently objective testing is carried out and the importance of reviewing a diagnosis.

Why Does it Matter?

Misdiagnosis of asthma has the potential to cause harm. Children may be prescribed unnecessary and potentially harmful medications. For those with an alternative diagnosis, doses of inhaled corticosteroids (ICS) may be relentlessly increased in view of lack of symptomatic response. However, it should be noted that many of the children over diagnosed with asthma in the Dutch and Canadian studies^{3,4} were either on low dose ICS or as needed SABAs implying that in fact these children had very few symptoms and had received a diagnosis of asthma for relatively trivial symptoms. If almost half of children diagnosed with asthma are in fact healthy children, this reinforces the view of asthma as a mild disease and, as highlighted by the National Review of Asthma Deaths⁵, the potential for adverse outcomes including death, is poorly recognized among health care professions. This complacency puts those with genuinely poorly controlled disease at risk. A correct diagnosis is the cornerstone of good asthma management and effort should be made to ensure that the diagnosis is underpinned by objective tests.

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#3. The Relation Between Wheeze Phenotypes and Asthma Later in Life

John Henderson

School of Social and Community Medicine, Faculty of Health Sciences, University of Bristol UK

Email: A.J.Henderson@bristol.ac.uk

Many children who start wheezing in early childhood will outgrow their symptoms at some point during their life, although wheezing may relapse and remit over the life course, with temporal variations in frequency and severity. Wheezing and asthma during the first few years of life are heterogeneous in their manifestations; in addition to temporal variations in onset, progression and characteristics of symptoms, wheezing illnesses vary in their environmental trigger factors, responses to treatment and associations with other variables such as allergic sensitization and lung function. These observations have led to speculation that wheezing illnesses in early childhood may not be representative of a common disease process but that there exist several discrete wheezing phenotypes that are underpinned by different biological processes or *endotypes*. A greater understanding of phenotypic heterogeneity and an ability to discriminate between discrete phenotypes in early life, either through clinicopathological features or biological markers of underlying processes, could advance the opportunities for stratified interventions to alter the natural history of asthma and wheezing across the life course.

Wheezy Bronchitis and Asthma: The Early Years

One of longest running population-based studies of asthma outcomes in the world started in Melbourne in 1964¹ and has now reported on follow up to age 50 years of participants who were recruited in childhood at age 7 or 10 years². At recruitment, children were classified into 4 categories; mild wheezy bronchitis, moderate wheezy bronchitis, asthma and severe asthma. At successive follow up surveys, severe asthma in childhood was associated with the greatest risk of persistent or frequent asthma in adulthood. Furthermore severe asthma was associated with lower lung function (FEV₁/FVC) that was established during childhood and, despite no acceleration of the rate of decline of FEV₁ during adulthood, this group had a much greater risk of COPD in mid-adult life than subjects who had no history of asthma or wheezing. Similar findings of lung function deficits existing in mid-childhood and persisting to adulthood were observed in the Dunedin study in association with wheeze that persisted throughout this transition³. The Tucson Children's Respiratory Study was seminal in showing how early childhood phenotypes based on temporal patterns of wheezing related to these asthma and lung function outcomes in later life. This prospectively followed birth cohort showed that most early onset wheeze became asymptomatic in mid-childhood, did not progress to asthma and was associated with low lung function soon after birth. In subsequent follow ups of this birth cohort, the Tucson

group also showed that this transient early wheezing phenotype was associated with persistence of low lung function through adolescence to early adulthood^{5,6}.

Early Wheezing Phenotypes and Later Outcomes

We developed the Tucson paradigm using a data-driven approach to analyze parental reports of wheezing illness to age 7 years in a large birth cohort in the UK. This confirmed the association of transient early wheezing with low lung function in mid-childhood and identified three phenotypes of wheezing that persisted until mid-childhood, which were characterized by their age of onset⁷. These have since been replicated several times in independent cohorts with evidence of external validity through comparison with phenotypes based on clinical observations. What emerged from this work was that wheezing that began early (within the first 6-18 months after birth) and persisted until mid-childhood had the strongest associations with a clinical report of asthma and with low lung function compared with non-wheezers and other more transient phenotypes. Further insight into this was gained from analysis of the Manchester Asthma and Allergy Study (MAAS), which had links to individual health records and showed that the persistent wheezing phenotype could be stratified into those with and without frequent health care utilization; essentially a more severe form of persistent wheeze that was termed persistent *troublesome* wheeze. Interestingly, genetic studies have suggested that these sub-phenotypes (persistent wheeze and persistent troublesome wheeze) have distinct associations with genetic loci that are not shared by other phenotypes. Recent follow up of our early childhood phenotypes to adolescence has confirmed that early-onset, persistent wheezing is associated with asthma, low lung function, bronchodilator responsiveness and increased FeNO in adolescence. This phenotype was also the most strongly associated with any allergic sensitization in mid-childhood in our cohort. In the MAAS study with longitudinal assessment of sensitization, further modeling of atopic status has indicated that the strongest association with hospitalization for wheeze/asthma, poorer lung function and higher airway reactivity¹⁰.

The Current State of the Art

Pooling resources, combining data and expertise and applying sophisticated statistical approaches to data interrogation has enabled us to reach a position where the target phenotype for intervention is almost certainly that associated with early onset, troublesome wheezing associated with evidence of multiple atopic sensitization. The jury is still out on whether the other phenotypes that have been identified through latent class analysis and other clustering approaches represent discrete biological entities or different manifestations of the same fundamental process. The next challenge is to extend analyses to include triangulation with detailed clinical and biomarker information to fully understand the endotypes associated with persistent, allergic asthma and to target interventions to these pathways to prevent or modify the long term morbidity of this condition.

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Asthma Across The World

#1. The Challenges of Asthma Treatment in Low and Middle-Income Countries

Paulo Márcio Pitrez

PUCRS Porto Alegre, Brazil

Email: pmpitrez@pucrs.br

Severe asthma has been the focus of research and discussion worldwide. In children, this spectrum of disease results in an important impairment of quality of life, involving school performance, leisure, and emotional aspects, with high direct and indirect costs to society. Many low and middle-income countries (LMIC) have a high prevalence of severe asthma in children, particularly in Latin America. However, studies on severe childhood asthma in these countries are scarce. As an example, Brazil, a continent-wide country in South America, with

350,000 hospitalizations/year for asthma, and approximately 7 deaths/day from the disease is one of the countries with the highest prevalence of severe asthma in the World (10%). The major challenges in the management of severe asthma in children in these countries are usually the correct diagnosis of this clinical presentation by well-trained professionals, availability, and referral to tertiary centers and difficulty for accessing controller medications with higher costs. Many children with severe asthma are difficult-to-treat ("problematic asthma"), and a percentage of these children are resistant to conventional pharmacological therapy (high doses of corticosteroid, long-acting beta-2, and leukotriene receptor antagonists), representing one of the greatest challenges in the clinical management of asthma. This type of severe asthma has been classified as severe therapy-resistant asthma (STRA), strongly associated with the atopic phenotype in children. It is important to emphasize that many patients with problematic asthma do not present STRA, but more often: 1) another disease; 2) inadequate inhalation technique; 3) adherence-to-treatment problems; 4) relevant environmental factors; 5) or comorbidities (allergic rhinitis, obesity, severe gastroesophageal reflux, among others). In LMIC populations, this presentation of the disease still deserves greater understanding and dissemination. Moreover, any child with uncontrolled asthma using high-dose inhaled corticosteroid, long-acting beta-2 agonist (LABA), and anti-leukotriene, deserves to be carefully evaluated, with clinical follow-up of at least 6 months by a specialist in the area, for an adequate diagnosis and management. Hence, due to the complexity of the correct diagnosis of problematic asthma in children, well-trained professionals, with multidisciplinary teams, are essential but are a major constraint in LMIC settings. Regarding pharmacological treatment in children with STRA, steps 4-5 of the GINA guidelines are indicated but are also related to higher cost and difficult-to-access treatments in LMIC, such as anti Ig-E (omalizumab). Omalizumab has shown significant clinical benefits in many children with STRA. However, its high cost is a limitation in these countries. A lower-cost option in this group of children would be the use of daily systemic corticosteroids, but some children do not respond to this treatment and their use is associated with serious adverse events. In conclusion, the burden of severe asthma in children is high, with large social impact in LMIC. A review in guidelines with a closer look and discussion of more effective ways of managing severe asthma in settings with limited economic resources is essential for reducing the burden of disease in children with asthma in LMIC.

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#2. Are the Risk Factors of Asthma in China the Same as Those in Western Countries

Gary Wong

Department of Paediatrics, Prince of Wales Hospital, Shatin, NT, Hong Kong, China
Email: wingkinwong@cuhk.edu.hk

Asthma is one of the most common chronic disorders in childhood. From the 50's to the 80's, many epidemiological studies have confirmed an increasing trend of asthma which was in parallel of economic development and urbanization (1,2). Researchers from around the world have been trying to determine the factors which might be responsible for inducing such trend. The well-known factors associated with asthma were atopy, air pollution and exposure to tobacco smoke, urbanization, dietary changes such as consumption of fruits and vegetables, infections including viral and bacterial cause, personal factors such as low birth weight and born by Caesarean section (3). To determine the exact mechanisms of how these factors may be responsible for asthma have been a very difficult task. One thing is clear that not one or two of these factors were responsible for the increasing trend of asthma in the Western world. Studies in China have revealed some very interesting findings which may help us to understand asthma in the Western world. Over the past two decades, there has been extremely rapid economic development which was unprecedented in China's history. In parallel, there was rapid increase in the prevalence of childhood asthma as documented by the data from Guangzhou by standardized methodology (4). Although sensitization was a factor associated with asthma, high rate of sensitization was documented many years before the rise of asthma prevalence. Level of air pollution was very high in many Chinese cities. Yet, the prevalence of

asthma in a highly polluted city of Chongqing was relatively low. Perhaps the most striking contrast was the difference of asthma and allergies between urban and rural environment. Similar rural protection against asthma has been found in Western countries (5). Exposure to farm animals such as cows and consumption of unpasteurized farm milk were the major factors. In rural China, dairy cows and consumption of farm milk are extremely rare. In our last study of more than 15,000 children from Southern China, exposure to domestic poultry was the most significant factor explaining the rural protection. Furthermore, gene expression studies suggest that there is a marked up-regulation of various immune regulatory genes in the rural population. Environmental exposures may be responsible for such differences resulting in the rural protection against asthma and allergies.

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#3. What Are the Barriers to Treatment in the Developed World?

Dr Louise Fleming

National Heart and Lung Institute & Royal Brompton Hospital, London, UK
Email l.fleming@imperial.ac.uk

Asthma is the most common chronic disease in children globally and over 14% of the world's children are likely to have had asthma symptoms in the past year¹. Countries in the developed world have among the highest prevalence of reported asthma². Although death rates are highest in low and middle income countries, death rates remain high in some developed countries and exceed those of many low income countries³. Therefore greater available resources, both financial and in terms of access to effective asthma medications, are not reflected in asthma outcomes. There are three key areas that act as barriers to effective asthma treatment in developed countries:

1. Lack of Attention to the Basics of Asthma Management

The diagnosis of asthma in most children is based on symptom reporting rather than objective testing⁴. This likely accounts for the very high prevalence seen in some countries and leads to complacency as it appears that asthma is a common and trivial disease. Ineffective risk stratification means that the appropriate resources are not directed to those who need them most. In recent years there has been a large increase in the number of generic inhaled corticosteroid (ICS) and ICS/long acting beta agonist (LABA) combination inhaler devices available. Prescribing multiple different devices and switching between devices does nothing to improve inhaler technique.

2. Organization of Health Care

There is good evidence that a coordinated national plan for asthma, involving all levels of care including community pharmacies, school, primary, secondary and tertiary care can lead to improved asthma outcomes and cost savings⁵. However, this has not been widely replicated and in most developed countries there is patchy provision of specialist care, poorly defined care pathways and a lack of effective education for patients and carers (including health care professionals).

3. Blocks in the Pipeline for the Development of New Drugs

Despite legislation aimed at ensuring that all new drugs are tested appropriately in children⁷ the pipeline for the development of new drugs remains particularly slow for children. The therapeutic target for most novel biologicals is identified from studies of adult asthma and may be less relevant for pediatric disease⁶. Relatively small numbers of children (usually adolescents) are recruited for phase 2 and 3 trials and the results for children are rarely analyzed and published separately. Licensing of novel drugs for children often lags behind adult licensing, restricting access to these drugs for those who may benefit.

It should be noted that access to effective treatments and healthcare in developed countries cannot, for the most part, be compared to low and middle income countries. However, the differential in available resources is not always reflected in outcome and more needs to be done to ensure that these resources are not squandered and that asthma care is delivered effectively.

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Asthma Therapy

#1. Ultra-LABA, LAMA, Combination Products, Selective Glucocorticoid Receptor Agonists in Pediatric Asthma

Ricardo M Fernandes

Department of Pediatrics Santa Maria Hospital, Lisbon Academic Medical Centre Clinical Pharmacology and Instituto de Medicina Molecular, Faculty of Medicine Therapeutics University of Lisbon, Portugal
Email: rmfernandes@campus.ul.pt

Inhaled bronchodilators and corticosteroids are the cornerstone of asthma therapy, by targeting the underlying inflammation and airway obstruction that characterize this condition.

Their use has revolutionized the management of asthma across levels of severities, with marked reductions in morbidity and mortality across ages. While most commonly used drugs from these groups have been commercially available for decades, considerable progress has been made in improving their therapeutic ratio and reducing adverse effects. Rational use of inhaled corticosteroids (ICS) and long-acting β_2 agonist (LABAs) has been supported by a better understanding of their mechanism of action, enhanced drug delivery and adherence, and accumulating evidence on their efficacy and safety.

Gaps in current treatment options remain, however. Recently there has been a resurgence of pharmacological research in this field, fueled by an increased use of double and triple combined therapies, the focus on new therapeutic targets (e.g. cholinergic system), and extensive research on bronchodilation in COPD. A wealth of candidate drugs have entered the asthma pipeline of clinical development, including ultra-LABAs combined with ICS, long-acting muscarinic receptor antagonists (LAMAs) alone or combined, selective glucocorticoid receptor agonists (SEGRAs) and bifunctional drugs. These drugs hold the promise of overcoming some of the pharmacokinetic and pharmacodynamic limitations of available molecules. They may also allow to better treat patients with asthma phenotypes that are poorly responsive to current management options, or in whom efficacy comes at the expense of an excessive burden of adverse effects.

Ultra-LABAs (With ICS)

Ultra-LABAs have a prolonged duration of action which allows for once-daily dosing.⁽¹⁾ This is likely due to retention within the cell membrane and persistent presence of the drug near β_2 adrenoreceptors (ARs). Their use in asthma is limited to combined therapy with ICS, given the well-known possible safety issues of monotherapy for this indication. Vilanterol is a highly selective partial β_2 agonist compound that is currently the only molecule approved for use in asthma in adolescents, in combination with fluticasone furoate (FF/VI).⁽²⁾ Efficacy and safety were demonstrated in clinical trials including

adolescent and adult asthmatic patients on an ICS with adding inhaled VI, as well as when comparing FF/VI to placebo or currently used ICS or ICS/LABA active comparators. Adolescents aged 12 to 17 years of age comprised 8% of the asthma population in the FF/VI clinical development program. Approval for this age range was granted by the European Medicines Agency (EMA) based on these data, but on the contrary, the Food and Drug Administration (FDA) considered that adequate risk-benefit was not shown. Data from early phase trials in children aged 5-11 years failed to show significant improvements in lung function, despite good tolerability. The FF/VI combination is currently an option from GINA step 3 onward for adolescents in countries with regulatory approval, as FF covers low- and high-dose ICS categories (3). There are putative benefits regarding treatment adherence of once-daily dosing, although a recent Cochrane review highlighted the low to moderate quality of evidence on FF/VI for asthma, with no conclusions drawn for the pediatric population due to scarce data (4).

Not all currently available or under study ultra-LABAs have ongoing pediatric clinical development plans in asthma. Data from early phase trials of nearly full agonist indacaterol combined with mometasone are available, some of which have included adolescents. At least one further large trial is ongoing before regulatory submission, and others focused on children (6-12, 12-18 years) are planned. No data on pediatric patients is available or yet officially planned for olodaterol and abediterol, whose product development plans in combined therapy for asthma are uncertain or preliminary, respectively (5). Whether ultra-LABAs are prone to safety issues due to loss of bronchoprotective effect (functional desensitization) or other mechanisms is yet uncertain.

LAMAs

Raised parasympathetic tone provides a rationale for the use of antimuscarinic agents in asthma.⁽⁶⁾ Tiotropium administered by mist inhaler was the subject of a large clinical development program, including over 1800 children and adolescents aged 1-17 years. In adults, evidence synthesis has shown that the addition of tiotropium to ICS/LABA reduces exacerbations, while its use as a replacement for LABA leads to heterogeneous results for different outcomes. Results from pediatric trials have been presented and published throughout 2016 and early 2017, leading to recent FDA approval for children 6 years and older, with EMA approval in children still pending (7, 8). Results suggest that in children and adolescents with moderate and/or severe asthma, use of tiotropium as add-on to ICS, with or without other maintenance therapies, is generally well-tolerated and safe. Lung function parameters generally improve, reflecting its efficacy as a bronchodilator, but not all trial primary endpoints were achieved across age ranges and asthma severity. Further, observed improvements in measures of asthma control were not statistically significant. The place for tiotropium in the management of pediatric asthma is thus still unclear. GINA guidelines suggest its use as add-on therapy for adult or adolescent patients in Steps 4 or 5 with a history of exacerbations (3). Further data are needed to directly compare the efficacy of tiotropium versus LABA, to identify any predictors (e.g. fixed airway obstruction) to clarify any benefit on outcomes such as exacerbation, and to establish the long-term effects on airway modeling. While the use of other LAMAs in adult asthma has

been the subject of early phase trials, no data is available yet in children or adolescents.

SEGRAs, Bifunctional Drugs and Combined Therapies

Fixed-dose combined therapies may provide synergy between each drug component, as well as enhance compliance. Aside from previously mentioned combined treatments, several double LABA/LAMA and triple ICS/LABA/LAMA combined therapies are currently in clinical development. There is also growing interest in the development of drugs with two different primary pharmacological actions in the same molecule (bifunctional drugs) (9). In an effort to obtain efficacious corticosteroids with fewer adverse effects, there has been a focus on ligands of the glucocorticoid receptor which preferentially induce transrepression with little or no transactivating activity (SEGRAs or dissociated steroids). Several of these compounds have entered clinical development.

From Novelty to Evidence and Practice

While new additions to the therapeutic toolbox are greatly welcome, many challenges lie ahead before these drugs become valid options in the current management of pediatric asthma. Not all companies have development plans for the pediatric age range; when planned, they may encounter trial recruitment and extrapolation issues, with results expected within up to a decade. Aspects such as patient and caretaker preference, type of device and real-life experience in implementing these new interventions in children with existing treatments must be considered. Further, availability of some drug/device combinations may vary around the world, due to regulatory and economical motives. There is need for solid evidence on the efficacy and safety of these medicines based on patient-relevant endpoints across different ages to evaluate whether there is added therapeutic value against currently existing options, including existent and soon to be available biologicals. This would allow to clarify their role in the current stepwise or in future phenotype-oriented treatment approaches.

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#2. Biologicals in Asthma Treatment

Oliviero Sacco, Antonino Capizzi, Mariangela Tosca, Giovanni A. Rossi.

Correspondence information: Giovanni A. Rossi Department of Pediatrics Pulmonary and Allergy Disease Unit and Cystic Fibrosis Center G Gaslini Institute, Genoa, Italy.

Email: giovannirossi@gaslini.org

Introduction

Asthma is a heterogeneous disease of the airways characterized by reversible airflow obstruction, bronchial hyperresponsiveness and airway inflammation [1]. For the majority of patients, current treatments, based on inhaled glucocorticoids (ICS), bronchodilators and or leukotriene pathway inhibitors, offer good control of the disease. However, this is not true for 10-20% of them, this refractory patient population being at increased risk of morbidity and mortality and making up the greater asthma economic costs [1]. Based on cluster analyses, molecular phenotyping, biomarkers and differential responses to therapies, over the last decade there has been an increasing appreciation of the heterogeneity of asthma [1,2]. Indeed, there is substantial diversity in the clinical and inflammatory features of the disease, with several studies identifying clusters of patients with features corresponding to early-onset atopic/allergic asthma, late onset atopic or non-atopic asthma, exercise induced asthma, paucigranulocytic asthma, asthma associated with obesity, etc. [2]. These various phenotypes are characterized by different types and degrees of inflammatory and immune responses [3]. This approach has also led to the recognition of potential distinct endotypes, such as the type 2 T helper (Th2) lymphocyte-associated early onset allergic endotype, the late onset endotype, the interleukin (IL)-5 associated eosinophilic endotype, the mast cell associated exercise-induced endotype, the late onset obese endotype, the neutrophilic and/or the non-inflammatory non-corticosteroid responsive endotype [3]. Although the endotype characterization of asthmatic patients is an area of active research, to date only a few specific pathways targetable by biological agents have been identified.

Biological Agents

Also termed biologicals or biologics, they are therapeutics synthesized by living organisms and directed against specific determinants. For the

treatment of allergic diseases, for example, these include agents targeting: a) the immunoglobulin (IgE); b) the Th2-type lymphocytes; c) the Th2-promoting cytokines IL-4, IL-5, IL-9, IL-13, and IL-31; d) the pro-inflammatory cytokines IL-1b, IL-12, IL-17A, IL-17F, IL-23 and tumor necrosis factor (TNF)- α ; e) the chemokine receptor CCR4; f) the lymphocyte surface and adhesion molecules CD2, CD11a, CD20, CD25 and CD52 [4]. Almost all the biologicals that are currently available or tested for the use in asthmatic patients are targeted against components of the Th2-"like" asthma endotype.

The Th2 Pathway as Potential Treatment Target for Biologicals

The Th2 pathway is characterized by an eosinophilic inflammation driven by Th2 lymphocytes that, in response to various agents (allergens, parasites and viruses) produce IL-4, IL-5, IL-9 and IL-13 [5]. IL-4 causes a shift in Th0 cells to differentiate into Th2 cells and stimulate IgE production by B-lymphocytes. Upon antigen binding, IgEs activate mast cells and eosinophils to release their toxic granules and cytokines regulating of eosinophil maturation, recruitment and activation. IL-5 and IL-9 act locally as chemo-attractant for eosinophils and mast cells, whilst IL-13 induces IgE synthesis and release, mucus production by epithelial cells and favor goblet cell metaplasia [5]. Eosinophilic inflammation is not only related to allergy, since some patients with severe asthma and eosinophilic inflammation do show atopic sensitization and have normal serum IgE [5].

The Th2 "Blockers"

These include the anti-IgE, the anti-IL-5 and anti-IL-5R, the anti-IL-13 and the IL-4 receptor α humanized monoclonal antibodies (hMAbs).

The anti-IgE. The first Th2 cytokine blocker has been Omalizumab, an anti-IgE recombinant hMAb registered for treatment of patients with severe persistent allergic asthma. The most important findings of a Cochrane review were that Omalizumab reduced steroid use and exacerbations by about 40%, improved asthma control questionnaire (ACQ) scores and health-related quality of life scores [6]. Treatment efficacy in these patients, however, seems to be more related to the presence of eosinophilic airway inflammation than to serum IgE levels [5].

The anti-IL-5 or Anti-IL-5R. Both basophils and eosinophils express the IL-5 receptors. The first randomized controlled trial in patients with asthma showed that the IL-5 antagonist Mepolizumab reduced blood eosinophil counts and prevented blood eosinophilia during the late-phase response following allergen challenge, but had no effects on the late asthmatic response and on bronchial hyperreactivity [7]. However, a subsequent trial in patients with eosinophilic asthma demonstrated that Mepolizumab treatment reduced asthma attacks by about 50%, a finding confirmed by a subsequent study that also showed a significant oral corticosteroid sparing effect [8].

Anti-IL-13. A trial with the anti-IL-13 Lebrikizumab in patients with moderate-to-severe asthma showed an improvement in FEV1 particularly in those with high serum periostin concentrations or high FeNO and a strong trend to reduced exacerbations [9].

IL-4 receptor α blockers. IL-13 and IL-4 are closely linked and exert similar functions by binding and activating the IL-4 receptor α subunit. Thus, blocking the IL-4 receptor α subunit affects both IL-4 and IL-13

signaling. In a trial with the IL-4 receptor- α antagonist Dupilumab, a subgroup of patients with persistent moderate-to-severe asthma and blood eosinophilia >300/L showed significant fewer exacerbations, after withdrawn from long acting β_2 -adrenoceptor agonist and from inhaled corticosteroids treatment. In addition Forced Expiratory Volume in 1 second (FEV₁) improved significantly and ACQ score also dropped in the treatment group that also showed a reduction of fractional exhaled nitric oxide (FeNO), IgE, thymus and activation-regulated chemokine (TARC) and eotaxin-3 levels [10].

Preliminary Data for Non-Th-2 Asthma Endotypes

Some hope is provided by the beneficial effects of long-term low-dose azithromycin in patients with non-eosinophilic asthma and by preliminary data on efficacy of Navarixin (SCH 527123), an IL-8 receptor-b (CXCR2) antagonist, whilst no positive effects were reported on the treatment with Brodalumab, an anti-IL-17 hMAb, in moderate-to-severe asthmatics [5].

Conclusion

The results of these few studies show that, like for other disorders, the possibility of successfully introducing biologicals in the treatment of asthma largely depends on the possibility of identifying specific patient subgroups, selected by measurable biomarkers that are directly influenced by the treatment.

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Heart and Lung Interactions

#1. Diagnosis and Treatment of Pediatric Pulmonary Hypertension

Rui Anjos, João Rato, Graça Nogueira

Department of Pediatric Cardiology, Santa Cruz Hospital Centro Hospitalar de Lisboa Ocidental Lisbon, Portugal
Email: ranjos@netcabo.pt

Introduction

Pediatric pulmonary hypertension (PH) is a rare but devastating disease that may present in all pediatric age groups. PH is a pathophysiological disorder associated with multiple clinical conditions which can complicate the majority of cardiovascular and respiratory diseases. It is associated with considerable morbidity and mortality.

In pediatric patients, the more prevalent causes of PH are congenital heart disease and idiopathic pulmonary arterial hypertension¹. Connective tissue diseases, portopulmonary hypertension, HIV infection or chronic thromboembolism, which are the main causes of PH in adults are much less frequent in children^{2,3}. Pediatric PH is distinct from adult PH in several ways. It is related to lung growth and development, including prenatal and early postnatal influences. Impaired functional and structural adaptation of the pulmonary circulation during transition from fetal to postnatal life may cause neonatal PH. The timing of pulmonary vascular injury is determinant of subsequent response of the developing lung to hypoxia, hemodynamic stress and inflammation. A normal pulmonary vascular bed is essential for a normal lung structure, metabolism and gas exchange and to tolerate exercise workloads. Perinatal factors may contribute to an increased risk for late development of PH in adulthood. Adult PH and pediatric PH differ in vascular function and structure, genetics, natural history, response of the right ventricle to an increased load and to PH specific therapies^{4,5}.

Definition and Clinical Presentation

PH is defined as a mean pulmonary artery pressure of > 25 mmHg at rest, after 3 months of age, measured by cardiac catheterization⁶. The Nice classification categorizes pulmonary hypertension (PH) into pulmonary arterial hypertension, PH due to left heart disease, PH due to lung diseases and/or hypoxia, chronic thromboembolic PH and PH due to unclear multifactorial mechanisms. *Pulmonary*

arterial hypertension (PAH) describes a group of patients with PH who have pre-capillary PH, with a normal pulmonary artery wedge pressure (<15 mmHg) and a pulmonary vascular resistance index >3 Wood units (WU) · m²⁽⁶⁾.

The Pulmonary Vascular Research Institute introduced the term pediatric pulmonary hypertensive vascular disease (PPHVD) in 2011⁷. Their approach distinguishes between PH with and without pulmonary vascular disease (PVD) and between single and biventricular circulations. Patients with congenital heart disease (CHD) and single ventricle physiology often do not meet the criteria as defined above, but may benefit from similar pharmacological strategies. For patients with Fontan-type hemodynamics, a pulmonary vascular resistance (PVR) index >3 WU · m² or a transpulmonary gradient >6 mm Hg has been suggested as a definition of PPHVD⁷.

Diagnosis and Monitoring

Children with suspected or confirmed PH should be referred to a specialist PH pediatric center. Centralization of care and concentration of expertise is beneficial for the management of these patients. A detailed medical history and careful physical examination are essential. As the diagnostic criteria are hemodynamic, cardiac and pulmonary artery catheterization is the gold standard to establish the diagnosis and indeed the only method for direct accurate measurement of pulmonary artery pressures. This is complemented with acute vasodilator testing with inhaled nitric oxide⁴. PH patients should have a complete assessment of hemodynamics using echocardiography, ECG, chest X-ray, functional testing (lung function, cardiopulmonary exercise), abdominal ultrasound and in some cases a contrast CT angiography of the pulmonary arteries or a cardiac MRI. Laboratory evaluation including routine biochemistry, hematology, immunology, HIV testing and thyroid function is recommended in all patients with PAH to identify specific associated conditions. Echocardiogram and ECG should be repeated every 3 to 6 months or more frequently if there is clinical deterioration.

Pediatric Pulmonary Hypertension Treatment

The management of pulmonary hypertension has evolved dramatically in the last few years. Many drugs are now approved for adult pulmonary hypertension, but in the pediatric age group, therapy is frequently used off-label, adapted from adult trials. Clinical trials on the pediatric population are under way and their results will be extremely important for the management of children with PH.

Conventional Therapy

The general management of PH includes the treatment of right ventricular (RV) failure with drugs such as loop diuretics and spironolactone. Diuretics should be used with caution as these patients are preload dependent⁴. Some clinicians use digitalis for improvement of RV function. Severe hypoxemia should be treated with oxygen therapy. The use of anticoagulants is controversial, but it is suggested in children with RV failure and dilation⁸. Physical activity is encouraged, but strenuous exercises should be avoided. Immunization plans should be followed strictly, particularly to avoid respiratory infections.

Targeted Therapy

Development of pulmonary hypertension involves several pathways leading to remodeling of the pulmonary vascular bed. These are the targets for current pulmonary hypertension drugs and include overexpression of endothelin, a potent vasoconstrictor peptide, and decreased activity of vasodilator and antiproliferative mediators such as prostacyclin and nitric oxide.

Calcium Channel Blockers (CCBs)

Before initiation of targeted therapies, patients should undergo acute vasodilator testing with inhaled nitric oxide. The test is positive when there is a 20% fall in mean pulmonary artery pressure, an increase or lack of decrease of cardiac output and no change or decrease in the ratio of pulmonary vascular to systemic vascular resistances⁴. This should lead to a trial of CCBs such as nifedipine, amlodipine or diltiazem. CCBs cause relaxation of vascular smooth muscle and should be used with caution in severe ventricular dysfunction as their negative inotropic effect may further decrease cardiac contractility. They are not recommended in the first year of life.

Endothelin Receptor Antagonists (ETRA)

Endothelin is mediated by two receptors, type A and B, and its blockade is the mechanism for ETAs. Bosentan is the oral dual ETA approved for pediatric use. It causes PAP and PVR decrease and improves exercise capacity. Serious side effects include liver enzyme elevation, anemia, impaired fertility and teratogenicity. Regular liver function testing is recommended in children receiving bosentan⁴. Ambrisentan, an oral ET A-receptor antagonist, has a once daily formulation and no repercussion on liver enzymes⁸. Macitentan, a novel dual ETA, also showed no signs of hepatic toxicity and fewer drug interactions than bosentan⁸. A phase III trial in pediatric patients is currently ongoing.

Phosphodiesterase Type 5 Inhibitors (PDE5i)

Sildenafil is the currently approved PDE5i for pediatric use. It acts by preventing the breakdown of smooth muscle cell cyclic guanosine monophosphate, improving pulmonary vasodilation, and shows antiproliferative effects. Oral sildenafil should be used cautiously in the pediatric population, with careful dosing according to weight and frequent assessments, due to reports of increased mortality in patients using higher doses⁴. Side effects include headache, flushing, nosebleeds and hypotension. Tadalafil is a PDE5i with a longer duration of action. Its use in the pediatric population is being studied⁸.

Prostacyclin Analogs

Prostacyclin acts by increasing pulmonary vasodilation and inhibiting vascular remodeling. Its analogs include epoprostenol, treprostinil, iloprost and selexipag. The first two can be delivered through a continuous intravenous infusion, the treatment of choice for severe pulmonary hypertension with RV failure⁴. Epoprostenol is given through a central venous line, which places the patient at risk for adverse events. Due to a short half-life, there is a risk for rebound PH in case of interruption of administration. Its adverse side effects include bradycardia, hypotension and thrombocytopenia, which are dose-dependent. Treprostinil has a longer half-life that enables its subcutaneous infusion through a mini pump. Iloprost is administered

by nebulization and can cause acute bronchospasm in some patients. Selexipag is an oral selective prostacyclin receptor agonist and promising new therapy, with a favorable side effect profile, which showed a significant reduction of PVR in adults⁸.

Treatment Strategy and Combination Therapy

Treatment of pediatric pulmonary hypertension aims to improve survival, quality of life, exercise capacity and hemodynamics. It reduces the overall risk by improving clinical echocardiographic and hemodynamic risk factors. When these goals are not met on monotherapy, combination therapy is used. Combination therapy may be more efficacious as it addresses multiple pathophysiological pathways simultaneously. Whether this kind of strategy should be initiated early on by use of two or more drugs or sequentially by adding a second drug to a previous one is still under study. In high risk patients, inhaled or intravenous prostacyclin should be considered. If deterioration occurs despite maximal therapy, techniques such as atrial septostomy or pulmonary-to-systemic shunts can be applied. Lung or heart-lung transplantation is the last therapeutic resort (Figure 1).

Special Situations

Congenital Heart Disease

Cardiac high-pressure, high-flow lesions like ventricular septal defects can lead to PH. Children with cyanotic congenital heart disease and pulmonary high-flow, high-pressure defects are at highest risk. Patients considered operable should undergo surgery at early stages, followed by targeted therapy if needed⁴. Older patients are at increased risk for developing more severe forms of PH, even if they survive surgery, and it has been suggested that surgery may worsen their prognosis.

Acute Pulmonary Hypertensive Crisis

Characterized by sudden increase in PAP and PVR, pulmonary hypertensive crisis carries a high risk. Its prevention involves maintaining adequate oxygen saturation, acid base homeostasis and sedation as needed to avoid agitation. Inhaled nitric oxide is the standard therapy as it improves pulmonary vasodilation, RV function and cardiac output.

Congenital Diaphragmatic Hernia

Increase in PVR is caused by vasoconstriction, decreased vascular growth, pulmonary vascular remodeling and left ventricular dysfunction. Treatment involves low ventilating volumes and permissive hypercapnia, high-frequency oscillatory ventilation if needed, inhaled nitric oxide, and as a last resort, extracorporeal membrane oxygenation. Surgical repair is mandatory, generally after clinical stabilization. Regular echocardiography is recommended as pulmonary hypertension may persist⁴. Cardiac catheterization should be eventually considered, as it is more sensible to subtle vascular abnormalities.

Pulmonary Disease

Chronic diffuse lung disease like bronchopulmonary dysplasia can lead to PH. Echocardiography should be recommended in the evaluation of these patients⁴. Hypoxemia should be avoided.

Persistent Pulmonary Hypertension of the Newborn

Defined by the persistence of the physiologic PH of the fetus after birth. Treatment includes oxygen therapy, optimizing lung volume and cardiac function and inhaled nitric oxide if needed.

Prognosis

Pediatric patients in the REVEAL registry showed 1, 3 and 5-year estimated survival rates from time of diagnosis of $96 \pm 4\%$, $84 \pm 5\%$ and $74 \pm 6\%$, respectively³. Other reports have also shown improved survival rates for pediatric PAH. Some patients, such as those with PAH and repaired CHD, have to be addressed carefully as they may present a more unfavorable outcome⁹.

While adults with classical Eisenmenger hemodynamics have a better survival than patients with idiopathic pulmonary arterial hypertension, children with PAH-CHD and those with IPAH have a similar mortality with a 5-year survival reported to be 71% and 75%, respectively³.

Conclusions

PH remains a major challenge and a significant source of morbidity and mortality in many childhood diseases. Although there are few randomized pediatric trials, treatment strategies in children have improved their prognosis over the past decade, especially after the introduction of new therapeutic agents.

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Figure 1 Legend

Algorithm for treatment of Pulmonary Hypertension, adapted from Ivy DD¹⁰

CCB – calcium channel blocker; ERA – endothelin receptor antagonist; HPAH – hereditary pulmonary arterial hypertension; inh – inhalation; IPAH – idiopathic pulmonary arterial hypertension; IV – intravenous; PDE-5i – phosphodiesterase 5 inhibitor; SQ – subcutaneous

#2. The Lung in Congenital Heart Diseases

Paul Aurora

Departments of Paediatric Respiratory Medicine and Cardiothoracic Transplantation, Great Ormond Street Hospital for Children, London.

Correspondence: Dr Paul Aurora Consultant in Paediatric Respiratory Medicine and Lung Transplantation Department of Paediatric Respiratory Medicine Great Ormond Street Hospital for Children, Great Ormond Street. London. WC1N 3JH Email: p.aurora@ucl.ac.uk

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Introduction

The cardiovascular and pulmonary systems are closely related in both health and disease. This means that both systems need to be considered when evaluating symptoms of cough or breathlessness; that cardiac disease can affect pulmonary function; and that lung disease can affect cardiac function. In addition, primary ciliary dyskinesia can cause simultaneous cardiac and pulmonary disease. I propose below to summarize our understanding of these different areas.

The Diagnostic Challenge

Many children who present with “respiratory” symptoms should also be evaluated for congenital heart disease (CHD) or other cardiac disease. In summary:

- Stridor may result from extrinsic compression of the airways, most commonly by a great vessel, pulmonary artery sling, or dilated left atrium or ventricle

- Wheeze and/or cough may be the consequence of pulmonary edema
- Reduced exercise tolerance and/or hypoxia can result from a cardiac lesion or from pulmonary hypertension.

Many of these cardiac conditions can be difficult to diagnose from history or examination, and targeted investigation may be required. In particular, atrial septal defect and idiopathic pulmonary arterial hypertension may present with very non-specific symptoms, so a high index of suspicion is required.

Compression of Airways

This can occur due to abnormal vessel anatomy; increased blood flow through the pulmonary system due to left to right shunt; or a combination of the two. In the failing heart, cardiac dilatation can lead to compression^{1,2}. The most common causes of vascular compression are abnormalities of the aortic arch, congenitally corrected transposition, common arterial trunk, or pulmonary atresia with ventricular septal defect. All these conditions result in abnormal location of a pulsatile vessel which can compress a major airway. A vascular ring is when trachea and esophagus are surrounded by a vascular structure deriving from the aorta. A pulmonary artery sling is a rare condition where the left pulmonary artery arises from the right pulmonary artery, and then loops back between the lower trachea and esophagus. Congenital absence of the pulmonary valve is a rare condition which has a heterogeneous presentation. In the most severe cases, neonates may have very severe pulmonary regurgitation, leading to grossly dilated pulmonary vessels, compression of intrapulmonary bronchi due to increased pulmonary blood flow, and cardiac failure. Dilatation of the left atrium can result from any condition causing left to right shunt, and this in turn can compress the left main bronchus or left lower lobe bronchus. This consequence is also seen in dilated cardiomyopathy where dilatation of both left ventricle and left atrium occur, and *post* cardiac transplantation if the donor is larger than the recipient.

Pulmonary Edema

Pulmonary edema can result from large left to right shunt, and also from conditions that obstruct pulmonary venous return and therefore increase pulmonary venous pressure.

This in turn increases pressure in pulmonary capillaries and imbalances hydrostatic pressures dictating flow of water across the alveolar capillary membrane. The result is accumulation of water in the pulmonary interstitium and the alveoli. Physiologically this results in reduced lung compliance, and in impaired oxygen transport into the pulmonary capillary system. Many children with this pathology will also have engorged peribronchial vessels, which shows as bronchial cuffing on lung imaging, and causes compression of small airways (so-called "cardiac asthma"). Diuretics can provide very effective palliation until definitive therapy is possible.

Conditions Leading to Reduced Pulmonary Blood Flow, and Fontan Circulation

Any condition that produces a right to left shunt, e.g., arteriovenous malformations, tetralogy of Fallot, will result in poor ventilation-perfusion

matching. The total volume of blood passing through the pulmonary circulation is reduced, with some passing directly from the caval system to the systemic arterial system. The child will therefore display hypoxemia, either with or without mild hypercarbia. The Fontan procedure is the commonest (but not only) situation where the right ventricle is bypassed or absent, and venous blood from the caval system is directly connected to the pulmonary artery. In this case the volume of blood passing through the pulmonary circulation is normal, but the child has a low pressure pulmonary circulation, dependent on low resistance. Many children with this anatomy develop collaterals from the systemic venous system to the pulmonary venous system, leading to progressive cyanosis. With some anatomies (e.g. pulmonary valve stenosis) systemic arterial to pulmonary arterial collaterals may develop. Many children with Fontan circulation have pulmonary hypoplasia, with a restrictive pattern seen on lung function testing. The etiology is not fully understood. A minority of children with Fontan circulation may develop plastic bronchitis, particularly if they have failing cardiac function. In this condition airways become obstructed by mucoid bronchial casts which are difficult to expectorate, and may grow large enough to have a branching pattern. Management of this condition is challenging, as mucolytic agents provide very little benefit. Cardiac transplantation is immediately curative.

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is defined as pulmonary artery pressure of ≥ 25 mmHg at rest, and can be primary – now termed idiopathic pulmonary arterial hypertension (IPAH) – or secondary to cardiac disease or pulmonary disease³. The medical management of IPAH has changed dramatically over the last 2 decades with multiple agents now available for palliative relief. Unfortunately all have disadvantages, and none are curative, so most subjects eventually proceed to lung transplantation. PAH secondary to cardiac disease is common, and seen in up to 28% of adult CHD patients. Most research has focused on the severe end of the spectrum, also known as Eisenmenger syndrome, where pulmonary artery pressure can be suprasystemic, leading to right to left shunt across the cardiac communication and subsequent hypoxemia. More recently, attention has been addressed to earlier stages of disease, and particularly in investigating why some subjects are more prone to develop secondary PAH than others. It has also been noted that some subjects respond well to PAH therapy, and a trial of different combinations should be considered.

Primary Ciliary Dyskinesia and CHD

It is increasingly recognized that primary ciliary dyskinesia (PCD) does not only result in situs inversus, but also more complex organ laterality defects that include CHD⁴. The child may be born with cardiac isomerism or dextrocardia, but also a variety of septal defects and outflow tract abnormalities. It is assumed that embryonic nodal cilia, based at the embryonic node, play a role in established correct organ laterality in the developing embryo. Genetic analysis of all aspects of the PCD phenotype is challenging, given the large number of genes involved. However it has been established that genetic mutations encoding for both outer dynein arm and inner dynein arm proteins have been associated with CHD in humans. In contrast, no association has been found for mutations encoding for central apparatus and radial

spike proteins. For the clinician, the first challenge is diagnosis. The pulmonologist caring for a child with PCD must have a low threshold for detailed cardiac evaluation, and the cardiologist caring for a child with known CHD must have a low threshold for ciliary studies. Once the diagnosis is established then treatment of CHD should be completed as standard, but with appropriate cautions for children with bronchiectasis or abnormal circulation of cerebrospinal fluid.

Transplantation for Cardiac Disease and Pulmonary Hypertension

In children who have severe ventricular dysfunction as a result of CHD, cardiac transplantation may be the only therapeutic option^{5,6}. Long term survival following cardiac transplantation in children is now excellent, but there are specific challenges for children with CHD, and some cases where a pulmonologist may be asked to give an opinion. The most common concerns relate to abnormal vessel anatomy (sometimes necessitating modified transplant technique), previous thoracic surgeries, HLA sensitization due to previous transfusion, and presence of systemic to pulmonary collaterals. In addition, children who have PAH secondary to cardiac disease pose a particular challenge. The current consensus is that the pulmonary vascular resistance (PVR) should be quantified by right heart catheterization, and evaluated for reversibility. If the PVR measures ≥ 5 Woods Units, then straightforward cardiac transplantation is contraindicated due to high risk of post-operative right heart failure. Previously such children would have been referred for heart-lung transplantation, but there is shortage of donors of heart-lung blocks, and a relatively poor long term outcome compared with cardiac transplantation alone. As a result, some centers now advocate cardiac transplantation whilst supporting the right heart with a right ventricular mechanical assist device (RVAD) *pre* and *post* transplantation. Results are encouraging, with the pulmonary hypertension receding once pulmonary blood flow has been normalized. Another situation where the pulmonologist may be consulted is in children with a failing Fontan circulation. Many children in this situation will have protein losing enteropathy and also may have plastic bronchitis (which has been termed a protein losing bronchopathy). The key point for the pulmonologist is that this is not a contraindication to transplantation, and there are multiple reports of both conditions correcting rapidly post transplantation.

Conclusion

The physiology of heart and lungs are closely intertwined. This obliges the physician to be alert to both pulmonary and cardiac diagnoses in a child with breathlessness, and also requires that the pulmonologist has a good understanding of the impact of cardiac disease upon the lungs and upon pulmonary circulation. Close communication between the pulmonologist and cardiologist is essential.

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#3. Pulmonary Bleeding in Childhood

Andrew Colin

Correspondence Information: Andrew Colin, M.D., University of Miami Batchelor Children's Institute Department of Pediatrics Division of Pediatric Pulmonology 1580 NW 10th Ave 1st Floor (D-820) Miami, FL 33136
Email: acoln@med.miami.edu
Phone: 305-243-3176
Fax: 305-243-1262

A comprehensive discussion of the topic of lung bleeding is beyond the scope of this presentation; at previous meetings of CIPP, updates of the topic were offered, and at the risk of some repetition, an updated talk will be presented. The focus will be on specific clinical etiologies, better understanding of the natural history of Idiopathic Pulmonary Hemosiderosis (IPH), and the use of flexible bronchoscopy as a tool for improved diagnosis and active intervention in pulmonary bleeding.

Definition and Clinical Presentation

Hemosiderosis is a pathological finding not specific to any disease, etiology or process and is characterized by the finding of hemosiderin-laden macrophages (HLM) in the alveolar spaces. It is a condition that may have various underlying primary and secondary causes.

Episodes of alveolar hemorrhage typically present as the triad: hemoptysis, anemia and diffuse radiological alveolar infiltrates, with clinical characterization of dyspnea or respiratory distress, cough and varying degree on hemoptysis, the latter being frequent absent.

Laboratory features are:

- Iron-deficiency anemia
- Alveolar (often fleeting) opacities on CXR
- In advanced stages, restrictive lung disease can become a spirometric feature
- Pathology reveals HLM and may present with chronic free iron in pulmonary tissue and subsequently pulmonary fibrosis

Incidence and Causes of Hemosiderosis

Lung bleeding is rare in infancy and childhood. The incidence varies by sites of reporting; 0.24 cases per million are reported in Sweden and 1.23 cases per million are reported from Japan.

This low incidence also underlies the paucity of systematic information on the causality of bleeding. In a 10-year review from a large referral center, 228 children and young adults were reported: Cystic fibrosis (CF) represented 65%, congenital heart disease 16%. The remaining 19% were infections (other than CF), neoplasms (2.6%), and other causes (typically classified as idiopathic).

Clinical cases to exemplify some definable causes of lung bleeding that will be discussed at this presentation include bleeding related to cardiac defects, in this case cor triatriatum; metabolic disorders, exemplified by Lane-Hamilton syndrome (hemosiderosis associated with celiac disease); and Pulmonary-renal syndromes, exemplified by granulomatosis with polyangiitis (formerly Wegener's granulomatosis).

Classification: When lung bleeding is not readily diagnosed in relation to etiologies such as described above, the cases often pose a significant classification challenge. A systematic approach to classification of DAH in childhood (Susarla & Fan, 2007) separates disorders without pulmonary capillaritis to ones with and without cardiovascular cause. The disorders with pulmonary capillaritis typically carry a more ominous prognosis and include idiopathic pulmonary capillaritis, Granulomatosis with polyangiitis, microscopic polyangiitis, systemic lupus erythematosus, Goodpasture's syndrome, antiphospholipid antibody syndrome, Henoch-Schönlein purpura, IgA nephropathy, polyarteritis nodosa, Behcet syndrome, Cryoglobulinemia, Drug-induced capillaritis, and Idiopathic pulmonary-renal syndrome.

Frequently, however, attempts to define etiology fail, and many of the hemorrhagic cases are classified as "Idiopathic Pulmonary Hemosiderosis" (IPH). It is important to recognize, however, that IPH is not a veritable diagnosis, and includes variable etiologies that still require better definition. A recent longitudinal French study (Taytard et al, 2013) of 25 children with IPH gave more insight on features of clinical expression and outcomes of these patients. It expanded on the potential role of auto-immunity in disease development. It also contributed to pointing to the relatively large number of such patients who required immunosuppressants after failing the universally used corticosteroids. This study also pointed to the potential role of genetic factors, and indeed a recent publication reported two novel missense mutations in iron transport protein transferrin causing hemosiderosis (Athiyarath et al., 2013)

The definitive **diagnosis** of bleeding in the lung in the non-hemoptysizing patient is challenging and eventually relies on bronchoscopy, as will be further detailed below. **Physical examination** is non-specific and ranges from subtle tachypnea, dyspnea, variable crackles and wheezing to pulmonary hypertension or frank respiratory failure. Fever and chest discomfort/

pain are infrequently observed. **Laboratory** work up beyond the anemia is suggestive but non-specific. **Radiographic changes** are non-specific and range from minimal infiltrates to massive parenchymal involvement; the feature that can separate hemorrhagic processes from other infiltrates is their fleeting nature. However, in patients with small frequent episodes of bleeding the radiographs may reflect chronic diffuse interstitial involvement and change only minimally with acute recurrence. CT scan is suggestive but also not specific. MRI is cited as offering more specificity on presence of blood with decreased signal on the T2-weighted images, but this is rarely recognized by radiologists. **Pulmonary function testing** is infrequently available at the age range under discussion and is non-specific. However, diffusion studies (DL_{CO}) may result unexpectedly high because of rapid uptake of the tracer gas by hemoglobin in the alveolar spaces.

Acute Idiopathic Pulmonary Hemorrhage of Infancy (AIPH)

The Centers for Disease Control (CDC) have classified AIPH as a nosologic entity: a clinically confirmed case is an illness in a previously healthy infant aged <1 year, with a gestational age ≥ 32 weeks, and no history of neonatal medical problems that could cause pulmonary hemorrhage. The cases are characterized by abrupt onset of overt bleeding or evidence of blood in the airway, diffuse pulmonary infiltrates on chest radiograph, diffuse alveolar hemorrhage (DAH) on bronchoscopy, and often severe presentation leading to acute respiratory distress or failure.

Infantile airway bleeding is an uncommon occurrence but has historically emerged in clusters; in Greece, in Cleveland, and Massachusetts. The Cleveland outbreak (Dearborn et al 2002) in the mid 90s was the best characterized and included over 30 cases of AIPH. Many of the infants came from the same geographic area, were African-American, male, with severe disease that appeared to be beneficially affected by use of corticosteroid that reduced the high mortality (16%). The most recent cluster we were able to find was in five infants in the Boston area, (MMWR Morb Mortal Wkly Rep 2004) with no mortality. The clustered nature of the presentations appears to point toward a common underlying cause of the bleeding. Indeed, an initial association of the Cleveland series was made with *Stachybotrys chartarum* (atra), a mold that may be found in water-damaged homes; but ultimately, this association has not been substantiated. Similarly, in the Boston series, the cause was assumed to be related to an underlying susceptibility to bleed, with von Willebrand Disease (VWD) being ultimately proposed in 3 of the infants. This underlying vulnerability was deemed to underpin the bleeding that would be precipitated by injury to the lungs, by a common environmental cause, possibly a viral infection. However, since no such direct trigger that could unify the cases was identified, no final etiology was identified and no further publications emerged from these series.

Flexible Bronchoscopy in Pulmonary Hemorrhage – Diagnosis and Therapeutic Intervention.

Flexible bronchoscopy is key in the initial diagnosis of identifying the source of the bleed from the lung, and in particular defining DAH. In the latter, bronchoscopy will define the bleeding in the absence of overt airway bleeding, when bronchoalveolar lavage (BAL) results in persistently blood-tinged return fluid. Controversies exist about the role of repeated bronchoscopy in defining the degree of the bleeding, however, monitoring via scoring of the status of the bleeding for therapeutic decisions and long-term follow-up was widely used in the AIPHI series from Cleveland. The most widely used scoring system is the Golde Score (Finley et al, 1975) that we have used successfully in our practice.

The use of flexible bronchoscopy for therapeutic interventions for bleeding has been limited in the pediatric practice. The largest report on a series of 14 pediatric patients with acute life-threatening pulmonary hemorrhage used CO₂ laser bronchoscopy, Nd-YAG laser bronchoscopy, endoscopic balloon occlusion of a lobe or main bronchus, topical airway vasoconstrictors and endoscopic tumor excision. A recent novel bronchoscopic intervention to control airway bleeding in DAH has been direct instillation of activated recombinant factor VII (rFVIIa). This agent has previously been administered systemically to control recalcitrant bleeding in the lung, with disappointing results. However, direct instillation of rFVIIa into the airway has now been repeatedly documented in both adults and children. Our group has reported 2 cases (Reiter et al, 2014) and a recent publication from Korea reported 6 cases (Park & Kim, 2015) of successful control of recalcitrant pulmonary bleeding. Our procedures were undertaken as interventions of last resort; in both cases the hemorrhage was visualized during the procedure and its resolution following the treatment was immediate, unequivocal, and definitive. An editorial following our case report (Heslet, 2014) emphasized that the intervention on the air-side of the alveolus constitutes the key advantage of the direct instillation, and advocates for early and liberal use of this intervention for DAH, considering its remarkable ease and efficacy and apparent absent side effects.

Prognosis: There is limited information about long-term outcome of pulmonary hemosiderosis. Older studies suggest that the overall prognosis may not be favorable in the “idiopathic” cases. However, a more recent large multicenter French study is more promising, with a satisfactory respiratory outcome in 23/25 patients, with a median follow-up of 5.5 yrs. (Taytard et al., 2013) Clearly, these cases require careful follow-up and appropriate treatment that consists of corticosteroids and often other immunosuppressive therapies. Importantly, some cases with DAH may declare themselves in later life as having well-defined autoimmune diseases. While the infant population with AIPH discussed above likely reflects a different subclass within the “Idiopathic” group, individuals with recurrent bleeding and mortality have been reported.

Infection Disease Corner

#1. Infection Disease Corner. Non-tuberculous Mycobacteria

Malena Cohen-Cymerknoh

Pediatric Pulmonary Unit Hadassah-Hebrew University Medical Center Jerusalem, Israel

Email: Malena@hadassah.org.il

There has been a dramatic increase over the last three decades in the total number of non-tuberculous mycobacteria (NTM) species and many of them have clinical significance. This change has been attributed, in part, to improved culturing techniques, coupled with greater disease awareness and a true increase in disease prevalence. These organisms are ubiquitous and are readily recovered from environmental sources such as soil, water, plants and animals. NTM may cause both asymptomatic infection and symptomatic disease in humans. The factors predisposing to infection are likely due to an interaction between host defense mechanisms and the load of clinical exposure.

Historically, different classification systems have been proposed, but NTM are most commonly classified by growth rate—either *slowly growing* or *rapidly growing*. The most common clinical manifestation of NTM disease is lung disease, but lymphatic, skin/soft tissue, and disseminated disease are also important¹. The diagnostic criteria of NTM lung disease, according to the official ATS/IDSA statement should include: (1) typical findings on chest radiograph or chest high-resolution computed tomography (HRCT) scan; (2) ≥ 3 sputum specimens for acid-fast bacilli analysis; and (3) exclusion of other disorders, such as tuberculosis. Lung disease due to NTM occurs commonly in patients having already structural lung disease, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis (CF), pneumoconiosis, prior TB, pulmonary alveolar proteinosis, esophageal motility disorders and in patients who are awaiting or have undergone lung transplantation^{1–3}.

The prevalence of NTM isolation from sputum within the CF population is rising due to increasing survival and better NTM recognition. The underlying structural airway disease and altered mucociliary clearance may be predisposing factors. The impact of NTM positivity on the clinical course of CF has been evaluated in several studies but still remains controversial^{4–6}. Nosocomial spread of NTM infection in CF was previously considered unlikely; however, recent reports revealed frequent human-human transmission^{7,8}.

Species diversification of NTM within the CF population appears to vary with geographical distribution. In the United States, *Mycobacterium avium complex* (MAC), a slow growing NTM, is the most frequently recognized pulmonary pathogen (2). In Europe and in other countries, however, *Mycobacterium abscessus* appears to be the major pathogen in CF^{8,9}.

A relationship between NTM infection and aspergillus infection, with or without ABPA was found, and it might be associated with a specific immune dysregulation involved in this subgroup of CF patients^{8,10}. Additionally, corticosteroid and itraconazole treatment were also found to be associated with increased incidence of NTM in CF.

Treatment for NTM pulmonary disease should be for at least 12 months and involves multiple antibiotics. Some patients with NTM isolates may not meet all of the ATS criteria for disease, and they require close monitoring of their clinical status with serial CT scans and sputum/bronchoalveolar lavage surveillance.

Further research is required to improve the identification of NTM in CF respiratory samples, to understand the pathophysiology of NTM infection within the CF lung and to develop more effective drug regimen for NTM-CF pulmonary disease.

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#2. Protracted Bacterial Bronchitis and Chronic Wet Cough

Petr Pohunek, Tamara Svobodová

Correspondence information: Petr Pohunek Pediatric Pulmonology Pediatric Department 2nd Faculty of Medicine University Hospital Motol Prague, Czech Republic
Email: petr.pohunek@LFMotel.cuni.cz

Introduction

Protracted bacterial bronchitis (PBB) has been defined as a condition with isolated wet coughing lasting for more than four weeks with no evidence of any specific cause of cough and resolving fully with prolonged antibiotic treatment.¹ It is considered a rather benign condition if properly treated but may advance to chronic suppurative lung disease (CSLD) and bronchiectasis.² It affects mainly younger children, more than half of the patients are in the age 0 to 3 years, about one third are 3 to 7 years old, and only about 10% are older than 7 years.

Etiology

The leading pathogen involved in PBB is nontypable *Haemophilus influenzae* (approx. 50%), followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis* (approx. 20% each). Combination of more pathogens occurs.³ Infection by *Pseudomonas aeruginosa* or other more resistant pathogens does not occur in simple PBB. If found in a child with chronic cough, the search for underlying etiology should be undertaken (e.g. cystic fibrosis, primary ciliary dyskinesia, immunodeficiency).

Risk Factors

Main risk factors for protracted bacterial bronchitis are

- Reduced mucociliary clearance after viral respiratory infections
 - Lack of reconvalescence after a viral bronchitis may lead to impaired airway clearance (secondary ciliary dyskinesia, persistent bronchial inflammation) and facilitation of secondary bacterial infection.
- Airway stability disorders
 - Tracheo/bronchomalacia has been detected in children with PBB more often than in the general population. In one study evaluating children with PBB in the age below 60 months, the authors found laryngomalacia or tracheomalacia in 74%,³ another study found tracheomalacia in 30% of young children with PBB.⁴ How far is the malacia a causative factor or to what extent instability of the airways may be secondary to prolonged infection and protracted coughing remains to be studied.
- Immunodeficiency
 - Disorders of humoral immunity can be associated with insufficient protection and may facilitate bacterial growth in the airways.

- Environmental burden
 - Important environmental risk for the development of PBB is environmental tobacco smoke (ETS). In many countries the frequency of smoking in the families with children is as high as 40–50%.
 - Local heating using wood or coal has been described as a significant risk factor for the pediatric airways.⁵
- Industrial pollution
 - Industrial pollution has been shown as a risk factor for respiratory infections in children. Most important part of industrial emissions is small particle particulate matter (PM₁₀) whose concentration may rise under local adverse climatic conditions. A correlation of PM₁₀ exposure with increased respiratory symptoms has been repeatedly documented.⁶

Pathogenesis

PBB usually develops as a consequence of an insult that has impaired the airway defense. With some risk factors, this may start gradually based on continuous damage of the mucosa (e.g. recurrent aspiration, environmental triggers, GER) with no apparent initial acute event. High enzymatic activity of neutrophils enhances the process. In some studies the fraction of neutrophils in the BAL was as high as 90%. Bacterial infection, retention of mucus and high proteolytic activity of the neutrophils can lead to CSLD, damage to the bronchial wall and gradual development of bronchiectasis. If diagnosed early, this process can be interrupted by antibiotic treatment and even the development of mild bronchiectasis can be reversed. Some pathogens can interfere with defense mechanisms forming a biofilm or cleaving immunoglobulins.

Clinical Presentation

Main symptom of bacterial bronchitis is wet coughing with or without sputum production. The wet sound of the coughing suggests intrabronchial secretions of various quality and consistence. The ability to produce sputum is age and training dependent. Infants and very young children are not able to spit out sputum; however, this can be successfully trained by a physiotherapist as early as in the third year of life. Coughing is usually present both during day and night, often more pronounced in the mornings as secretions accumulate overnight. Coughing may worsen after physical exercise. Occasionally the patient may wheeze based on the obstruction by mucus. This is only transient, variable and changes after coughing. Recurrent wheezing may signal bronchial hyperresponsiveness and should raise suspicion of asthma. In PBB, fever is generally absent. The infection is limited to the bronchial tree and does not lead to a systemic inflammatory response. Fever and elevation of acute phase proteins is associated with acute exacerbation or more severe affection of lung parenchyma, such as pneumonia.

Diagnosis

Children with protracted wet coughing should be diagnosed early in general practice. The general practitioner should detect and analyze the symptoms. Differential blood count, CRP and erythrocyte sedimentation rate belong to standard first-line investigations. GP

should also trace possible environmental risks, such as smoking, local heating or other local risks in the household.

Detailed investigations are important mainly in children with recurrence of PBB. Chest X-ray, sweat test, assessment of clinical risks for primary ciliary dyskinesia help to exclude severe underlying condition. In cooperating children the pulmonary function testing with flow-volume loop should be done. Reversibility should be tested using inhaled rapid acting beta-2 agonist.

If the child is able to produce sputum, the sample should be sent for cultures and microscopic evaluation before any antibiotics would be administered. In the treated child, stopping of antibiotics for at least 48 hours may increase the yield of the analysis. In the non-expectorating child, deep suctioning from the hypopharynx in the morning or after physiotherapy may help.

The most effective method of microbiological sampling is bronchoscopy. It is not indicated in children with single episode of PBB. Even in children with recurrent PBB, it is usually not necessary if they expectorate sufficiently. However, bronchoscopy may exclude an underlying pathology. Flexible bronchoscopy performed with spontaneous breathing allows visual assessment of airway anatomy and excludes aspirated foreign body. It also helps to assess mucosal inflammation, observe stability of the airways during breathing and coughing, perform bronchial toilette, remove mucus plugs and directly sample the mucus. In addition, a standardized bronchoalveolar lavage should be performed and the specimen sent to microbiology, differential cytology and staining for lipid-laden macrophages. Anaerobic and mycotic cultures should also be considered.

Additional examinations must include detailed ENT assessment to exclude focal infection in the upper airways area (adenoids, sinuses). Immunological testing should mainly check the humoral immunity, including concentration of vaccination specific antibodies and total serum IgE. Allergic sensitization should be tested only in context with symptoms and history.

If a development of bronchiectasis is suspected, the diagnostic method of choice is high resolution computerized tomography (HRCT).

Treatment and Prognosis

Uncomplicated PBB is easily treated; however, untreated persistent bacterial infection and accompanying inflammation is associated with risk of developing CSLD and bronchiectasis. The antibiotic treatment is based on expected or confirmed microbial etiology. Mostly, broad spectrum antibiotics targeted against *Hemophilus* spp., *Pneumococcus* or *Moraxella* are used. Production of the penicillinase should be respected in the selection of antibiotics. Uncomplicated PBB should resolve after two week course of appropriate antibiotic. This was also shown in a randomized controlled trial analyzing two-week course of amoxycillin-clavulanate against placebo. Children in the active arm showed significantly higher resolution rate (48%) than children in the placebo arm.⁷

Good effect of antibiotics was confirmed also in a systematic review.⁸ Even though there are no consistent data on the effect of physiotherapy in PBB, it is useful to use at least some basic techniques of airway clearance techniques, especially in young children.

Even though the antibiotics are usually very effective, relapses occur in about 70% of cases with good effect of repeated antibiotic course.³ In a child with high frequency of recurrence, a prolonged course of antibiotics may be considered. If an underlying condition is found, it is critical to treat this pathology together with the treatment of bronchitis.

Conclusion

Protracted bacterial bronchitis is a condition that should be suspected in children with protracted wet coughing. Quick diagnosis and early initiation of proper treatment should lead to complete resolution and prevention of severe sequelae, such as chronic suppurative lung disease or bronchiectasis.

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#3. Complicated Community-Acquired Pneumonia: Different Types, Clinical Course and Outcome

Eitan Kerem

Department of Pediatrics and CF Center Hadassah University Hospital Jerusalem, Israel
Email: ek@mail.huji.ac.il

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality, especially in children under 5 years of age. Complications associated with pneumococcal pneumonia include the development of

pleural effusion, pleural empyema, necrotizing pneumonia, and lung abscess. An increase in the incidence of pleural empyema was reported by many studies from the United States and in Europe. Although the incidence of invasive pneumococcal disease has decreased since the use of pneumococcal conjugated vaccine (PCV), developed countries have seen an emergence of empyema and necrotizing pneumonia episodes caused by nonvaccine serotypes. Between 1995 and 2003, the rate of pleural empyema steadily rose from 14 to 26 per million pediatric hospital admissions in the UK. The prevalence of parapneumonic empyema was shown to increase from 22% in 1994 to 53% in 1999 amongst pneumonia cases caused by *S. pneumoniae* in eight American hospitals. Of the 50 cases of pleural empyema that occurred from 1988 to 1994 at a pediatric hospital in Cincinnati, 40% of the cases were caused by *S. pneumoniae*. A study from Jerusalem found that the incidence of empyema and necrotizing pneumonia doubled between the years 2000–2009, almost all the cases were caused by *S. pneumoniae*. Seventy percent of the cases occurred before the age 5 years. Many authors also reported an increase in pneumonia-associated lung abscesses and cavitations. The reasons for this increase in the prevalence of suppurating complications in children with pneumonia have not been clearly identified. Suppurating complications were associated with age, recent chicken pox, infection with *S. pneumoniae* (especially serotype 1), and therapy with antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) prior to hospital admission.

Accumulation of fluid in the pleural space may follow the development of pneumonia in as many as 28% of children. The successful management of such fluid—which may either represent a parapneumonic effusion or be contaminated with micro-organisms, leukocytes, and fibrin to form an empyema, is a crucial component of the overall care of these patients. Controversy exists regarding the appropriate management strategy for empyema or complicated parapneumonic effusion in children. Current options include primary chest tube placement (either open or with radiological guidance) or video-assisted thoracoscopic surgery (VATS) with removal of pleural fluid and exudate. Primary chest tube drainage may be favored by some clinicians because of the perceived advantages of radiographic drainage for localized fluid collections, avoidance of general anesthesia, and the smaller thoracostomy tubes used. However, the fibrinous pleural fluid in the setting of empyema often clogs these small drains, resulting in inadequate drainage. Intrapleural administration of fibrinolytics may augment drainage, although this measure is not helpful in all cases. Open placement may lead to suboptimal placement of the tip of the tube. These shortcomings have led to the use of primary VATS-assisted drainage of the pleural space in pediatric patients with empyema and parapneumonic effusion. A VATS-based approach offers the potential for better lung expansion after removal of pleural debris and exudate, excellent magnified vision, optimization of the location of the chest tube, and reduced chest wall and muscle trauma compared with traditional thoracotomy.

Necrotizing pneumonia, also termed massive pulmonary gangrene, is a sequela of pneumonia in which the lung tissue becomes necrotic. Recent attention has focused on *S. pneumoniae* as the major causative

agent in children, and with limited intervention the prognosis is good. Surgical intervention may lead to bronchopleural fistula with prolonged course. Several cases of death associated with VATS were reported.

The management of children with pneumonia is generally based on the age of the patient and the clinical presentation. Initial antibacterial therapy for CAP is usually empirical, as culture and antibacterial sensitivity test results are rarely available at initial diagnosis. Any agent selected for empirical therapy should have good activity against the pathogens commonly associated with CAP, a favorable tolerability profile, and be administered in a simple dosage regimen for good compliance. Because *S. pneumoniae* is the most common bacterial cause of pneumonia and its associated complications, current guidelines for antibacterial of CAM recommend that the initial treatment will be directed to eradicate this microorganism. Narrow-spectrum antibiotics are advocated in the first instance. Inappropriate use of antibiotics can result in treatment failure and adverse drug reactions, and contribute to emerging pathogen resistance. Consideration of a drug's pharmacodynamic and pharmacokinetic properties is also important. Agents with low maximum plasma or tissue concentrations and long half-lives may be more likely to expose bacteria to resistance-selective concentrations. The strategy of administration is also important; low doses of beta-lactams and long treatment duration are risk factors for the carriage of pneumococci non-susceptible to penicillin, whereas short-course, high-dose therapy minimizes this risk. Convenience and tolerability are also essential considerations in pediatrics.

For non-severe pneumonia, oral amoxicillin is the antibacterial of choice with low failure rates reported. Randomized controlled trials in children in the developing and in the developed countries showed that, in previously well children, oral amoxicillin and IV benzyl penicillin have equivalent efficacy for the treatment of pneumonia. Both were successful in curing children with CAP.

Pneumococcal isolates not susceptible to penicillins and third-generation cephalosporins have been well described *in vitro*, and rates between 10% and 40% have been reported from worldwide surveillance. There is significant geographical variation, with high rates in Spain, France and parts of Southeast Asia and the USA. Furthermore, macrolide resistance is also a problem in some communities. The main mechanism of resistance is via the alteration of penicillin-binding proteins, which can be overcome by achieving adequate local drug levels; i.e., it is a decreased sensitivity rather than an absolute resistance. There is as yet no evidence of clinical treatment failure of infections outside the central nervous system using high-dose penicillin. Since most pneumococci remain sensitive to high-dose penicillin-based antibacterials, amoxicillin or penicillin remains the antibiotic of choice in pneumococcal pneumonia. The emergence and spread of resistance to commonly used antibiotics has challenged the management of CAP. Multiple sets of CAP guidelines have been published to address the continued changes in this complex disease. Severely ill children are traditionally treated with parenteral antibacterials. It has been shown that penicillin resistant pneumococci were not associated with more severe disease. It has been shown that

penicillin resistance is not a factor in outcome from invasive *S. pneumoniae* community-acquired pneumonia.

Pneumococcal macrolide resistance is mediated via alteration of the 50S ribosomal binding site, thereby preventing binding and the subsequent inhibition of bacterial protein synthesis. A second mechanism is via the presence of efflux pumps for the antibiotic. It is often associated with penicillin non-susceptibility. Rates of usage and resistance of the newer macrolides have substantially increased over recent times and vary by geographical region. There are reports of treatment failure of pneumococcal disease using macrolides alone; thus, this approach is not recommended.

If parenteral therapy is required and pneumococcus is the likely pathogen, benzylpenicillin or an aminopenicillin can be used. Broader-spectrum agents have no additional benefit. For the severely unwell, toxic child with or without effusions, where rarer pathogens are a possibility, or in the rare scenario of high pneumococcal penicillin resistance (mean inhibitory concentration >2 mg/l), therapy should include a third-generation cephalosporin (e.g. ceftriaxone) with a macrolide if atypical agents are potential pathogens, or a penicillinase-resistant beta-lactam (e.g. oxacillin) or vancomycin if *Staphylococcus aureus* or MRSA infection is likely. However, treating all children with CAM with these antibiotics may change the microflora of pneumonia causing bacteria and increase the rate of infections with other less common and more resistant microorganisms.

Respiratory Viruses and Their Relation to Disease

#1. Viral Bronchiolitis in Children

Oliviero Sacco, Antonino Capizzi, Roberta Olcese, Donata Girosi, Giovanni A. Rossi.

Department of Pediatrics, Pulmonary and Allergy Disease Unit and Cystic Fibrosis Center, Istituto G Gaslini Institute, Genoa, Italy.
Email: giovannirossi@gaslini.org

Introduction

Bronchiolitis is the first, and most common, acute lower respiratory tract viral infection in infants less than 12 months of age and the leading cause of hospitalization in this age group [1]. Although most children have only mild symptoms, between 2% and 3% of infants <12 months old are hospitalized with a diagnosis of bronchiolitis which, in U.S.A. accounts for 57,000 to 172,000 hospitalizations annually, with extremely elevated hospital charges for care related to this disorder [1,2]. In addition, 12% of the hospitalized infants require admission to the intensive care unit for impaired general conditions, recurrent apnea episodes or respiratory failure requiring mechanical ventilation [1,2]. Bronchiolitis is also associated with a disproportionate number of deaths among children younger than 5 years of age in resource-limited nations [3]. These numbers are much lower in industrialized countries, but deaths for bronchiolitis show an incidence which is nine times higher than that of influenza virus infections [3]. Large epidemiological studies have also demonstrated a clear relationship between bronchiolitis early in infancy and subsequent bronchial hyperreactivity into childhood and adulthood [4]. Viral but also host factors establish the magnitude of the

structural and functional damage to the respiratory structures and ultimately the extent, severity and duration of the first infection and of the later consequences [5].

The Etiology of Bronchiolitis

The pathogen most frequently causing bronchiolitis in infants is respiratory syncytial virus (RSV), followed by human rhinovirus (HRV). Other respiratory viruses such as metapneumovirus (MPV), human bocavirus (HBoV), enterovirus (EV), adenovirus (ADV), influenza virus (IV), human coronavirus (HCoV) and parainfluenza virus (PIV) have been also implicated [1–3]. Bacterial co-infections are rarely described in infants with bronchiolitis [1–3]. With the exception of HRV infection, which peaks in the spring and fall, all the epidemiological reports have shown that, in general, seasonal bronchiolitis epidemics peak between December and March every year [6]. Some other differences in the clinical presentation of bronchiolitis due to the various viruses have been reported. For example, it has been shown that HRV-associated bronchiolitis may result in a shorter hospitalization length than bronchiolitis attributable to RSV and, consistently, that RSV infection seems to cause more severe disease [1–3]. In addition, one constant characteristic is that infants hospitalized with RSV-induced bronchiolitis have the tendency to be younger than those hospitalized with other viruses [4]. Finally, although differences in the response to medical intervention have not been identified consistently, it has been suggested that infants hospitalized with HRV and RSV may have a distinct response to anti-inflammatory therapy: treatment with systemic corticosteroids seems to be more likely to reduce recurrent wheezing in the infants with RV bronchiolitis, as opposed to those with RSV bronchiolitis [4,5]. These differences probably reflect the involvement of different pathogenetic mechanisms [5].

Risk Factors for Severe RSV Bronchiolitis

A number of host-related risk factors for severe RSV bronchiolitis have been identified through a variety of epidemiological studies [1–3]. Because of the immaturity of the innate and acquired immune response and the incomplete development of the respiratory system, it is not surprising that risk factors can include prematurity, low birth weight and young chronological age [1–3]. Environmental factors that can also raise the risk of hospital admission rates are the number of siblings living permanently in the child's household, day care attendance and tobacco smoke exposure [1–3]. Other host-related risk factors are male gender and the presence of chronic pulmonary disease of infancy, congenital heart disease, structural or functional airway abnormalities, neuromuscular syndromes, immunodeficiencies, cystic fibrosis and Down syndrome [1–3]. However, epidemiological data show that the vast majority of infants hospitalized for this condition do not belong to these "at risk" groups, suggesting that viral or host factors, not included in the classical risk factors, may be accountable for disease severity and play a putative role in the magnitude of the subsequent respiratory morbidity [4,5].

Bronchiolitis and Recurrent Wheezing in Later Life

RSV-mediated infection induces severe respiratory symptoms almost exclusively in young children and in immune-deficient or immune-depressed patients. Infants with bronchiolitis and symptoms severe

enough to warrant hospitalization are at increased risk of developing recurrent wheezing or asthma, not only in childhood, but also in adult life [6]. The mechanisms explaining the higher incidence of wheezing after severe bronchiolitis are unclear since it is not known whether viral bronchiolitis simply identifies infants who are at increased risk for subsequent wheezing [5]. Most of the information comes from RSV and HRV infections. Besides the direct cytopathic effect, the local host inflammatory response to RSV plays a primary role in the development of the signs and symptoms characterizing the disease. The combined effect of the virus and the inflammatory response to it leads to epithelial damage, sloughing off of the epithelium, mucus production and, ultimately, airway obstruction. Indeed, in infants with severe disease, the cytopathic effect induced by RSV is amplified by the presence of a potent inflammatory reaction, mediated by activated polymorphonuclear leukocytes and natural killer cells. This first innate response is associated with a defective host adaptive immune response, characterized by a Th2-type reaction. This leads to an inefficient γ -interferon-mediated stimulation of the CD8⁺ cytotoxic T-cells that ineffectively clear the virus and poorly stimulate macrophage phagocytic activity to endorse dead cell clearance [5]. The persistent airway hyperreactivity after the "early-life" RSV infection may be related, at least in part, to an abnormal neural control of airway smooth muscle tone induced by RSV [7]. The upregulation of nerve growth factor (NGF) and of TrkA and the neurokinin NK₁ receptors functions as promoter of acetylcholine release and as a signaling molecule inducing the production of neurokinin A and Substance P [7]. These mediators are involved in the pathogenesis of neurogenic inflammation and in bronchomotor tone dysregulation [5,7]. In addition, the persistence of a latent viral infection in sites, such as bone marrow cells, could maintain a constant stimulation of the immune system and explain the respiratory sequelae of RSV-induced bronchiolitis [7]. In contrast with RSV, HRV affects people of all ages and induces minimal, if any, airway cell cytotoxicity [5,6]. The HRV-induced cytopathic effect on airway structural and inflammatory cells is associated with an inflammatory reaction with the release of mediators leading, in predisposed individuals, to recurrent or persistent bronchial hyperreactivity [5,6]. A current hypothesis is that HRV infection may be favored by allergic sensitization. The Th2 bias, the characteristic 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 [6]. In addition, the release of Th2-type cytokines and chemokines could result in an amplification of the inflammatory response to infection, presenting with cold and asthma exacerbations [5,6]. As compared with children with RSV infections, those with HRV infections present more often atopic dermatitis and blood eosinophilia during acute viral infection [5,6] and causal role for allergic sensitization in favoring more severe HRV-induced illness is supported by the demonstration that allergic sensitization may precede HRV-associated wheezing and may lead to an increased risk of wheezing illness caused by HRV but not RSV [8]. Thus, RSV seems to act as an "inducer" of subsequent airway hyperreactivity: its first infection is characterized by extensive airway damage and by induction of neurogenic inflammation, the latter possibly responsible for long-lasting bronchial hyperreactivity [5]. In contrast, HRVs seem to act as a "trigger", inducing extensive release of pro-inflammatory mediators

leading to recurrent or persistent bronchial hyperreactivity in allergic patients or in individuals predisposed to atopic sensitization [5].

Management of Bronchiolitis in Infants

Prevention of bronchiolitis includes: a) environmental prophylaxis to decrease transmission of respiratory infections and b) pharmacological prophylaxis, specifically for RSV bronchiolitis, with the administration of a humanized monoclonal antibodies (palivizumab) during the epidemic season in particular "at risk" categories [3,9]. Despite decades of research, there is no licensed RSV vaccine or effective therapeutic agent on the market, but currently a large number of candidates are evaluated in preclinical phase 2 or are undergoing clinical trials [10]. There are still controversies regarding the best therapeutic approach to bronchiolitis. Supportive treatment, the only approach recommended by the recent International Guidelines, relies mainly on oxygen therapy and hydration [3,9]. The development of next-generation tools for the management of RSV infection has recently largely focused on three major target areas: the viral entry machinery, the viral RNA-dependent RNA-polymerase complex and the viral component assembly. Out of the many RSV inhibitors described in recent years, none has completed phase 3 clinical trial [10].

Conclusion

A more comprehensive knowledge of bronchiolitis pathogenesis, induced by different viruses, and of the interaction with the host defenses will hopefully allow to produce newly designed effective vaccines and antiviral therapies to prevent and control the infection of these major respiratory pathogens.

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#2. The Drakenstein Child Health Study: New Insights Into Childhood Pneumonia

Heather J Zar

Department of Paediatrics and Child Health Red Cross War Memorial Children's Hospital and MRC Unit on Child & Adolescent Health University of Cape Town Cape Town, South Africa

Correspondence: heather.zar@uct.ac.za

Childhood pneumonia is the predominant cause of death or illness in children under 5 years outside the neonatal period.^{1,2} Asthma is the commonest non-communicable disease in children occurring in approximately 15% of adolescents worldwide.³ 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.² Further, the prevalence of asthma in African adolescents is higher than the reported global average.⁴ 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.⁵

The Drakenstein Child Health Study is a unique, multidisciplinary, South African birth cohort, to investigate the impact of antenatal and early life exposures on child health.^{6,7} A core focus of the study is on the incidence, risk factors, etiology and long term impact of early lower respiratory tract infection (LRTI) or pneumonia on child health.⁸ The study investigates 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.⁶

Methods: Pregnant women from a poor, peri-urban community in South Africa with high exposure to infectious diseases and environmental risk factors were enrolled in the second trimester at 2 clinics – TC Newman (serving a mixed ancestry population) and Mbekweni (serving a Black African population). Women were followed through

pregnancy and child birth (all at Paarl hospital); mother-child pairs are followed until children are at least 5 years. 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 visits⁹; tobacco smoke exposure is investigated using urine cotinine measures. Follow-up of children is synchronized with routine primary care visits. Study visits are conducted at the Paarl Hospital and at the TC Newman and Mbekweni clinics, which provide a strong primary health care program including a strong HIV prevention and treatment program and national immunization program that includes 13-valent pneumococcal conjugate vaccine given at 6, 14 weeks and 9 months. Active surveillance for pneumonia is done; microbiological investigations include a 33 multiplex PCR performed longitudinally on nasopharyngeal specimens and at each pneumonia episode. Lung function [tidal breathing measures, multiple breath washout testing, tidal exhaled nitric oxide and respiratory function using the forced oscillator technique (FOT)] is measured in children at 6 weeks, annually and during LRTI episodes¹⁰

Results: 1140 mother-child pairs were enrolled; all children have completed 1 year of follow-up. More than 2700 child years of follow-up have been accrued with high cohort retention. The population is poor (with the Mbekweni population relatively poorer than that from TC Newman), mostly single mothers and 20% of mothers were HIV-infected. Rates of tobacco smoke exposure were very high, with approximately a third of pregnant women active smokers.¹¹ At birth, 56% of neonates had cotinine levels indicative of exposure, with 19% having levels of an active smoker.¹¹ Immunization coverage for the EPI schedule, including 13-valent pneumococcal conjugate vaccine, given at 6, 14 weeks and 9 months was high.¹² By Feb 2017, there were 965 pneumonia cases [723 (79%) ambulatory and 197 (21%) hospitalized; pneumonia incidence 0.31 episodes per child year; e/cy]. The highest incidence occurred in children 1–6 months of age. Using a case control analysis, RSV, influenza virus or *B. pertussis* were most strongly associated with pneumonia; bocavirus, parainfluenza virus, adenovirus or CMV were less strongly associated with pneumonia.¹³ RSV was the commonest pathogen identified occurring in 24% of cases. However there were several organisms identified at the time of LRTI, with a median of 5 organisms detected on NP swabs. Longitudinal analysis of NP specimens showed high rates of carriage of *S. pneumoniae*, *M. cattarrhalis* or *S. aureus* as well as several potential organism interactions up to 3 months prior to pneumonia. Lung function showed tracking through the first year of life; LRTI in infancy impaired lung function at 1 year of age.¹⁴ The pneumonia case fatality rate was 1%.

Conclusion: Pneumonia is common in this cohort despite high rates of immunization. RSV is a predominant pathogen, but several pathogens occur concurrently. Dysbiosis of the NP microbiome precedes the development of pneumonia. Early life LRTI impacts on lung health and reduces lung function in infancy. Early life exposures may predispose to acute LRTI and result in long term chronic disease over the life course. New interventions are needed to prevent early life LRTI and promote long term health.

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#3. Treatment Alternatives for RSV Disease in Infants

Fernando P. Polack

Professor, Department of Pediatrics at Vanderbilt University Scientific Director of the INFANT Foundation in Buenos Aires, Argentina
Email: fernando.p.polack@Vanderbilt.Edu

Respiratory syncytial virus (RSV) is the main cause of hospitalization in infants in industrialized and developing countries [1]. Millions of children are hospitalized and an estimated 66,000-199,000 die every year worldwide due to RSV disease [2]. In addition, RSV has been causally linked to recurrent wheezing and associated with pediatric asthma [3-5].

Recognition of the acute and chronic burden of RSV lower respiratory tract infections (LRTI) sparked a wave of initiatives to develop preventive and therapeutic products against the pathogen in recent years. A promising strategy under evaluation to prevent severe RSV disease is immunization of pregnant women against the virus. Maternal immunization aims to elicit high levels of protective antibody in pregnant women, fostering transplacentally acquired antibody-mediated protection in infants during the first months of life [6-8].

Other interesting approaches to RSV prevention in infants are under study, including but not limited to passive prophylaxis with long-lived monoclonal antibodies against a neutralizing epitope in the RSV fusion (F) protein and immunization with recombinant live attenuated RSV vaccines [9-10].

The surge of old and novel approaches to prevent RSV suggests that we may witness a significant change in the landscape of respiratory infections in the near future, if the main cause of infant hospitalization worldwide is tamed. While the burden of RSV disease may decrease, predicting the magnitude of change is premature. Yet, numerous important lessons will emerge from this worldwide effort. First, RSV is responsible for a significant proportion of infant hospitalizations worldwide [1,2]. Second, decreasing its impact may affect other acute and chronic consequences of RSV infection, from secondary bacterial infections and mortality to recurrent wheezing and asthma [2-5]. Finally, RSV prevention may inform about other factors influencing maternal-infant health such as human milk protection and/or the acute and long-term effects of respiratory illness during pregnancy.

This presentation intends to address questions that may emerge during or after RSV prevention.

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Not Your Every Day Patient

#1. Ciliopathy Syndromes: Current Diagnostic Approach and Management

Thomas Ferkol

Washington University School of Medicine Pediatrics Allergy Pulmonary Medicine
St Louis, Missouri, United States
Email: ferkol_t@wustl.edu

Ciliopathies are a growing, genetically heterogeneous collection of disorders related to cilia dysfunction. The first ciliopathy described in humans, primary ciliary dyskinesia (CILD1: MIM 244400) is an inherited disorder characterized by impaired motor ciliary function. The frequency of primary ciliary dyskinesia is roughly between 1 in 12,000 to 20,000 live births, based on population surveys, but these values likely underestimate its incidence in the general population. In most families, the disease is transmitted by an autosomal-recessive pattern of inheritance, though rare instances of autosomal-dominant or X-linked inheritance patterns have been reported. Primary ciliary dyskinesia does not have an apparent racial or gender predilection.

Primary ciliary dyskinesia has several characteristic features. Neonatal respiratory distress is a common feature, and most affected newborns develop increased work of breathing, tachypnea, and upper and middle lobe atelectasis on chest radiographs. Often diagnosed with transient tachypnea or neonatal pneumonia, infants frequently require supplemental oxygen flow or ventilator support for days to weeks. Daily, year-round productive (wet) cough that begins in infancy is a common clinical manifestation of primary ciliary dyskinesia. Persistent, non-seasonal nasal congestion and rhinitis presenting in early infancy is typical. Chronic otitis media is present in most patients with primary ciliary dyskinesia, and middle ear findings may be helpful in distinguishing primary

ciliary dyskinesia from other chronic lung diseases. Although primary ciliary dyskinesia is considered a rare lung disease, its prevalence in children with chronic respiratory infections has been estimated to be as high as 5%. Extrapulmonary manifestations include left-right laterality defects, most often *situs inversus totalis*, which occurs in nearly 50% of patients with primary ciliary dyskinesia. Respiratory ciliary dysfunction is also found in patients with heterotaxy and congenital heart defects, which demonstrates the importance of cilia function in normal cardiac development. Male infertility is common due to impaired sperm motility. Ultrastructural defects in ciliated cells lining fallopian tubes have led to speculation that subfertility and ectopic pregnancies occurs in women, but this association has not been conclusively established.

Historically, the diagnosis of primary ciliary dyskinesia was based on compatible clinical phenotypes and specific ultrastructural defects of the ciliary axoneme. Unfortunately, ultrastructural examination of cilia as a diagnostic test for primary ciliary dyskinesia has significant drawbacks. Ciliary defects can be acquired, and nonspecific changes may be seen in relation to exposure to environmental pollutants or infection. Normal ciliary ultrastructure does not exclude primary ciliary dyskinesia, and is found in approximately 30% of affected individuals. Newer tests, such as measurements of ciliary beat patterns using high-speed videomicroscopy and nasal nitric oxide measurements, increasingly have been used as diagnostic or screening tools. Immunofluorescent staining for ciliary proteins is another approach that holds promise, and may address some of the limitations of transmission electron microscopy.

Genetic testing has become a powerful diagnostic tool for primary ciliary dyskinesia. Through a collaborative international research effort, over 35 genes have been linked to the disease, and more than 70% of all patients tested have biallelic mutations of these genes. As gene discovery continues, the percentage will rise. Many of mutated genes have been linked to specific ultrastructural defects and ciliary dysmotility, including genes that encode components of the outer dynein arm, inner dynein arm, dynein regulatory complex, nexin, and the radial spokes and central apparatus. More recently, mutations in genes coding for several cytoplasmic proteins have been found, which appear to have important roles in cilia assembly or protein transport.

Genetics has provided unexpected insights into phenotypes of primary ciliary dyskinesia. For instance, biallelic mutations in the dynein axonemal heavy chain 11 (DNAH11) gene, which encodes an outer dynein arm protein, clearly leads to disease, but is not associated with ultrastructural defects, and cilia have normal (or more rapid) beat frequency. Several patients with mutations in Cyclin O (CCNO) and Multiciliate differentiation and DNA synthesis associated cell cycle protein (MCIDAS) were found to have symptoms consistent with primary ciliary dyskinesia and had only rare cilia on the epithelial surface. Mutations in CCDC39 and CCDC40, proteins in the nexin-dynein regulatory complex that act as "rulers" determining the precise repetition of structural proteins along the axoneme, yield inconsistent ultrastructural abnormalities characterized by absent inner dynein

arms in all axonemes, but misplaced radial spokes and microtubular disorganization in only some cilia. A cross-sectional study showed that children who had microtubular disorganization, primarily due to biallelic mutations in CCDC39 or CCDC40, had more severe lung disease. In contrast, individuals with biallelic mutations in RSPH1 have milder respiratory phenotypes.

In contrast to motor cilia, primary (sensory) cilia are solitary, immotile organelles that are located on the surface of most nondividing cells. Originally considered vestigial remnants, these structures have specialized sensory functions, and genetic defects can lead to diverse syndromes and conditions, such as polycystic kidney disease, Meckel-Gruber syndrome, Bardet-Biedl syndrome, Ellis-van Creveld syndrome, retinitis pigmentosa, and various skeletal dysplasias. Some primary ciliopathies have been found to have clinical features suggestive of both motile and sensory cilia dysfunction, suggesting overlap.

To date, no therapies have been shown to correct ciliary dysfunction, and management focuses on aggressive mucociliary clearance and treatment of bacterial infections. Hopefully, future advances in cilia genetics and biology will identify therapeutic targets that could restore ciliary structure and function.

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#2. Non-CF Bronchiectasis: Not Your Average Patient?

Catherine Byrnes

Associate Professor Department of Paediatrics University of Auckland & Paediatric Respiratory Starship Children's Hospital Specialist Auckland, New Zealand
Email: c.byrnes@auckland.ac.nz

Unfortunately, a child with non-cystic fibrosis (CF) bronchiectasis is becoming more common. The incidence and prevalence of pediatric and adult bronchiectasis is increasing in developed countries (1, 2), especially in socioeconomically deprived and indigenous populations (3). This may be due to a true increase in disease, an association with reduced antibiotic use in the community with encouraged antimicrobial stewardship, improved recognition, and/or increased use of chest CT scans enabling diagnosis.

Bronchiectasis prevalence is more difficult to ascertain in developing countries. About 1% of children hospitalized with pneumonia are suspected to develop bronchiectasis (4). Overcrowding, poor housing, and smoke exposure (cigarette, cooking fire) also increase risk (5). Combined with poor access to healthcare and under-diagnosis, bronchiectasis is likely to have a high prevalence. Certainly, it is probably common enough to lose its 'orphan disease' status. Differing associations are reported from studies across countries, e.g. nearly 20% secondary to TB in China, mostly post-infectious in India, associated with high rates of HIV in South Africa. Access to investigations is also an issue.

Presentation: In children, bronchiectasis commonly presents as a chronic wet cough with recurrent respiratory infections. Wheeze/asthma is reported in 40-74%. Persistent chest x-ray abnormalities following respiratory infection, particularly focal changes, is another common pathway (1, 2). Early pneumonia is a key risk factor, with symptoms/x-ray changes persisting in two-thirds of high risk children one year after a single admission at <two-years-age (6).

Diagnosis: There is often significant delay between onset of symptoms and definitive diagnosis. The current diagnostic guidelines suggest referral after more than 4 weeks of wet cough, or 3 episodes of productive wet cough per year (1). However, in different studies, children had a mean of two hospital admissions and four infections in the first year of life; a mean of two years of chronic cough; or a mean of five chest x-rays (range up to 35) before a chest CT scan was requested (3). This suggests that community health practitioner awareness of bronchiectasis is still low and that significant barriers to early diagnosis exist, particularly CT scan access due to economic/geographical constraints or concerns regarding radiation dose or general anesthetic. Treatment can be commenced based on a suspicious history if there will be a delay in obtaining a definitive diagnosis.

Etiology: In the pediatric populations described in the literature, post-infectious etiology and idiopathic (also likely to be post-infectious in the main) is a major cause. The number with an underlying disorder is variable (e.g. aspiration, immunodeficiency, primary ciliary dyskinesia, presence of a foreign body) but seen in 52% when 12 studies involving 989 children were combined (7). Available guidelines suggest a range of appropriate investigations which individual history and examination will inform. The most

common infecting organism in children is non-typable *Haemophilus influenzae*, with *Streptococcal pneumoniae* and *Moraxella catarrhalis* frequently cultured. *Pseudomonas aeruginosa* is rare, and in our New Zealand clinic seen only in those with severe disease or with chronic aspiration. The presence of *Staphylococcus aureus* indicates the need to exclude cystic fibrosis.

Bronchiectasis pathogenesis involves complex interactions between host, microbes and the environment. Initial infection with impaired mucociliary clearance and dysregulated inflammation ultimately results in the destruction of airway walls, with mucus retention increasing the susceptibility to further infection and inflammation, resulting in progressive airway damage. Respiratory secretions (BAL, sputum) show a neutrophilic inflammation with high levels of pro-inflammatory mediators and neutrophil chemoattractant factors. In addition to inflammatory over-stimulation, there is recent suggestion about impaired interferon-gamma response to *Haemophilus influenzae* and reduced macrophage activity (8).

Treatment: Airway clearance with chest physiotherapy and exercise is the mainstay of bronchiectasis management with infective exacerbations treated with a longer than usual course (2 weeks) of antibiotics (1, 2). Prolonged courses of antibiotics, oral azithromycin or nebulized gentamicin for 6 months or more, have shown reduced infections, reduced hospital admissions and improved cough scores, but with the issue of increased bacterial resistance. Importantly, this resistance is seen less with better adherence.

A recent Cochrane review on interventions in bronchiectasis indicated a paucity of data on which to base management, and very few trials with children (9). Nebulized hypertonic saline was inconclusive and nebulized RhDNase increased exacerbations and therefore must be avoided. Small, and possibly questionably clinically relevant, responses in lung function, dyspnea, or cough-free days were reported for inhaled corticosteroids alone and with long acting beta agonists with few participants. A single study suggested benefit with nebulized indomethacin. Other anti-inflammatory agents and other nebulized antibiotics (amikacin, ciprofloxacin) are being trialled. Adherence in a serious issue, with one adult study reporting adherence at 16%! (10)

Prognosis: In children, long term outcomes seem dependent on severity at diagnosis, and the subsequent rate of exacerbations (11, 12). However, unlike adult disease, improvement and even reversibility is associated with pediatric bronchiectasis. Early referral and diagnosis are essential.

The Future: Knowledge on true prevalence, etiology, pathogenesis, and management of bronchiectasis is lagging behind other respiratory diseases, with a burst of research in the last decade. Certainly the new development of databases (Europe, UK, USA, and Australia, websites listed below), with increasing international collaboration, will add new insights. Already cluster research on determining different phenotype groups and severity scores (the 'Bronchiectasis Severity Index' and the 'FACED' score) have been developed but these use parameters irrelevant to children.

There are significant differences between children and adults in bronchiectasis disease progression and treatment. Trials in children

are essential. There is very little evidence for management and while new drugs will be useful, we can do better with those we already have. The development of pediatric databases and severity scores would be helpful and is in evolution. Family-led organizations and websites would be a powerful step forward. It is probable that a significant burden of disease exists in the developing world – with the lack of access to diagnostic facilities and available therapies a major concern.

Registries for persons with bronchiectasis:

EMBARC, Europe www.bronchiectasis.eu

United Kingdom: www.bronch.ac.uk

United States of America: www.copdfoundation.org/research/bronchiectasis-research-registry/

Australia: The bronchiectasis toolkit bronchiectasis.com.au

<http://lungfoundation.com.au/health-professionals/bronchiectasis-registry/>

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#3. Allergic Bronchopulmonary Aspergillosis (ABPA)

Malena Cohen-Cymerknoh

Pediatric Pulmonary Unit Hadassah-Hebrew University Medical Center Jerusalem, Israel

Email: Malena@hadassah.org.il

Allergic bronchopulmonary aspergillosis (ABPA) is a lung hypersensitivity disease mediated by an allergic late-phase immune response to specific antigens of *Aspergillus fumigatus* (Af). It is characterized by clinical deterioration associated with elevated serum IgE and precipitin levels and evidence of immediate cutaneous reactivity to Af.

ABPA occurs almost exclusively in asthma or cystic fibrosis (CF) patients. The prevalence of ABPA in patients with CF was reported to range from 1 to 15%¹ and increases with the patient's age.

Immune mediated mechanisms of lung destruction in ABPA are not completely understood. *Aspergillus fumigatus* antigens stimulate a polyclonal antibody response which is essentially responsible for the elevated levels of total IgE as well as Af-IgE and Af-IgG antibodies. Increased interleukin (IL)-4, IL-5, IL-10, and IL-13 production due to the cellular Th-2 immunological response suggests an immunocompetent host². Genetic risk factors include expression of HLA-DR2 and HLA-DR5 genotypes, whereas HLA-DQ2 protects against ABPA³.

The diagnosis of ABPA includes a set of minimally essential criteria, including (1) asthma, (2) immediate cutaneous reactivity to Af, (3) total serum IgE >1,000 ng/mL, (4) elevated specific IgE-Af/IgG-Af, and (5) central bronchiectasis in the absence of distal bronchiectasis. A "truly minimal" set of diagnostic criteria was proposed in 2013, and includes items (1), (2), (3), and (5) of the aforementioned minimally essential criteria⁴.

Since CF shares similar symptoms and radiological findings with ABPA, the Epidemiologic Study of Cystic Fibrosis (ESCF) adapted a set of less strict criteria for the diagnosis of acute ABPA in patients with CF⁵, and includes the presence of 2 of the following 3: (1) immediate skin reactivity to Af antigens, (2) precipitating antibodies to Af antigens, and (3) total serum IgE >1,000 IU/mL; and at least 2 of the following 6: (1) bronchoconstriction, (2) peripheral blood eosinophilia >1,000/ μ L, (3) history of pulmonary infiltrates, (4) elevated specific IgE-Af/IgG-Af, (5) Af in sputum by smear or culture, and (6) response to steroids. However, later on, the 'ABPA in CF' consensus criteria stated that serum IgE >500 IU/mL is considered diagnostic⁶.

In CF lungs, ABPA can be a cause of an acute deterioration in pulmonary function. Suspicion should be raised if there is no clinical response to conventional antibiotic therapy. Symptoms may include increased wheezing, fever, malaise and thick sputum with brown or

black bronchial casts. A high level of clinical suspicion is necessary for the early recognition and specific treatment for ABPA should immediately be started in order to prevent further lung damage.

Corticosteroids are the most effective drugs for treating ABPA. The dosing schedule and duration of therapy remain poorly defined. Patients with CF and ABPA often require prolonged therapy with oral corticosteroids, which is associated with severe side effects. Monthly pulses of high-dose IV methylprednisolone therapy (10 to 30 mg/kg/day for 3 consecutive days) were shown to be an effective treatment for CF patients with ABPA. It induced significantly less side effects when compared with conventional oral therapy, and furthermore, patients treated with pulse IV methylprednisolone seemed to respond faster to therapy⁷. Antifungal oral treatments (e.g., itraconazole and voriconazole) have been proposed as adjunctive therapies in patients with steroid-dependent ABPA or with steroid-related adverse effects⁸. The exact role of antifungal agents in the treatment of ABPA is still debated. By decreasing the fungal load, antifungal agents help control the antigenic stimulus and thus diminish the inflammatory response. However, no definitive evidence exists regarding their efficacy in patients with CF and ABPA.

Omalizumab, a monoclonal antibody against IgE, has also been tried in the management of ABPA. A significant clinical improvement with reduction in hospitalization and exacerbations in patients with concomitant CF and ABPA was demonstrated⁹, and could be beneficial as a steroid sparing therapy in these patients¹⁰. However, more data is required to clarify the role of omalizumab before this expensive therapy can be recommended as a treatment approach.

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The Scene in CLD In Low And Middle Income Countries

#1. The Role of Nutrition in Chronic Lung Diseases in Childhood

Manuel E. Soto-Martínez

Pediatric Pulmonologist – Clinical Epidemiologist Respiratory Department Hospital Nacional de Niños (National Childrens Hospital) San José, Costa Rica
Email: msotom@hnn.sa.cr or quiquesoto@gmail.com

Introduction

Chronic lung diseases, such as asthma or COPD, affect millions of people and are a major cause of premature death in children and adults worldwide. It is now generally accepted that many chronic lung diseases result from complex genetics and environmental interactions. Therefore, increasing attention has been given to many environmental and lifestyle factors, such as air pollution, smoking, physical activity and diet. Research shows that early nutrition plays a critical role in healthy lung development, and can underpin the increasing propensity for many respiratory and other non-communicable diseases. Diet may be an important modifiable risk factor for the development, progression and management of chronic lung diseases in children and adults (e.g. bronchopulmonary dysplasia (BPD), asthma, cystic fibrosis (CF) and COPD).

Under-nutrition and over-nutrition may have significant effects on pulmonary function, poor growth and risk for chronic lung disease. In early life, malnutrition has been related to impaired immunity, which results in more frequent and severe respiratory infections. Additionally, nutritional depletion is a common problem in patients with severe chronic lung diseases such as BPD, CF, and others. Hypermetabolism, malabsorption and depletion of fat free mass are associated with increased morbidity and significant impairment of health status.

Obesity has also been related to poor lung function, an increase in the prevalence of asthma and asthma severity. In addition, several of these nutritional deficiencies rarely occur in isolation. Dietary intervention has a potential role in reducing acute respiratory illness related morbidity and mortality, especially in developing countries. In most chronic lung diseases, nutritional interventions have proven to be

effective in preventing or improving outcomes, but evidence is scarce in others.

Micro- and Macronutrients Related to Chronic Respiratory Diseases

Pregnant women (hence, their babies) and children under 5 years of age are particularly vulnerable to micronutrient deficiency, increasing their susceptibility to acute and chronic lung diseases in childhood. In addition, multiple micronutrient deficiencies coexist in the same individuals. Vitamin A deficiency is related to impaired immune function and cell differentiation.

Zinc deficiency has been associated with a higher incidence of acute respiratory infections, a major cause of death in children under 5 years in developing countries [1].

Instead, nutritional interventions or diets rich in fruits and vegetables seem to be protective. A recent meta-analysis on the effect of childhood nutrient intake and the risk of developing wheezing or asthma showed that there was some evidence of protective effects from Vitamin A, D and E, zinc, fruit and vegetables, and of a Mediterranean diet against the development of asthma [2]. Also, Saadeh et al. showed that fruit and green vegetable intake was associated with a low prevalence of wheezing and asthma in school children aged 8-12 years old [3]. Adequate dietary vitamin C intake has also been related to reduced wheezing in some observational studies in children.

Vitamin D has been extensively investigated in the last 20 years. It has a well-established immunomodulatory effect within the lung. Epidemiological studies show significant associations between vitamin D and several acute and chronic lung diseases such as asthma. There is some evidence on the role of vitamin D deficiency in disease onset, progression and exacerbation in respiratory infections, asthma and COPD [4].

Several observational studies have shown associations between asthma and high intake of omega-6 Long chain polyunsaturated fatty acids (LCPUFAs), whereas omega-3 LCPUFA have been shown to be anti-inflammatory, as they decrease inflammatory cell production of pro-inflammatory prostaglandin E2, Leukotriene B4 and activity of nuclear factor-kappaB (NF- κ B). Maternal dietary intake of oily fish was found to be protective of asthma in children 5 years of age if born to mothers with asthma. A systematic review of omega-3 fatty acid supplementation studies in women during pregnancy found that the risk of asthma development in children was reduced (OR 0.349, 95% CI 0.15, 0.78) [5].

Asthma

Various dietary patterns have been linked to the risk of respiratory diseases. In asthma, dietary exposures (nutrients and diet), and the periods of introduction (antenatal or childhood) are relevant to disease pathogenesis. Several cohort studies have suggested a link between reduced maternal consumption of some micronutrients and childhood asthma. In a systematic review, it was noted that higher maternal intake of vitamin D, vitamin E, and zinc was associated with lower odds of wheeze during childhood [6]. In relation to dietary patterns, the Mediterranean diet (high intake of minimally processed plant foods and low intake of dairy food, fish, poultry and minimal intake of red

meat) has been found to have a protective effect for allergic respiratory disease in several epidemiological studies [7]. On the contrary, the "Western" dietary pattern (characterized by high consumption of refined grains, cured and red meats, desserts and sweets, french fries, and high-fat dairy products) has been associated to obesity and increased risk of asthma in children.

Observational studies on vitamin D in children with asthma have shown a strong relationship between low levels of vitamin D and lower lung function, increased corticosteroid use, and asthma exacerbations [8].

Over-nutrition and resulting obesity are clearly linked with respiratory disease, particularly asthma [9]. Obese children with asthma have a decreased lung function, reduced response to inhaled corticosteroids, lower quality of life and higher morbidity. Recently, Forno et al. reported that obesity is associated with airway dysanapsis, which is associated with severe disease exacerbations in obese children with asthma [10]. In the obese state, several causal mechanistic pathways have been reported: anatomical changes of airway, circulating free fatty acids which activate immune responses leading to increased inflammation, production of adipokines, higher concentrations of circulating leptin, epigenetics and also microbiome.

Chronic Lung Disease of Prematurity (CLDP) or Bronchopulmonary Dysplasia

Inadequate growth, weight gain and malnutrition are well-recognized complications of BPD. Given the fact that nutrition plays an important role in lung development and maturation, specific nutritional deficiency in combination with other risk factors may aggravate pulmonary injury involved in BPD. Some of these factors for BPD development include oxygen toxicity, immaturity, mechanical ventilation, infection and inadequate nutritional support. Infants with BPD have low energy intake and increased energy utilization when compared to term infants [11]. This results in a negative energy balance which leads to malnutrition. Following discharge, some infants with BPD are at high risk for persistent growth failure. Possible explanations include increased energy expenditure, poor oral feeding skills and tolerance, concomitant dysfunction of other organs, and recurrent infections and hospitalizations. Therefore, an adequate nutritional intervention is essential to match the increased energy requirements in infants at risk of and with BPD.

Although there is no consensus regarding the optimal nutritional management for BPD, many have suggested specific nutrient supplementation (e.g. glutamine, Selenium, LCPUFAs, cysteine, l-arginine, l-citrulline, inositol, vitamins A, E and C, and others) to prevent or treat BPD. Theoretically, some of these nutrients may curb hyperoxia-induced injury or improve alveolar development. However, evidence for supplementation is still controversial for most of these and their effects on BPD need to be further studied [12]. Current evidence shows that supplementation of vitamin A and omega-3 LCPUFA are effective in preventing BPD.

Cystic Fibrosis (CF)

There is an intimate close relationship between nutritional status and CF prognosis. Early nutritional interventions and monitoring for

respiratory disease in infants and preschoolers with CF is priority to improve long-term outcomes. Poor nutrition leads to poor lung function and increased number of infections. But poor lung function also causes increased energy utilization and growth failure, which ends with unsatisfactory outcomes. Most CF patients are pancreatic insufficient and approximately one third of patients are below the 5th percentile of weight for age. Several studies have shown that malnutrition in early life is related to impaired lung function during childhood [13]. Micronutrient deficiencies also occur in CF patients because of their pancreatic insufficiency and secondary malabsorption. Vitamin A and E deficiency, as well as zinc and magnesium, may be present when either intake or nutrient absorption is inadequate. These deficiencies may also increase susceptibility to respiratory infections and malnutrition.

Normal growth in patients with CF is associated with improved pulmonary function and survival. Yen, et al. [14] showed that better nutritional status at age 4 years in children with cystic fibrosis was associated with better lung function, fewer complications and greater survival. Oral supplements have been used with conflicting evidence, therefore, they should be considered with other nutritional and behavioral approaches. Gastrostomy tube feeding has been shown to improve weight and (in some studies) pulmonary function. Also, poor adherence to pancreatic enzymes has been related to difficulties in correcting malabsorption, hence, worst nutrition and outcomes.

Conclusion

Nutrition plays an important role in the development and management of chronic lung diseases in childhood. Many epidemiological studies have shown that malnutrition as well as obesity may have deleterious consequences in terms of lung function and probably survival. A timely nutritional intervention, beyond the general principle of a "balanced diet", is always recommended as part of a more comprehensive approach to children with chronic lung disease.

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#2. The Preterm Epidemic in LMICs and Its Impact on Respiratory Morbidity

Renato T. Stein

School of Medicine at Pontificia Universidade Católica RGS Porto Alegre, Brazil
Email rstein@pucrs.br; rstein@pucrs.br

Preterm birth (PTB) has a significant impact in public health globally, and is associated with increased morbidity and mortality, affecting a series of socio-economic variables. The frequency of PTBs ranges from 5 to 18%. Recent reports associate PTB to 965,000 deaths in the neonatal period, and an additional 125,000 deaths in children aged one to five years, representing the leading cause of both neonatal and childhood mortality. (1) The impact of PTB affects surviving premature infants, with increased risk of cerebral palsy, impaired learning and visual disorders, and chronic/recurrent respiratory diseases that start in the early years, with specific subgroups being affected for life. (2) The great majority of PTBs occur in poor regions of the world with over 60% in sub-Saharan Africa and South Asia.

Currently, 80% of infants born with weights between 500 and 750 g will survive and close to 75% of those born from 26 to 27 weeks of gestational age at tertiary centers will survive to 5 years of age. (3) These cohorts' main feature is now chronic lung disease, meaning that more babies survive the neonatal period, but present later morbidity and mortality, due to sequelae of prematurity such as Bronchopulmonary Dysplasia (BPD). Another series of preterm infants born less than 32 weeks of gestational age showed that 25% were hospitalized in the first two years of life (4).

A series of intervening variables are at play that affect the immature pulmonary systems of preterm newborn babies, influencing the normal development of the respiratory tract, and consequently both the process of alveolar growth, and formation of an adequate pulmonary microvasculature. The risk for respiratory morbidity is inversely associated with birth weight (which is dependent of gestational age at birth).

A long list of pulmonary findings in children born preterm include increased incidence of pneumonia and bronchiolitis (5) frequent re-hospitalizations for respiratory diseases (6), chronic and recurrent coughing and wheezing, bronchial hyperreactivity (7) and pulmonary function abnormalities (8).

These changes are not only present in the first months or years of life. Children born with less than 32 weeks of gestation have a significant burden of respiratory disease at mid-childhood with structural abnormalities. Lung function is lower in children born preterm, and this is associated with increased structural lung damage (9).

In a recent meta-analysis over 1.5 million children worldwide were analyzed for the chance of wheezing in the first years of life and preterm birth was found to be an independent associated variable with a 1.7-fold higher risk (10). In the subgroup of very low birth weight (VLBW) this risk was three times greater. RSV lower respiratory tract illness (LRTI) was the most significant infectious agent associated with this respiratory morbidity. The possibility of early life interventions that may attenuate the severity of these severe cases may be through the recent advent of monoclonal antibodies specific for RSV. A recent double-blind placebo-controlled trial has shown that treatment with Palivizumab has shown a 61% reduction in total wheezing days in the first year of life for healthy preterm infants (born at 33-35 WG). This approach serves a fascinating proof of concept that the blocking the severe events caused by RSV very early in life can have lasting protection, at least in the first year of life (when recurrent wheezing is common in most settings) for babies born prematurely.

Also interesting is the perspective that new vaccines and monoclonal antibodies already being tested in the pipeline targeted at RSV, which may completely change the current scenery which, as of today, is very conservative, since we do not have effective therapeutic options to change the course of both acute and recurrent wheeze in this population.

Populations in LMICs should benefit greatly from these new approaches since the burden of disease in these communities seems to be even greater than that observed in more affluent societies.

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#3. Advances in the Diagnosis of Pulmonary Tuberculosis (PTB) in Children

Heather J Zar

Department of Paediatrics and Child Health, Red Cross War Memorial Childrens Hospital, and MRC Unit on Child & Adolescent Health, University of Cape Town, South Africa

Correspondence Prof Heather J. Zar Dept of Paediatrics and Child Health 5th Floor, ICH Building Red Cross War Memorial Children's Hospital Cape Town, South Africa

Tel: 2721-658-5324

Fax: 2721-689-1287

Email: heather.zar@uct.ac.za

Pulmonary tuberculosis (PTB) is the commonest form of childhood TB globally. Timely and accurate diagnosis is essential to promote effective treatment including therapy for drug resistant TB, delineate the burden of childhood TB, and prevent complications from dissemination or progressive disease. Clinical scoring systems, radiological findings and tuberculin skin testing, usual methods for diagnosis, have been hampered by poor interobserver agreement, and low sensitivity and specificity especially in the context of HIV infection.¹ As a result, under-diagnosis as well as potential over-diagnosis of PTB remains challenging in children living in high TB burden countries.

However, several diagnostic advances have occurred in the last 5 years. Improved microbiological confirmation has been supported by strategies to promote better specimen collection, including induced sputum, the realization that repeated specimens are needed in children

and better, rapid molecular diagnostic tests, particularly Gene Xpert (Xpert MTB/RIF) that enables rapid diagnosis and simultaneous detection of resistance to rifampicin. A single induced sputum (IS) provided a similar culture yield to 3 gastric lavages, while a sequential second IS specimen increased the yield from culture by approximately 15%.² In primary care settings, sputum induction was also effective, increasing the diagnostic yield for PTB by 20%.³

A meta-analysis reported a pooled sensitivity and specificity for Xpert MTB/RIF on a single IS of 62% and 98% respectively, compared to culture in children with PTB.⁴ The performance of Xpert on gastric lavage was similar. Xpert testing of repeated IS specimens provided a higher yield with 2 specimens detecting approximately 75% of children with culture confirmed disease, almost 3 fold that of smear.⁵ A Tanzanian study of older children, reported a similar sensitivity for Xpert on sputum specimens and an incremental increase with subsequent specimens. While most studies have focused on hospitalized children, Xpert on respiratory secretions was reported to be useful for diagnosis in children with suspected PTB presenting with mild disease at primary care health facilities, although the microbiological yield (both by culture and Xpert) was much lower than that obtained in hospitalized children.⁶ The World Health Organization has recommended that Xpert replace smear as the first line investigation in children living in areas of high HIV prevalence or where drug resistant TB is a concern.

Xpert is an attractive test to perform on specimens that are less invasive to collect. A South African study reported that Xpert on 2 sequential NPAs was useful for microbiological confirmation in hospitalized children, providing similar sensitivity to repeated Xpert testing of IS.⁷ However, NPAs provided a lower yield than IS specimens for culture. Xpert on stool specimens may offer a promising strategy, particularly in HIV-infected children, but further studies are needed.⁸

Xpert MTB/Rif Ultra (Ultra) can detect disease with fewer bacilli than Xpert and so may offer an improved rapid diagnostic, as childhood PTB is paucibacillary. Studies in children are underway.

Other diagnostic tests include urine lipoarabinomannan (LAM), host genome expression profiles and improved immunological assays. LAM has low sensitivity and specificity in children including HIV-infected children, making it unsuitable for diagnosis.⁹ A host genome signature associated with TB in children has been identified¹⁰, but further work to develop this as an available diagnostic test is needed. Serological testing has not been successful. Gamma interferon testing does not provide major advantages over tuberculin skin testing and does not distinguish infection from disease. The T cell activation marker (TAM-TB) test is a novel immunodiagnostic test that can distinguish active disease from infection, relying on predominance of an effector memory cell phenotype. In a study in Tanzania, TAM-TB assay showed good diagnostic performance in children, but further studies are needed.

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Non-invasive Ventilation

#1. Long-Term Noninvasive Ventilation in Pediatrics: Clinical Indications and Experience

Brigitte Fauroux

Pediatric Noninvasive Ventilation and Sleep Unit, Hôpital Necker Enfants-Malades, Paris, Paris Descartes Faculty, Paris, France Research unit Inserm U 955, team 13, Créteil, France

Correspondence: Pr Brigitte Fauroux Pediatric Noninvasive Ventilation and Sleep Unit, Hôpital Necker Enfants-Malades 149 rue de Sèvres Paris, France

Tel 33 1 71 19 60 92

Fax 33 1 44 49 35 15

Email: brigitte.fauroux@aphp.fr

Introduction

Long-term noninvasive ventilation (NIV) involves the delivery of ventilatory assistance through a noninvasive interface, as opposed to invasive ventilation via a tracheostomy. The number of children

treated at home with this type of respiratory support is expanding exponentially around the world (1, (2, (3). Increasing pediatric conditions may benefit from long term NIV. However the indications and benefits have not been validated and rely mainly on recommendations and clinical experience.

Diseases that May Benefit From Noninvasive Ventilator Support

NIV comprises: 1) continuous positive airway pressure (CPAP) which utilizes the delivery of a constant positive pressure in the airways aiming to maintain airway patency throughout the entire breathing cycle and, 2) biphasic positive airway pressure (BiPAP) which aims is to assist the breathing of the patient by delivering a supplemental higher positive pressure during each inspiration.

NIV is indicated for disorders that cause disequilibrium in the respiratory balance, which comprises the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive. In healthy subjects, the respiratory load, i.e. the effort the subject has to perform to generate a breath, is low, the capacity of the respiratory muscles is normal, and the central drive appropriately commands the respiratory muscles. In disorders characterized by an increase in respiratory load, or by a weakness of the respiratory muscles, the central drive increases its demands of the respiratory muscles. However, when this imbalance exceeds a certain threshold, hypoventilation, defined by hypercapnia and hypoxemia, occurs. Severe upper airway obstruction, airway malacia, cystic fibrosis, bronchopulmonary dysplasia or bronchiolitis obliterans, may be responsible for an excessive respiratory load (4, (5, (6, (7, (8, (9, (10). Neuromuscular diseases that involve the motor neuron, the peripheral nerve, the neuromuscular junction, or the muscle may cause excessive respiratory muscle weakness. Disorders of the central drive are rare and may be congenital, such as the Ondine's curse (or congenital central hypoventilation syndrome) or acquired due to compression of or injury to the brainstem. Other disorders involving an impairment of two or more of these components, such as achondroplasia and mucopolysaccharidoses, may cause upper airway obstruction and brain stem compression.

The choice of the type of NIV depends of the pathophysiology of the respiratory failure. CPAP is the simplest type of noninvasive respiratory support, which is indicated in case of "isolated" obstruction of the upper or lower airways. BiPAP is indicated when the two other components of the respiratory balance are impaired, i.e. the central drive and/or the respiratory muscles. In lung diseases associated with an increase in respiratory load, the aim of NIV is to "unload" the respiratory muscles (5, (6, (11, (12). As these patients have a normal central nervous system and a preserved respiratory muscle capacity, a ventilatory assistance that preserves the patient's own breathing pattern by allowing the patient to "trigger" assisted breaths, will be the most appropriate and comfortable (5, (6). Conversely, in patients with weak respiratory muscles, the role of BiPAP will be to "replace" the respiratory muscles by delivering a positive pressure during inspiration. A "controlled" mode with a back-up rate (i.e. a minimal number of breaths delivered per minute by the ventilator) close to the normal respiratory rate during sleep for age, is thus recommended. CPAP is thus clearly NOT the treatment of sleep-disordered

breathing in patients with neuromuscular disease. Finally, in the case of an abnormal central drive, the ventilator should be able to "take over" the command of the respiratory muscles by means of a controlled mode.

Indications and Benefits of NIV

There are no validated criteria to start long term NIV in children. In clinical practice, NIV may be initiated in an acute setting, after NIV weaning failure in the pediatric intensive care unit (PICU), on abnormal nocturnal gas exchange alone or associated with a high apnea-hypopnea index (AHI) on a polysomnography (13). The main challenges or difficulties for NIV initiation in children are 1) the timing and type of investigation, such as a polysomnography, a polygraphy, or an overnight gas exchange recording, that should be performed for NIV initiation and, 2) the values or thresholds of the parameters that are retained for NIV initiation, such as the oxygen and/or carbon dioxide level, and/or AHI, with the assumption that their correction will be associated with a benefit of NIV (13). These difficulties are due to the lack of markers of end-organ morbidity associated with sleep-disordered breathing and chronic respiratory failure in children. Neurocognitive dysfunction and behavioral disturbances are the most common and severe consequences of obstructive sleep apnea (OSA) in children but these deleterious effects are highly variable from one child to another (14).

A sleep study is part of the routine evaluation of a child with OSAS. Polysomnography represents the gold standard but polygraphy or continuous monitoring of nocturnal gas exchange may be used as an alternative if full polysomnography is not available (15). Usual indications for CPAP are residual OSAS after adenotonsillectomy (defined by an AHI>5 events/h) and OSAS related to obesity or craniofacial abnormalities (15). In practice, CPAP is prescribed in children with complex OSAS due to anatomical or structural abnormalities of the upper airways such as craniofacial malformations, Down syndrome, Prader Willi syndrome or morbid obesity (16, (17, (18). BiPAP is indicated if nocturnal hypoventilation persists despite optimal CPAP (15). CPAP is associated with an improvement in sleep parameters such as the AHI and gas exchange, attention deficits, behavior, sleepiness and quality of life (16).

There is less consensus regarding the type of investigation and criteria for BiPAP initiation in children with neuromuscular diseases. First, BiPAP may be justified without a sleep study when the child presents episodes of acute respiratory failure triggered by a respiratory infection or an anesthetic procedure, as these events are markers of an insufficient respiratory reserve (19). Concerning the timing of a sleep study, there is a lack of validated recommendations. This may be partially explained by the heterogeneity of neuromuscular disorders in children (20, (21). Symptoms suggestive of sleep-disordered breathing cannot be used as predictors or markers of nocturnal hypoventilation as they did not differ between neuromuscular children with or without documented nocturnal hypoventilation (22). Concerning the predictive value of lung function and other respiratory parameters, a large prospective study in children with neuromuscular disorders did not identify a sensitive and specific daytime lung function or respiratory muscle test that was associated with, or predictive of, nocturnal

hypoxemia or hypercapnia (23). The type of neuromuscular disorder should thus be taken into account as nocturnal hypoventilation occurs preferentially in disorders characterized by a prominent diaphragmatic weakness. Children with a COL6 myopathy should thus be screened systematically for sleep disordered breathing (24). Prioritized screening is also recommended for infants or young children with congenital myopathies or rapidly progressive neuromuscular diseases (25). In children with neuromuscular disease, the documentation of nocturnal hypoventilation by means of a polysomnography is recommended but not essential prior to starting BiPAP because "isolated" abnormal nocturnal gas exchange may be sufficient (26). Indeed, 9 out of 10 patients with neuromuscular disease or thoracic deformity and isolated nocturnal hypercapnia without daytime hypercapnia progressed to overt daytime respiratory failure within a period of 2 years (26). Moreover, in the presence of an abnormal overnight gas exchange recording or full polysomnography, the criteria that are used to define "nocturnal hypoventilation" are highly variable which has practical consequences, as long term NIV indication relies upon hypoventilation detection (27). The scoring of polysomnography in patients with neuromuscular disease requires a specific expertise. Indeed, instead of apneic and hypopneic events, these patients may present a progressive simultaneous decrease in airflow and thoracic and abdominal movements accompanied or not by a change in gas exchange, suggestive of global inspiratory muscle weakness (28). Paradoxical breathing with opposition phase on the thoracic and abdominal belts may be the consequence of diaphragmatic dysfunction or weakness of the intercostal muscles and should not be falsely interpreted as "obstructive events" (28, (29, (30).

In clinical practice, periods of "reduced ventilation" or paradoxical breathing, more than obstructive and/or central apnea-hypopneas, especially during rapid-eye movement sleep, associated with a pulse oximetry (SpO_2) < 90% and/or a transcutaneous carbon dioxide (PtcCO_2) value > 50 mmHg, are indicative of an insufficient respiratory muscle performance and justify long term BiPAP in children with neuromuscular disease. In clinical practice, however, many children with a progressive neuromuscular disease such as spinal muscular atrophy or Duchenne muscular dystrophy are started on NIV empirically. Indeed, the limited access to sleep studies should not delay the access of these patients to an effective treatment, the most important requisite being that patients should be followed by a pediatric team having an expertise in NIV.

There is no consensus regarding the clinical situations or criteria that justify the initiation of BiPAP in children with cystic fibrosis. Like adult patients with chronic obstructive pulmonary disease, BiPAP is recommended as a first line treatment for an acute hypercapnic respiratory exacerbation, without any evidence from prospective randomized studies (31, (32, (33). BiPAP is also largely prescribed for patients on the lung transplant list and those with an insufficient improvement with oxygen therapy (34). This contrasts with a recent Cochrane review that concluded that the improvement of nocturnal gas exchange and less oxygen desaturation and respiratory muscle fatigue during chest physiotherapy were the only proven benefits of BiPAP in cystic fibrosis (35).

In conclusion, screening with at least an overnight gas exchange recording to detect nocturnal hypoxemia and/or hypercapnia, and if possible with a more complete sleep study, should be a priority in all children with upper airway obstruction, and any type of neuromuscular or lung disease that may be associated with nocturnal hypoventilation. Symptoms of sleep-disordered breathing are insufficiently sensitive and specific and tend to appear late in the course of the different diseases. As poor sleep quality is associated with neurocognitive dysfunction, abnormal behavior and decreased quality of life, a trial of one to three months of NIV with a thorough evaluation before and after the NIV period, seems a reasonable option.

Conclusion

Long term NIV is an extremely efficacious respiratory support which has transformed the scope of chronic respiratory failure and severe sleep-disordered breathing in children by avoiding tracheotomies and allowing the child to live at home with a good quality of life for the child and his family. The tremendous heterogeneity of the disorders, ages, prognosis and outcomes of the patients underlines the necessity of management by experienced, multidisciplinary centers, having technical competencies in pediatric NIV, and an expertise in sleep studies and therapeutic education.

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#2. Controversies and Update on Non Invasive Ventilation in the NICU

Amir Kugelman

Department of Neonatology Rambam Medical Center Ruth Children's Hospital
The B&R Rappaport Faculty of Medicine, Technion Haifa, Israel
Email: amirkug@gmail.com

There is no debate that non invasive ventilation (NIV) is the preferred mode in modern Neonatology for the treatment of respiratory distress syndrome (RDS).^{1, 2} Yet, there is a controversy as to which mode of NIV to use in different conditions. NIV has a role in the initial treatment of RDS with the aim to decrease the rate of endotracheal ventilation and the incidence of chronic lung disease (CLD).^{1, 2} NIV is also used post extubation in order to decrease the need for reintubation during the resolution of RDS and to treat apnea of prematurity.^{1, 2} The available options of NIV include nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV) and high flow heated humidified nasal cannula (HFNC).

NCPAP is the most common modality of NIV. Large randomized controlled trials (RCT) concluded that early NCPAP is a safe alternative to immediate intubation even in extremely low birth weight (ELBW) infants.^{3, 4} For the initial treatment of RDS, most centers use NCPAP, some of them escalate to NIPPV before intubation and some use NIPPV as an initial mode of non invasive support. A recent meta-analysis⁵ including ten trials, enrolling a total of 1061 infants, showed significantly reduced risk of meeting respiratory failure criteria (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.51 to 0.82) and needing intubation (typical RR 0.78, 95% CI 0.64 to 0.94) among infants treated with early NIPPV compared with early NCPAP. The meta-analysis did not demonstrate a reduction in the risk of CLD among infants randomized to NIPPV (typical RR 0.78, 95% CI 0.58 to 1.06). There was no evidence of harm. The authors concluded that early NIPPV does appear to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation and endotracheal tube ventilation among preterm infants with RDS.

Synchronized NIPPV vs. NCPAP for later use, post extubation at RDS resolution, as a "bridge" to spontaneous unsupported breathing was shown to be more effective than NCPAP. An updated meta-analysis⁶ showed that NIPPV reduces the incidence of extubation failure and the need for re-intubation within 48 hours to one week more effectively than NCPAP; however, it has no effect on CLD or on mortality. Synchronization may be important in delivering effective NIPPV. The device used to deliver NIPPV may be important; however, data are insufficient to support strong conclusions. Synchronized NIPPV may be more effective than NCPAP also for apnea of prematurity.² A meta-analysis, regarding apnea of prematurity, suggests that synchronized NIPPV is more efficacious with apnea that is frequent or severe. However, the studies performed addressed

short-term outcomes and as such could not address properly the rate of reintubation. Thus, more studies are needed before recommending synchronized NIPPV as standard of care for apnea of prematurity.

It is possible that the additive effect of NIPPV compared to NCPAP is related to synchronization. This is debatable, as one study in stable premature infants did not find benefits in synchronization. Yet, the infants were stable and exposed to the studied mode for a short time. Neutrally adjusted ventilation assist (NAVA) might answer this question. NAVA is a new mode of synchronized NIPPV, which utilizes changes in the electrical activity of the diaphragm (Edi) to trigger the ventilator. There are currently no large RCT that compare NIV-NAVA to non synchronized NIPPV.

Recently, HFNC is frequently used as a mode of NIV. High flows result in washout of anatomical and physiological dead space and contribute to improved fractions of alveolar gases with respect to carbon dioxide as well as oxygen and decrease the work of breathing and the energy cost of gas conditioning. HFNC probably creates positive end expiratory pressure (PEEP) that may contribute to its beneficial effect. This PEEP usually is lower than the PEEP administered via NCPAP or NIPPV. The PEEP is not monitored during HFNC; this raised concerns regarding the safety of HFNC in terms of air leak. A Cochrane review⁷ concluded that HFNC has similar rates of efficacy to other forms of non-invasive respiratory support in preterm infants for preventing treatment failure, death and chronic lung disease. Most evidence is available for the use of HFNC as post-extubation support. Following extubation, HFNC is associated with less nasal trauma, and may be associated with reduced pneumothorax compared with NCPAP. Yet, more studies, especially in the initial treatment of RDS and in ELBW infants, are needed before adopting HFNC as an alternative mode of NIV in these conditions. Following this Cochrane, in the international HIPSTER multicenter, randomized, noninferiority trial,⁸ 564 preterm infants (gestational age, ≥ 28 weeks 0 days) with early respiratory distress who had not received surfactant replacement were assigned to treatment with either HFNC or NCPAP. The primary outcome was treatment failure within 72 hours after randomization. Treatment failure occurred in 71 of 278 infants (25.5%) in the high-flow group and in 38 of 286 infants (13.3%) in the CPAP group (risk difference, 12.3 percentage points; 95% confidence interval [CI], 5.8 to 18.7; $P < 0.001$). The rate of intubation within 72 hours did not differ significantly between the high-flow and CPAP groups (15.5% and 11.5%, respectively; risk difference, 3.9 percentage points; 95% CI, -1.7 to 9.6; $P = 0.17$), nor did the rate of adverse events. They concluded that when used as primary support for preterm infants with RDS, high-flow therapy resulted in a significantly higher rate of treatment failure than did NCPAP. For post extubation, in very preterm infants, Manley et al.⁹ in a multicenter, randomized, noninferiority trial, assigned 303 very preterm infants to receive treatment with either HFNC or NCPAP. The primary outcome was treatment failure within 7 days. The use of HFNC was noninferior to the use of NCPAP, with treatment failure occurring in 52 of 152 infants (34.2%) in the HFNC group and in 39 of 151 infants (25.8%) in the NCPAP group. Almost half the infants in whom treatment with HFNC failed were successfully treated with NCPAP without reintubation.

While non-invasive ventilation is probably safe, its success depends on gestational age. The data indicate that surfactant may still have a significant role in the treatment of RDS, especially in ELBW infants. Recent studies reported on an intubation rate of ~50% in their NCPAP group in ELBW infants.^{1, 2, 3, 4} This leads us to non or less invasive modes of surfactant administration that may allow the infant to benefit from both, surfactant and NIV. These included the intubation, surfactant, extubation (INSURE) approach, and the minimal invasive surfactant therapy (MIST). Using the MIST, surfactant is applied to the trachea without endotracheal intubation by using a thin catheter in spontaneously breathing preterm infants receiving NCPAP. This technique was reported to reduce the need for mechanical ventilation.¹⁰ There are ongoing trials with inhaled surfactant. There is no consensus yet on which mode of non invasive surfactant administration is superior and when is the best time for the application of that mode when the infant is on NIV.

To summarize, NCPAP is still the most common mode of non invasive respiratory support world wide.¹ The available evidence supports the preference of early or later use of NIPPV/SNIPPV compared to NCPAP because of minimizing the use and the length of endotracheal ventilation.^{2, 5, 6} New modes of NIV such as NAVA and nasal high frequency ventilation, need to be further studied before concluding on benefits for the short and long term outcomes in premature infants. Less invasive modes of surfactant administration may enhance the impact of NIV, with the aim to reduce CLD.

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#3. Non-Invasive Ventilation in Pediatrics – Update 2017

Jean-Paul Praud

Pediatric Pulmonology Division University of Sherbrooke, QC – Canada
Email: Jean-Paul.Praud@USherbrooke.ca

Non-invasive respiratory support is increasingly used at all ages, from the most extreme preterm during his/her adaptation to extra-uterine life to the end-of-life elderly patient for dyspnea relief. Non-invasive respiratory support encompasses a number of modalities, such as high-flow nasal cannula, non-invasive continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV). This abstract will highlight a few recent publications focused on NIV used in pediatrics for acute as well as chronic respiratory failure.

Acute Non-Invasive Ventilation

Acute NIV in Neonates

A Cochrane meta-analysis (1) examined the risks and benefits of early NIV versus early nasal CPAP for preterm infants at risk of or in respiratory distress within the first hours after birth. Ten trials enrolling a total of 1061 infants met the criteria for inclusion in the analysis. The authors concluded that early NIV appears superior to nasal CPAP for decreasing respiratory failure and the need for intubation and endotracheal tube ventilation in preterm infants with respiratory distress syndrome. Larger trials are however needed to confirm these results and to assess the safety of NIV compared with nasal CPAP.

Another Cochrane meta-analysis by the same team (2) focused on the use of NIV delivered by nasal prongs or a nasopharyngeal tube after extubation in preterm newborns. Ten randomized and quasi-randomized trials enrolling a total of 1431 infants were included in the analysis. The authors concluded that the overall evidence indicates that NIV reduces the incidence of extubation failure and the need for re-intubation within the first week more effectively than nasal CPAP. In addition, the use of a synchronized form of NIV may be important although necessitates confirmation in larger trials. Similarly, the use of

a mechanical ventilator to deliver NIV appears more efficient than bilevel devices, although larger trials are again needed for confirmation. Finally, there was no difference between NIV and nasal CPAP for the rates of bronchopulmonary dysplasia, death or necrotizing enterocolitis.

Two publications from two different teams summarized data from animal model investigations and clinical observations on the use of nasal high frequency oscillatory ventilation (nHFOV) in neonates (3,4). Nasal HFOV has the advantages of both high-frequency ventilation (no need for synchronization, high efficacy in removing CO₂) and nasal CPAP (non-invasive interface, improved oxygenation via an increase in functional residual capacity). Data in preterm lambs suggest that nHFOV can decrease the incidence of bronchopulmonary dysplasia. In addition, reports of several case series have shown that nHFOV can be used in human neonates with apparent benefits compared to other NIV modalities. The authors underlined that while several surveys have reported that nHFOV is increasingly attempted in some neonatology centers, randomized controlled studies are rapidly needed to confirm if and when nHFOV is truly beneficial in human neonates.

Acute NIV in Children

Mortamet et al (5) assessed the available interfaces for delivering NIV in NIV-naïve children with acute respiratory failure. Given that NIV in the acute setting must be initiated rapidly and used around the clock for several days, the choice of the optimal interface is crucial and often makes the difference between NIV success or failure. The authors summarized the advantages and limitations of the various interfaces available for children, including the approach in choosing the optimal interface and to monitor its tolerance.

A Cochrane meta-analysis examined the use of NIV for acute asthma in children (6). Two trials enrolling a total of 40 children only were eligible to be included in the analysis. BiPAP devices were compared to standard care (no use of nasal CPAP however) in the two studies. While the asthma symptom score was significantly decreased, the very low number of children and the high risk of bias in the studies did not allow confirmation or rejection of any beneficial effect of NIV in children with acute asthma.

Chronic Non-Invasive Ventilation

Clinical Updates on Long-Term Home Ventilation

Home NIV has been the focus of two excellent comprehensive updates (7,8). Long-term home NIV may be indicated when central respiratory drive anomalies, respiratory muscle/thoracic wall dysfunction, upper airway obstruction and/or primary bronchopulmonary disorders are markedly disabling on a long-term basis and not amenable to CPAP therapy. Both articles underline the contrast between the exponential use of NIV in children of all ages worldwide and the lack of validated criteria, especially for initiating, titrating and monitoring treatment. The challenges faced by long-term home NIV in infants and children are numerous, and success is dependent on a highly specialized multidisciplinary center. Among others, the choice of the interface between the patient and the mechanical ventilator is a crucial factor. In addition, the training of caregivers, as well as the

availability of dedicated home-care personnel on an as-needed basis to support caregivers, is essential.

Interfaces for Long-Term Non-invasive Ventilation in Children

As already alluded to above, choosing the interface between the ventilator and the patient is one of the most challenging aspects of NIV in pediatrics, especially in infants. A recent article has addressed the problem of the optimal interface using innovative technologies in 50 subjects with a mean age of 10.4 years (9). The technologies under study included 3-dimensional imaging to assess the fit between a particular mask and the patient's face, measurement of skin hydration under the interface and high definition color photography to visualize early skin compromise (present in 72% of the studied patients). While skin injury was shown to be reduced with the use of a silicone foam dressing interposed between the plastic mask and the skin, no sign of any injury was observed when a water vapor-permeable cloth mask was used. An accompanying editorial underlined the need for intensive research focused on the ideal NIV interface, which should i) be comfortable and adaptable to a wide range of facial shapes; ii) prevent overhydration of the skin; iii) prevent unintentional leaks, increased dead space and patient-ventilator asynchrony.

Non-Invasive Ventilation and Gastro-Esophageal Reflux: Lessons From Newborn Ovine Models

Esophageal insufflation of gas during NIV can lead to gastric dilation. The latter can in turn increase gastro-esophageal reflux via transient relaxation of the inferior esophageal sphincter. We have previously reported that nasal CPAP (6 cmH₂O) virtually abolishes gastro-esophageal refluxes in newborn lambs. We further reported in 2016 that acute NIV (15/4 cmH₂O), either under the form of pressure support or neurally-adjusted ventilatory assist, also inhibits gastro-esophageal refluxes (10). Of note, no gastric dilation was observed at the pressures used. Explaining mechanisms are currently being investigated.

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Cystic Fibrosis

#1. Cystic Fibrosis: When the Diagnosis Is Unclear

Jane C Davies

Imperial College London and Royal Brompton & Harefield NHS Trust London, UK
Email: j.c.davies@imperial.ac.uk

CF is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein, an anion channel situated on the apical surface of epithelial cells which controls the flux of chloride, bicarbonate and sodium thereby regulating airway surface hydration. Patients lacking normal CFTR function have impaired mucociliary clearance and are prone to early infection and inflammation in the airways. CFTR is also expressed in the sweat gland where it reabsorbs chloride from sweat; patients with CF thus have raised levels of sweat chloride. The early observation of this fact led to development of the gold-standard diagnostic sweat test. Diagnostic cut-offs are established >60 mmol for CF and <30 mmol for the healthy population, with an 'intermediate' area between 30 and 60 mmol/l¹. In 1989 the gene responsible for CF was first identified and the common mutation, F508del, described. This is present on at least one allele in 70-85% of CF patients worldwide, with around 40-50% of patients being homozygous. There are now >2,000 mutations described, many of which are extremely rare and have not yet been fully understood. The cftr2 project is aiding progress rapidly in assigning reported CFTR mutations to 'CF-causing', 'not CF-causing' or 'variable clinical consequence' categories (www.cftr2.org).

Clinical manifestations of CF include early onset failure to thrive and diarrhea due to pancreatic exocrine dysfunction, respiratory symptoms such as chronic moist cough and bacterial infections, upper airway complications including sinusitis and nasal polyps, liver disease and later complications of diabetes mellitus and arthropathy. ~10% of CF babies are born with gut obstruction due to inspissated meconium and the diagnosis may even be suspected prenatally with echogenic bowel.

The vast majority of cases of CF are easy to diagnose: a constellation of suggestive clinical phenotype, raised sweat chloride (>60 mmol/l) and

two recognized disease-causing mutations allow a diagnosis to be confirmed, treatment to be initiated and screening offered to close family members. Many parts of the world have newborn screening programs by which most cases are now diagnosed in early infancy. These are most commonly based on the finding of a raised immunoreactive trypsinogen (IRT) followed by CFTR genotyping or a repeat IRT, but a number of different algorithms exist.

However, both in later life and in the newborn period, diagnostic dilemmas arise, for which additional tests may be needed. Examples of cases provide a useful framework to illustrate the issues:

Case 1

A 33-year old man presented to primary care seeking fertility testing and was found to be azospermic. On further questioning, he was well throughout childhood, but suffered from a prolonged bout of 'bronchitis' whilst travelling on his gap year through Asia; he admitted to some unhealthy behaviors including smoking tobacco and marijuana during the trip. Since then, he has had a persistent 'smoker's cough' despite having given up. He reported producing small amounts of clear phlegm most days, which could be yellow-green when unwell, and had been prescribed ~10 courses of antibiotics over the last 4-5 years. He was well-nourished with a normal bowel habit and reported no significant abdominal pain.

CT scan revealed moderate bilateral upper lobe bronchiectasis and a diagnosis of late-presenting CF was sensibly considered. Repeated sweat tests revealed chlorides between 35 and 49 mmol/l and first line genetic testing showed him to be heterozygous for the F508del mutation. He underwent nasal potential difference testing, which revealed a normal basal PD, but an almost complete absence of chloride secretion upon stimulation with a combination of zero-chloride Ringers and the cAMP agonist, isoprenaline; this is the most sensitive test for CFTR function in the airway epithelium. Subsequently, he was found to possess an additional mutation D1152H on his other allele. This is a mutation of 'variable clinical significance' often found in association with CF-like disease in one or more organs but a normal or borderline sweat test. In this patient the constellation of signs and CFTR-related tests was considered to support a diagnosis of CF.

Case 2

A well 4-week old baby girl was referred following a positive newborn screen for CF. Following a raised IRT, genotyping confirmed F508del/R117H-7T. The latter mutation, when in cis with the 7T, leads to residual, but variable CFTR function and together with a disease-causing mutation may lead to CF, albeit usually of a milder phenotype, but may also be found in completely healthy individuals. The baby was well-grown and had normal stools; there were no parental concerns. Sweat chlorides were 12 and 15 mmol/l, well below the upper limit of the normal range, 30 mmol/l. Consensus in Europe is that such babies are termed 'CF SPID' (Screen positive, indeterminate diagnosis)² and not cystic fibrosis. Some will develop lung complications in later life, so a degree of follow up is advised. The consensus guidelines for this group of babies will be detailed during the presentation. The baby underwent repeat sweat testing over the first two years of life, which remained normal. No clinical concerns evolved.

CF is therefore not the all-or-nothing disease it was once considered. The more we learn about CFTR, the more we recognize how much remains unknown. Many CFTR mutations lead to variable consequences; there may be additional factors such as environment, behaviors, or other aspects of genetic make up, so-called modifier genes, which determine whether people remain healthy or display manifestations of the disease. Nasal potential difference testing and other assays of CFTR function such as short circuit current on rectal biopsy (or, more recently, culture of organoids from the latter)³ may prove useful diagnostic aids. In some cases, borderline diagnostic tests in the context of single organ disease such as nasal polyps, will be termed 'CFTR-related disorder'. As diagnostic understanding evolves, new terms such as CFSPID are required. There are cohorts of patients described with CF-like disease who actually have mutations in ENaC⁴, so further investigation should be considered in these cases.

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#2. Anti-Inflammatory Therapy in Cystic Fibrosis

Judith A. Voynow, Edwin L. Kendig Jr.

Professor of Pediatric Pulmonary Medicine, Children's Hospital of Richmond at VCU, Richmond, VA, USA
Email judith.voynow@vcuhealth.org

Cystic fibrosis (CF) lung disease is marked by recurrent exacerbations of bronchitis with opportunistic organisms and neutrophil dominant inflammation. The relentless cycle of infection and inflammation results in airway injury and bronchiectasis leading ultimately to respiratory failure, the most common cause of death. A seminal feature of CF lung disease is excessive, unopposed neutrophil mediators, which degrade innate immune function and promote mucus obstruction of airways. Both airway epithelial cells and immune cells play critical roles in the initiation and progression of CF lung disease. The primary cause of CF lung disease is loss of function of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). However, there has been a long-standing debate concerning whether loss of CFTR causes an inherent hyper-inflammatory state, or whether loss of CFTR promotes persistent lung infection with local innate immune failure and a secondary hyperinflammatory state.

New insights from Cftr-deficient pigs and ferrets, which recapitulate pathologic features of human CF lung disease, reveal that there is no airway inflammation in newborn animals in the absence of infection. However, there is a growing body of evidence that CFTR deficiency impairs critical innate immune functions that enable lung infection. CFTR directly affects airway innate immunity via its function as a regulator of anion channels. CFTR regulates not only chloride efflux, but also bicarbonate and thiocyanate efflux. CFTR deficiency results in loss of bicarbonate and a more acidic airway surface milieu. This change in acid-base status inhibits antimicrobial peptides including beta-defensin and cathelicidin, hinders normal phagocytic cell clearance of bacteria, and affects mucin biochemical and biophysical properties resulting in failure of normal mucociliary clearance of microbes. Thiocyanate is critical for epithelial generation of hypothiocyanate, an important anti-microbial factor. Loss of both CFTR and apical purinergic-regulated chloride channels results in unopposed epithelial sodium channel activity and airway surface dehydration. The loss of airway surface liquid homeostasis increases mucus viscosity and prevents mucociliary clearance of microbes.

In addition to causing aberrant ion and water homeostasis, loss of CFTR is associated with depletion of protective factors in the airway epithelium including i) IL-10, an anti-inflammatory cytokine, ii) iNOS, a required factor to upregulate interferon, an anti-viral factor, and iii) glutathione, a major antioxidant. Furthermore, loss of CFTR also affects the balance of pro- and anti-inflammatory lipids resulting in a pro-inflammatory state in the airways. Patients with CF have increased arachidonic acid and decreased docosahexanoic acid compared to healthy control subjects. Arachidonic acid is the precursor for inflammatory lipids such as leukotrienes, thromboxanes and prostaglandins, while docosahexanoic acid is the precursor for anti-inflammatory lipids such as lipoxinA4, resolvins, and protectins which blunt neutrophil infiltration. The sphingolipids in the lung are also altered in CF. There is conflicting information concerning the impact of loss of CFTR on ceramide levels in macrophages and in epithelial cells. Either excess or deficient ceramide levels are observed in different Cftr-deficient mice. Importantly, if the homeostasis of ceramide is disturbed in either direction, mice are susceptible to increased inflammation. Furthermore, other sphingolipids such as sphingosine play important roles in response to microbes in the lung. Ceramide affects cell membrane lipid raft composition, receptor clustering and cell signaling. Ceramide also increases epithelial cell permeability and induces apoptosis. In patients with CF, long chain ceramides are increased and sphingosine is decreased in respiratory epithelial cells. Either inhibition of ceramide accumulation or augmentation of sphingosine with the FTY720 sphingosine-1P analog rescued Cftr-deficient mice from *P. aeruginosa* pneumonia.

CF immune cells also have dysregulated pro-inflammatory responses. There is a shift to Th17 differentiation by CF T cells. CF alveolar macrophages fail to clear infections yet have exaggerated inflammatory responses to stimuli. CF neutrophils have an overexuberant response to infections and release reactive oxygen species that damage proteins, lipids, and DNA, and release neutrophil elastase via neutrophil extracellular traps or necrosis.

Neutrophil elastase (NE) activates a cascade of events in the airway that further promote infection and impair bacterial phagocytosis and killing. NE upregulates mucin expression and secretion and injures cilia all of which cause a failure of mucociliary clearance. NE cleaves opsonins and receptors on macrophages to prevent bacterial clearance and efferocytosis of apoptotic neutrophils. NE upregulates neutrophil chemokines such as C5a and IL-8 to further aggravate neutrophilic inflammation. NE cleaves tissue inhibitors of matrix metalloproteases and increases release and activation of other proteases such as MMP-9 which is inversely related to FEV1. NE also induces release of High Mobility Group Box 1 (HMGB1), a cytokine and alarmin, that activates the RAGE receptor and TLR-2, -4, and -9, and significantly inhibits macrophage phagocytosis and bacterial killing in a *Pseudomonas pneumonia* mouse model. Furthermore, other alarmins, S100A8, S100A9, and S100A12, the calgranulins, released from neutrophils activate TLR4 or RAGE and are pro-inflammatory signals via NF- κ B activation. NE degrades iron containing proteins such as lactoferrin in the airway, releasing non-heme iron that is required for bacterial growth and biofilm formation and also is taken up by epithelial cells and generates oxidative stress.

With the large number of inflammatory targets that lead to sustained infection and inflammation, it has been an enormous challenge to develop anti-inflammatory therapies for patients with CF. There is great hope that drugs that correct and/or potentiate normal CFTR function will abrogate the cycles of infection and inflammation that start early in life. However, although ivacaftor therapy for patients with the G551D mutation significantly improved lung function, weight gain, and sweat chloride levels, it did not decrease airway inflammatory mediators. This result may be due to initiation of therapy after bronchiectasis is established in patients. Once Ivacaftor is approved for infants, then the concept can be tested that correction of CFTR will prevent infection and inflammation.

Importantly, an early prospective, randomized and double blind study using oral glucocorticoids every other day for a year in patients with CF, provided proof of principle that anti-inflammatory therapy can improve lung function for CF patients. However, the side effects of chronic glucocorticoid therapy prevent their use routinely as an anti-inflammatory agent. The only approved anti-inflammatory therapies for CF currently are high dose Ibuprofen and Azithromycin. Although Ibuprofen slowed lung function decline in a randomized controlled prospective trial over 4 years, particularly in patients with chronic *P. aeruginosa* infection, it has not been widely accepted due to difficulties in obtaining levels to monitor therapy and potential side effects. Thrice weekly azithromycin therapy for chronic *P. aeruginosa* has been more widely accepted and therapy reveals a modest improvement in FEV1, decreased risk for pulmonary exacerbations, and decreased serum inflammatory markers. Chronic azithromycin therapy for patients with CF but not infected with *P. aeruginosa* also decreased the frequency of pulmonary exacerbations and cough but did not improve FEV1.

Since approval of ibuprofen and azithromycin, there have been several trials of anti-inflammatory therapies for patients with CF that target specific inflammatory mediators: proteases, reactive oxygen species, neutrophil chemoattractants, abnormal intracellular signals,

and abnormal lipids. To date, none of these drugs has moved forward to Phase 3 trials. In addition to targeted therapies, global anti-inflammatory medications approved for use in other inflammatory diseases are being tested for efficacy in patients with CF through the CFF Therapeutic Development Network. To shepherd these drugs through testing to confirm safety and efficacy, there are several challenges to be met. First, it is important to characterize the inflammatory biomarkers to be followed in trials. Although airway biomarkers detected through sputum or bronchoalveolar lavage are the most direct measures of airway inflammation, healthy young subjects do not expectorate and would require sputum induction, and BAL is invasive and not easily accessible for research purposes in children. Therefore identification of circulating inflammatory biomarkers would facilitate determination of anti-inflammatory efficacy in vivo. Second, confirmation of safety is critical early in the process since anti-inflammatory medications may have unpredicted side effects and increase susceptibility to infection. Third, it is important to select the correct population that is likely to respond to therapy- a personalized medicine approach to anti-inflammatory therapy. Just as different classes of CFTR mutations are responsive to specific CFTR corrector/potentiator therapies, it is possible that a patient's "inflammatory profile" will be used by clinicians to determine the best choice(s) for anti-inflammatory medication(s). Overcoming these challenges will forge a path to effective and safe anti-inflammatory therapies that break the vicious cycle of infection and inflammation and prevent CF lung disease progression.

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#3. Treating Resistant Bacteria *S. aureus*, *P. aeruginosa*, and Others

Matthias Griesse

Hauner Children's Hospital University of Munich Lindwurmstr. 4 80337 München
Tel ++49 89 44005 7871 Fax ++49 89 44005 7872
Email: matthias.griesse@med.uni-muenchen.de

The course of the most frequent life-threatening autosomal recessive disorder in Caucasians, Cystic fibrosis (CF), is strongly influenced by the presence of respiratory pathogens. During the last decades the care for CF patients has become more and more challenging due to both the selection of multi-resistant bacteria, as well as novel techniques identifying the pathogens present in the lungs.

Regarding Methicillin-Resistant *Staphylococcus aureus* (MRSA), we have established and assessed the long-term success of an eradication scheme introduced in 2002 for all newly colonized patients in our center. After intensive therapy, i.e. iv and oral combinations, MRSA was eradicated in 84% of the patients; those subjects had stable clinical course (mean FEV1 one year before MRSA 80.4%, 3 years after MRSA 81.0%).

Pseudomonas aeruginosa (*P ae*) was detected in the study by Burns et al. which combined bronchoalveolar lavage and serological results at high rates even in children younger than three years of age, indicating that *P. aeruginosa* infection occurs very early and may be intermittent or undetectable by culture. Secondary prevention, i.e. interventions after diagnosis of an airway colonization, is now established as a usual approach. Of interest, in the various studies, the success rate depends primarily on the definition of eradication and time points at least 1 or better 2 years after first detection should be used, to get reliable results. We also include the measurement of serum anti-*P ae* antibodies. A chronic *P ae* infection necessitates regular suppression therapy with antimicrobials in order to prevent deterioration of lung function.

Qvist T et al. identified, in 2016, infections with a significant impact on rate of decline in %FEV1 other than *Pseudomonas aeruginosa* which alone had a negative impact of -0.95% (95% CI -1.24 to -0.66). *Mycobacterium abscessus* complex led to a loss of -2.22% points per year (95% CI -3.21 to -1.23), *Burkholderia cepacia* complex to -1.95% (95% CI -2.51 to -1.39), and *Achromobacter xylosoxidans* to -1.55% (95% CI -2.21 to -0.90). Common approaches to address these microbacteria will be discussed. In the study of Qvist, clearing *M. abscessus* complex was associated with a change to a slower decline, similar in magnitude to the pre-infection slope.

The multitude of other bacteria in CF airways which can be detected by non-culture based techniques in a given patient, dosages, pharmacodynamics and interactions of drugs applied, comprehensive treatment including airway clearance, upper airway reservoir and implementation into everyday life need to be considered, when treating resistant bacteria in CF.

Neonatal Pulmonology.

#1. The Difficulty to Extubate Newborns in the Neonatal Intensive Care Unit

Petr Pohunek¹, Miloš Černý²

¹Pediatric Pulmonology, Pediatric Department; ²NICU, Perinatology Center, Department of Gynecology and Obstetrics. 2nd Faculty of Medicine, University Hospital Motol, Prague, Czech Republic
Email: petr.pohunek@LFMotol.cuni.cz

Introduction

Securing the airways to guarantee effective ventilation is the cornerstone of any resuscitation or management of respiratory failure. Endotracheal intubation is a reliable method providing access into the lungs both for delivery of air/oxygen and management of airway obstruction, such as direct suctioning. Indication of intubation and management of an intubated child is a special challenge in the intensive care setting that requires careful judgment and respecting the physiological needs of children of different age groups.

Indications of Intubation in the Neonate and Aspects of Safe Management

In the neonates, endotracheal intubation is often needed as an emergency procedure in the delivery room in the case of perinatal complication with respiratory failure. In other situations, endotracheal intubation may be chosen as an elective procedure to secure the airways and provide positive pressure ventilation. This may be the case in congenital defects such as Pierre-Robin sequence, macroglossy, laryngeal cyst, fetal hydrops, diaphragmatic hernia or diaphragmatic paresis. Short endotracheal intubation has been used for surfactant administration in extremely low birth weight babies (INSURE); however, recently, the less invasive surfactant administration (LISA) has been used more often to prevent possible complications of even a short intubation. The most frequent indication for endotracheal intubation is a respiratory failure requiring artificial ventilation. There is a broad spectrum of disorders that may lead to respiratory compromise in a newborn. In premature babies, the incidence of respiratory distress is rather high and often requires positive pressure ventilation with oxygen supplementation. Depending on gestational age and other factors, such as ventilator regime and fraction of oxygen, bronchopulmonary dysplasia of various severity develops and determines the intensity and duration of the respiratory support needed. Other reasons of perinatal respiratory failure may occur either directly associated with respiratory pathology (meconium aspiration, atelectasis, transient tachypnea of a newborn) or as a complication of other non-respiratory pathologies (sepsis, metabolic disorders, congenital heart defects, surgery for other congenital defects or postnatal complications). Current techniques of artificial ventilation based on synchronized and volume guaranteed regimes provide effective support that fully respects the physiological requirements of a newborn and assures adequate oxygenation while reducing the risks associated with positive pressure ventilation. Another critical issue is the choice of an endotracheal tube of appropriate size. Too large

diameter of an endotracheal tube may cause trauma or ischemic injury in the airways and lead to immediate complications or even late sequelae, such as airway stenosis.

Extubation of a Newborn in the NICU

The duration of endotracheal intubation is determined by the underlying pathology and the requirement of ventilator support. It is desirable to keep the intubation period as short as possible to reduce risk of possible complications. Too early extubation, however, inevitably carries risk of cardiopulmonary instability and often results in need for reintubation and reinstitution of artificial ventilation. On the other hand, prolonged intubation has been associated with increased risk of airway or lung injury, with increasing incidence of infectious complications, such as ventilator associated pneumonia and neurodevelopmental impairment mainly in extremely low birth weight children.¹ Continuous monitoring and evaluation of respiratory status of each child is therefore mandatory to allow for appropriate timing of extubation. The decision to extubate should be taken after careful evaluation of cardiorespiratory stability, the oxygen requirement and its trend and the overall status of the baby and its readiness for a switch to spontaneous ventilation. Extubation should be always properly planned and prepared. The worst scenario is an unexpected accidental extubation that usually leads to emergency reintubation and carries significant risk of hypoxemia, instability and even airway injury during rapid emergency reintubation.

Various protocols for weaning of mechanical ventilation and extubation have been proposed. The unifying concept is to assure effective spontaneous ventilation and to prevent ventilation inhomogeneity and alveolar collapse.

First step is reduction of sedation to guarantee unsuppressed central respiratory activity. If the child maintains adequate spontaneous triggering of breathing, the FiO_2 can be reduced together with inspiratory pressure (P_{in}). The recommended tidal volume that should maintain adequate ventilation and at the same time prevent any lung injury is at the level of 4.5 to 5.5 mL/kg BW. Compliance and resistance of the respiratory tract should also be taken in consideration. Before extubation, the tube should be used for last direct suctioning, if needed. If the monitoring of blood gases and vital signs and functions provides stable results, the child can be extubated and immediately switched to nasal CPAP. Especially in preterm babies with residual lung pathology, the nCPAP pressures should be kept higher (at the level of 7 to 9 cmH₂O) as this has been shown to be more effective than lower pressures (4 to 6 cmH₂O).² Especially in premature babies, a pharmacological support of the transition with caffeine or methylxanthine is recommended.³ Corticosteroids may be considered in children with BPD or history of difficult intubation where increased risk of edema in the airways is suspected. While they may improve the rate of successful extubation, the possible risks should be always weighed against the benefit.³ Nasal intermittent positive pressure ventilation (NIPPV) has been shown safe and effective for preventing reintubation in preterm children whose response to nCPAP was not sufficient.^{4,3}

Extubation Failure

If properly planned and prepared, extubation is usually successful. Nevertheless, even with proper preparation, about 1/3 of ventilated children present with extubation failure and need to be reintubated.⁵ Immediate or very early need for reintubation usually signals some anatomical problem with airway obstruction developing after removal of the "stenting" tube. It may also be associated with the switch from a positive pressure ventilation to spontaneous breathing and change of pressure gradients in the airways. Such problems are mostly observed in tracheo/bronchomalacia, external compression of the airways or some congenital airway defects. Upper airway or laryngeal pathologies may also lead to quick onset of respiratory problems. It may be helpful to evaluate the airways with an ultrathin bronchoscope after stabilization and reinstitution of adequate ventilation. Careful extubation on the bronchoscope may help to reveal the location of obstruction in many cases; however, this is not 100% reliable.

Several rather different time intervals have been used in published studies to define reintubation as extubation failure, therefore the comparison of published results is rather difficult. Mostly used intervals were 48 or 72 hours. From a practical point of view, as failure of extubation, we should understand a need for reintubation in a child with no new pathology that could explain the imminent respiratory failure. Indications for reintubation usually are

- frequent or major apneas,
- inability to maintain hemoglobin O_2 saturation above 88% (or $\text{PaO}_2 > 6.6$ kPa) on $\text{FiO}_2 < 0.6$,
- rising pCO_2 of > 8 -9 (10) kPa,
- increased work of breathing with rising respiratory rate, retractions or grunting,
- development of combined acidosis,
- intolerance of nCPAP or inappropriate response.

Failed extubation represents a high risk situation especially in very low birth weight children. It has been associated with high morbidity and even increased risk of death.⁵ Therefore, various attempts to predict successful extubation have been published, most of them based on scoring some of the physiological signs that characterize respiratory drive and respiratory strength. The simple ratio of dead space to tidal volume (VD/VT) failed to predict risk of extubation failure,⁶ while tidal volume at the moment of extubation, $\text{SpO}_2/\text{FiO}_2$ ratio, spontaneous breathing test (SBT) before extubation and Silverman-Anderson score starting 1 hours after extubation showed a significant predictive value for the risk of reintubation.⁷ More sophisticated studies have attempted to characterize the physiology of ventilation as a predictor of extubation failure. Electrical impedance tomography was shown to help assessing appropriate CPAP pressures to achieve optimal ventilation homogeneity and thus prevent the risk of reintubation.⁸ Measurements of tension-time index for diaphragm and respiratory muscles (TTdi, TTmus) were able to predict extubation outcome; however, they were not 100% sensitive or specific. Simple factors, mainly gestational age and birth weight, performed similarly in

prediction of extubation failure.⁹ Low pre-extubation pCO₂ also showed the potential to predict extubation success.⁵

Conclusion

Failed extubation in a newborn in the neonatal intensive care setting always represents a high risk situation and may be associated with significant deterioration of the child and even lead to cardiopulmonary instability and death. The right time for extubation should always be well judged based on the assessment of respiratory stability and evaluation of possible risks of failure.

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#2. Neonatal Pulmonology: "Year in Review" for the Pediatric Pulmonologist

Amir Kugelman

Department of Neonatology, Rambam Medical Center, Ruth Children's Hospital, The B&R Rappaport Faculty of Medicine, Technion, Haifa, Israel
Email: amirkug@gmail.com

Pediatric Pulmonologists might be asked to consult in the Neonatal Intensive Care Unit (NICU). Thus, they should be aware of the recent trends in Neonatology, as reflected in the published literature in the field of Neonatal Pulmonology.

A few large trials assessed the influence of prenatal steroids on the rate and the respiratory morbidity associated with TTN in late preterm and term infants. The most recent large multicenter, randomized trial, explored prenatal betamethasone treatment at 34 to 36 weeks of gestation.¹ The primary outcome of the study was the composite of treatment in the first 72 hours (the use of continuous positive airway pressure or high-flow nasal cannula for at least 2 hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 hours, extracorporeal membrane oxygenation, or mechanical ventilation) or stillbirth or neonatal death within 72 hours after delivery. The rate of primary outcome was lower in the betamethasone group compared to the placebo group (11.6% vs. 14.4%, $p = 0.02$), and the rate of severe respiratory complications was also lower in the betamethasone group (8.1% vs. 12.1%, $p < 0.001$). The rate of RDS, apnea and pneumonia were similar in the two groups, but rate of TTN was significantly lower in the study group (6.7% vs. 9.9%, $p = 0.002$). There was also a reduction in bronchopulmonary dysplasia (BPD), resuscitation at birth and surfactant use in the betamethasone group. While there are contradictory studies, this trial may support the role of steroids in the prevention of TTN in late preterm infants. Currently, there are no clinical trials that examined the effect of postnatal corticosteroids on TTN in late preterm and term infants.

The use of early systemic steroids in extremely preterm infants is not recommended because they may compromise brain development. In the Neurosis study,² 863 infants (gestational age, 23 weeks 0 days to 27 weeks 6 days) were randomly assigned to early (within 24 hours after birth) inhaled budesonide or placebo until they no longer required oxygen and positive-pressure support or until they reached a postmenstrual age of 32 weeks 0 days. The primary outcome was death or BPD. This study concluded that among extremely preterm infants, the incidence of BPD was lower among those who received early inhaled budesonide than among those who received placebo, but the advantage may have been gained at the expense of increased mortality. In a recent meta-analysis, Shinwell et al.³ assessed the safety and efficacy of inhaled corticosteroids for prevention or treatment of BPD or death in preterm infants. Inhaled corticosteroids were associated with a significant reduction in death or BPD at 36 weeks' postmenstrual age (risk ratio [RR] = 0.86, 95% confidence interval [CI] 0.75 to 0.99, $I^2 = 0\%$, $P = .03$; 6 trials, $n = 1285$). BPD was significantly reduced (RR = 0.77, 95% CI 0.65 to 0.91, $I^2 = 0\%$, 7 trials, $n = 1168$). The use of systemic steroids was significantly reduced in the treated infants. They concluded that very preterm infants appear to benefit from inhaled corticosteroids with reduced risk for BPD and no effect on death, other morbidities or adverse events. Data on long-term respiratory, growth, and developmental outcomes are eagerly awaited. The role of inhaled corticosteroids in established BPD in spontaneously breathing infants was studied by Kugelman et al.⁴ They administered the inhaled steroid hydrofluoroalkane-beclomethasone dipropionate (QVAR) that is unique in its small particle size resulting in

higher lung deposition. This was a double-blind, randomized, placebo-controlled, multicenter pilot study. The study was unable to detect a significant effect of inhaled QVAR on the respiratory course of established BPD. The study was underpowered. Possible benefits of QVAR could be masked by a tendency towards higher use of additional steroids in the placebo group.

Despite the near universal adaptation of gentle mechanical ventilation, surfactant use and non-invasive respiratory support, BPD remains one of the most common respiratory morbidities in very low birth weight (VLBW) infants. A recent meta-analysis⁵ reported on the efficacy of intra-tracheal administration of budesonide-surfactant mixture in preventing BPD in these infants. The analysis included only 2 studies and revealed that infants who received intra-tracheal instillation of budesonide-surfactant mixture demonstrated 43% reduction in the risk of BPD (RR: 0.57; 95%CI: 0.43-0.76, NNT = 5). Although mortality was not different between the groups, a 40% reduction was observed in the composite outcome of death or BPD in the budesonide-surfactant group (RR: 0.60; 95%CI: 0.49-0.74, NNT = 3). Thus, this review concludes that intra-tracheal administration of budesonide-surfactant combination was associated with decreased incidence of BPD alone or composite outcome of death or BPD in VLBW infants. However, there is a need for larger trials before this combination of therapies can be recommended as a standard of care.

In line with the trend of minimal invasive therapy, Kugelman et al.⁶ published a study on the impact of continuous capnography in ventilated neonates: a randomized, multi-center study. Study aim was to compare the time spent within a pre-defined safe range of carbon-dioxide (30-60 mmHg) during conventional ventilation between infants who were monitored with distal capnography (dETCO₂) and those who were not. Infants in the monitored compared with the masked group spent significantly ($p = 0.03$) less time at unsafe range of dETCO₂ levels (high: 3.8 vs. 8.8% or low: 3.8 vs. 8.9%, respectively). Intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) rate was lower in the monitored group ($p = 0.02$) and was found to be significantly ($p < 0.05$) associated with the independent factors: dETCO₂-monitoring and GA. The rate of BPD was comparable between the groups. The study concluded that continuous dETCO₂-monitoring was found to improve the control of carbon-dioxide levels within a safe range during conventional ventilation in the NICU.

Bradley et al.⁷ reported that nasal high-flow therapy (nHFT) is commonly used for non-invasive respiratory support in the NICU. The study objective was to determine which aspects of neonatal nHFT have achieved adequate evidence base to support consensus among experienced clinical investigators, and to document areas lacking consensus to promote future investigations. Consensus was reached for many aspects of nHFT including: need for adequate heating and humidification, need to prevent nares occlusion, maximum flow rate of 8 L/min, assessment of FiO₂ and work of breathing for either flow escalation or weaning, equivalence of nHFT to nasal continuous positive airway pressure (nCPAP) for non-invasive support of infants >28 weeks with resolving respiratory distress, and use of nHFT for non-invasive support of stable infants on nCPAP. A majority consensus occurred for initial gas flow rates in the range of 4-6 liters

per minute and for nHFT as primary therapy for mild respiratory distress. There was no consensus on the approach to discontinuing nHFT.

The goal of gentle support and minimally invasive respiratory therapy is to improve the long term respiratory and neurological outcome of the very premature infants. A recent study,⁸ incorporating new modalities of respiratory support revisited the definition of BPD. The objective of that study was to identify the optimal definition of BPD that best predicts respiratory and neurodevelopmental outcomes in very preterm infants. They concluded that defining BPD by the use of oxygen alone is inadequate because oxygen/respiratory support is a better indicator of chronic respiratory insufficiency. In particular, oxygen/respiratory support at 40 weeks' post menstrual age (PMA) was identified as the best predictor for serious respiratory morbidity, while it also displayed a good ability to predict neurosensory morbidity at 18 to 21 months.

To conclude, the trend in modern Neonatology is to be as gentle as possible, and to use new technologies and modes of therapy to achieve this goal.

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#3. Bronchopulmonary Dysplasia – Acute and Long Term Management to Prevent Chronic Lung Disease

Judith A. Voynow, Edwin L. Kendig Jr.

Professor of Pediatric Pulmonary Medicine, Children's Hospital of Richmond at VCU, Richmond, VA, USA
E-mail: judith.voynow@vcuhealth.org

Fifty years ago, Northway first described bronchopulmonary dysplasia (BPD). BPD affects approximately 10,000-15,000 preterm infants annually in the US. It is the major cause of chronic lung disease and morbidity for preterm infants. Preterm infants are diagnosed with BPD based on their requirement for supplemental oxygen or ventilator support. The most commonly used criteria are based on a physiological challenge test at 36 weeks post-menstrual age to assess the infant's requirement for supplemental oxygen.

The epidemiology and pathology of BPD have changed dramatically over the past 25 years. "Old" BPD occurred in preterm infants with surfactant deficiency (<34 weeks) following respiratory distress syndrome (RDS). The introduction of two therapies, antenatal steroids and intratracheal or aerosol surfactant, markedly improved outcomes and survival, shifting the demographics of BPD to earlier preterm infants (< 29 weeks gestational age). The "new" BPD, often called chronic lung disease of the newborn or CLD, is characterized by arrested alveolar-capillary development with larger, simplified alveoli, increased interstitial fibrosis, and abnormal pulmonary vasculature with decreased branching and precapillary arteriovenous anastomoses. Other comorbidities associated with BPD include patent ductus arteriosus with increased pulmonary edema, abnormal central respiratory drive with apnea and hypopnea, pulmonary inflammation and injury, and pulmonary hypertension related to hypoxemia and an abnormal pulmonary vasculature. Preterm birth, BPD and respiratory infections result in airflow obstruction that persists into adulthood and predisposes to chronic obstructive pulmonary disease. Therefore there is a pressing need to determine interventions to prevent BPD and chronic lung disease.

Several large multicenter trials have tested therapeutic strategies in the acute postnatal period to reduce the incidence of CLD sequelae. The two major interventions that are safe and effective are caffeine and intramuscular Vitamin A. Although dexamethasone treatment decreases the incidence of BPD, early administration of high dose dexamethasone increases the risk for gastrointestinal perforation, and poor neurocognitive outcomes. These complications have limited its use. In one trial, the DART Study, low dose dexamethasone was used after the second week of life in selected infants who failed extubation and treatment resulted in successful extubation and decreased supplemental oxygen requirement. Combined intratracheal therapy

with budesonide and surfactant was superior to surfactant alone in reducing the risk for BPD in preterm infants on mechanical ventilation. In contrast, a trial of late surfactant administered to intubated, mechanically ventilated infants at age 7 to 14 days (TOLSURF) did not decrease the risk of BPD at 36 or 40 weeks. There is no evidence that other postnatal drug therapies including inhaled nitric oxide (iNO), superoxide dismutase, glutathione precursors or cimetidine prevent BPD.

Non-pharmacological postnatal strategies to prevent or reduce the severity of CLD include alternative modes of non-invasive ventilation to decrease barotrauma and stretch injury associated with mechanical ventilation, and determination of the optimal range for oxygen administration. Several large multicenter trials compared the efficacy of alternative modes of non-invasive ventilator support. One therapy, synchronized nasal intermittent positive pressure ventilation (sNIPPV) compared to mechanical ventilation, resulted in decreased BPD in extremely low gestational age infants. Other modes of non-invasive support were considered equivalent to the comparison mode of therapy. For example, nasal continuous positive airway pressure (nCPAP) was equivalent to intubation, administration of surfactant and mechanical ventilation in risk for subsequent BPD. Further, a study comparing nCPAP and nasal intermittent positive pressure ventilation revealed no difference in BPD outcomes. A study from Australia in infants <32 weeks gestation, demonstrated that after extubation, high-flow nasal cannulae (flow rate 5-6 LPM) was noninferior to nCPAP (7 cm water) for infants to maintain ventilation and avoid reintubation. Altogether, the neonatal intensive care for extremely low gestational age infants is to shift to noninvasive ventilatory support such as high flow nasal cannulae and nCPAP as early as possible. If infants require intubation and ventilation, the consensus recommendation is for administration of surfactant.

Three large trials, Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT), Benefits of Oxygen Saturation Targeting (BOOST)-II, and the Canadian Oxygen Trial (COT) evaluated the impact of titrating supplemental oxygen to achieve a lower vs. higher saturation range and the impact of these levels of support on death, BPD, and other comorbidities including neurocognitive outcomes. The SUPPORT and BOOST trials with a combined recruitment of 3424 infants revealed that infants titrated to the lower saturation range of 85 to 89% had a greater mortality rate than infants assigned to the range of 91 to 95%. In contrast, the COT study revealed no difference in mortality between the low or high saturation range arms of their study. Given the concerns for increased mortality raised by the SUPPORT and BOOST trials, the current consensus is to titrate therapy for oxyhemoglobin saturations in the low 90's % range to prevent a potential increased risk of infant death.

The sequelae of BPD in the first years of life are variable as some infants diagnosed with BPD have no long term respiratory disease, while other infants not diagnosed with BPD may have persistent respiratory signs and symptoms. A review of pulmonary function studies for former preterm infants performed as infants, school-age children and adults reveal similar trends over time. Airflow obstruction is a common finding across all ages with small airways most affected as evidenced by decreased FEF25-75% predicted and increased ratio of

residual volume:total lung capacity. Adults had decreased airflow on spirometry, and there are reports of emphysema by CT scan and exercise intolerance. We now know that new alveolarization appears to continue beyond the preschool age period to childhood and adolescence, raising the potential for continued lung growth to potentially overcome neonatal injury. One study supports the concept that post-natal interventions may improve pulmonary outcomes. Using the raised volume rapid thoracoabdominal infant pulmonary function test, Filbrun et al. reported that airway flows significantly increased over 6 to 18 months of age in those preterm infants with optimal weight gain vs. those with less robust growth. A recent large multicenter observational study, the Prematurity and Respiratory Outcomes Program, recruited preterm infants, <29 weeks gestation from 13 hospitals in the United States, to evaluate the contribution of antenatal, perinatal and postnatal factors on respiratory symptoms and pulmonary mechanics over the first year of life.

There still remain many clinical uncertainties concerning the diagnosis of BPD and the risk for chronic lung disease. First, the diagnosis of BPD is based on the level of supplemental oxygen and ventilatory support at 36 weeks gestational age. There is currently a debate concerning whether these diagnostic criteria are determined at the optimal gestational age to predict future respiratory disease. Second, although there are much stronger data concerning perinatal factors that increase the risk for BPD, there is still uncertainty concerning which infants will develop chronic lung disease. There is a mandate to continue to follow the infants recruited for the large cohort studies internationally, so that insights can be gained to discover postnatal factors that either confer greater risk or may mitigate severity of future lung disease. Third, BPD is a relatively rare disease with variable phenotypes, therefore large numbers of subjects in multicenter clinical trials are required for definitively testing new therapies to determine whether there is a decrease in BPD or chronic lung disease. This raises the important issue that there is a need to establish BPD endotypes, to better inform therapeutic trials that target specific pathways. Investigations are underway to identify hosts factors – genetic and epigenetic associations, transcriptome, metabolome, and microbiome profiles that are associated with risk for BPD and chronic lung disease.

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Investigation and Decision Making

#1. Management of Severe Pectus Excavatum and Carinatum in Children and Adolescents

Jorge Correia-Pinto*

*Department of Pediatric Surgery, Hospital de Braga and CUF Porto, Portugal. ICVS/3B's – PT Government Associate Laboratory, School of Medicine, University of Minho, Braga, Portugal. (Address/contacts: Prof. Jorge Correia-Pinto, School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga; Portugal; Telephone: +351 253 604 910; E-mail: jcp@med.uminho.pt)

The Deformities of the Anterior Chest Wall (DACW) are distributed in a spectrum of morphology, severity, symmetry and associated abnormalities. Thus, deformations may occur in which the sternum protrudes posteriorly (*Pectus Excavatum*) or forwardly (*Pectus Carinatum*). Other findings like Pouter Pigeon deformity, Poland syndrome and sternal cleft are associated with DACW, but they will not be covered in this presentation as they have a quite different pathophysiology and treatment.

Pectus Excavatum

Pectus Excavatum may present at birth, but it is often only seen during childhood or even in adolescence. Most patients do not have an evident depression until the rapid growth of puberty, when they undergo prominence of the deformity. It usually arises sporadically, but about 25% of the patients have a direct relative with history of DACW. The etiology is not yet known, however, there are data suggesting the involvement of mechanical forces on the sternum. Conversely, changes in sternal morphology, such as absence of xiphoid or xiphoid bifid, are unlikely the cause because they do not have a higher frequency than the normal population. It is believed that what determines the positioning and rotation of the sternum is the distribution pattern of the ossification centers, which in turn depends on the mechanical forces exerted on the sternum during its

development and/or growth. The most accepted theory to explain the full spectrum of morphologies found in patients with *Pectus Excavatum* and *Carinatum* is the cartilage overgrowth at the sternum-costal junction, which, by exerting mechanical forces on the sternum body, causes a change in its position.

Patients with *Pectus Excavatum* are usually healthy, but in 10% of cases we may find this deformation as a manifestation of a syndrome. In our series, there are patients with connective tissue syndromes (e.g. Marfan, Ehlers-Danlos, muscular dystrophy, etc.) and neurofibromatosis (e.g. von Recklinghausen's NF1), but other syndromes are described in the international literature.

Most patients with *Pectus Excavatum* referred to Pediatric Surgery are asymptomatic. Usually, the motive that leads patients and family members to seek help is the impact the deformation imposes on their body image. Although many authors report alterations in cardiac function, pulmonary function and limitation in physical exercise, this is not the usual scenario. However, severe depression of the sternum results in a decrease in the sternum-vertebral distance and consequently in a reduction of the internal thoracic volume. In extreme cases, the intra-thoracic space conflict may compromise pulmonary expansion, cause obstruction to the flow of important vessels, and/or trigger arrhythmias by the pressure exerted on the heart. However, the predominance of patients who do not have any physiological impact on the cardiorespiratory system makes routine assessment of pulmonary and cardiac function of all patients with *Pectus Excavatum* controversial, with a more comprehensive study being reserved for severe cases presenting with symptoms.

Children and adolescents with *Pectus Excavatum* are aware of the physical deformation that makes them different. The psychological and consequently inter-individual impacts are obvious, especially in adolescence.

The imaging study to document the dimensions of the chest, evaluation of possible secondary alterations of the spine and intra-thoracic organs, and planning of the surgical procedure is considered essential. Computed tomography (CT) is currently the most commonly used imaging test, since it allows a three-dimensional evaluation of bone and cartilage deformation. The characterization and severity of depression can be evaluated by several indices, but Haller's index, used by many clinicians in the therapeutic decision, is the most cited, and is calculated by dividing the sternum-vertebral distance (from the posterior surface of the sternum to the anterior surface of the spine) and the transverse diameter of the thorax. Classically, a Haller index > 3.25 is considered an objective criterion for surgical correction, however experience has shown that other criteria should be taken into account for surgical indication.

Considering the inherent radiosensitivity to this population and in an attempt to avoid exposure to radiation and its adverse effects, our research group developed an image reconstruction methodology similar to that obtained from CT, using magnetic resonance and/or 3D laser scanner (without radiation), which could replace CT in the preoperative approach of these patients.

Physical exercise may play a role in correcting posture and attenuating deformation by developing certain muscle groups, especially in cases of slight deformation. In our series, the recommendation of training using rowing or canoeing has shown encouraging results in the treatment of mild *Pectus Excavatum*. However, it should be highlighted that physical exercise *per se*, namely swimming, is not a treatment for *Pectus Excavatum*.

Innovative, non-surgical approaches are under development and evaluation, including *vacuum bell* treatment. Treatment with *vacuum bell* is a promising alternative in selected cases of *Pectus Excavatum*, provided that the thorax is flexible, particularly in younger patients with mild to moderate deformation. The *vacuum bell* is a bell-shaped device that is centered at the deepest depression point in the anterior wall of the chest and exerts negative pressure on it. The effect of elevation of the sternum and ribs is immediate during application of the device. The duration of treatment is related to the age of the patient, severity of the deformation and frequency of use of the device. The application of *vacuum bell* may lead to the appearance of petechiae or subcutaneous hematoma and is not indicated in the presence of coagulopathies or vasculopathies.

For patients with severe *Pectus Excavatum*, the surgical treatment should be considered, according to patient perception of its self-image and the psychosocial impact that the deformation has on the patient's life. Thus, the surgical correction should only be performed after obtained informed consent from the parents and assent from the adolescents. The ideal age for surgery is the adolescence, because the thoracic structure is still elastic and flexible and, on the other hand, it is close to bone maturity and the end of growth, minimizing the likelihood of recurrence.

The two most widely used techniques are modifications of the open procedure described primarily by Mark Ravitch in 1949 and the minimally invasive procedure described by Donald Nuss in 1998.

The Ravitch technique has good results, but with not negligible operative morbidity and high recurrence rate, although this varies according to the experience of the group. It is, however, the technique recommended in situations of complex DPAT with combinations of *Excavatum* and *Carinatum*, as in cases of Pouter Pigeon morphology, and when there is significant asymmetry or a very extensive defect involving the upper costal cartilages.

The minimally invasive (Nuss technique) procedure is done through two 2-cm transverse incisions in the lateral wall of the thorax. Under continuous thoracoscopic visualization, one or two pre-bended personalized prosthesis are introduced behind the sternum and rotated to a convex position that elevates the sternum to the desired position. The prostheses rest on the anterior surface of the ribs where they are stabilized. Currently, it is possible to perform automatic and customized bending of the prosthesis before surgery, through a system that calculates the size and shape of the prosthesis based on the three-dimensional reconstruction of the costal grid of each patient. During the last years, there are cumulative evidence that implantation of 2 prostheses has advantages for cases of severe and extensive depression as well as in older adolescents, with a less elastic thoracic

structure. The prostheses are implanted for 3 years, after which they are removed and the treatment is completed. The esthetic result is very good-excellent in more than 95% of cases. Regarding the open procedure, it has the advantage of having discreet cutaneous incisions, rather than an incision in the anterior chest wall, operative time.

Pectus Carinatum

The classic presentation of *Pectus Carinatum* is the protrusion of the lower third of the sternum with maximal prominence at the xiphosternal junction which may be quite evident. In most cases, there is a narrowing of the lateral-lateral diameter of the thorax, the ribs protrude anteriorly with less curvature than usual and the sternum may be rotated due to different costal growth rates of the two hemithorax. Less frequently, *Pectus Carinatum* presents with unilateral protrusion of the costal cartilages associated with rotation of the sternum to the opposite side. Like *Pectus Excavatum*, it can occur sporadically, but many patients have relatives with a history of DACW of any type. It may also be part of a connective tissue syndrome or disease.

The classic treatment began to be surgical, usually a modification of the Ravitch procedure, which is still used in some cases of marked deformation. Currently, the first line is a conservative treatment described by Haje and Bowen, which consists of the use of compression braces, which exerts selective pressure on the sternum. It has the advantage of not being invasive and not scarring, but it requires the motivation of the patient to comply with the therapeutic scheme of daily and prolonged use (up to 2 years). Braces should be used throughout the day, except periods of physical exercise. The complications are local pain and skin abrasion. The major challenge of conservative treatment is patient compliance, complicated by the implications that the use of braces may have impact on patient social life, especially in adolescents, which implies a frequent follow-up of these patients. Monitoring should be strict providing continuous positive reinforcement. Although one-third of patients do not complete the recommended protocol, in those where it is achieved, the degree of satisfaction is quite good.

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#2. Should Congenital Thoracic Malformations Be Resected?

Andrew Bush

Imperial College and Royal Brompton Hospital London, UK
Email: A.Bush@rbht.nhs.uk

The routine performance of antenatal fetal anomalies scans on all pregnant women in the last three decades has thrown up many problems, largely the detection of abnormalities when there are no data on the long term significance of the findings, and this is particularly the case for congenital thoracic malformation (CTM, sometimes referred to as congenital pulmonary airway malformation, CPAM). The imaging findings, both antenatally and postnatally, do not relate closely to pathology. There is no doubt that a symptomatic CTM should be resected whatever the age of the patient. However, there is no agreement between centers about the approach to an asymptomatic CTM. Antenatally, interventions such as drainage of large cysts or fetal surgery are reserved for hydropic babies, since most CTMs diminish in size in the last trimester of pregnancy without treatment. Most babies with an antenatal CTM will undergo a chest radiograph soon after birth, which has low sensitivity, and high resolution computed tomography (HRCT) with contrast to delineate the vasculature, which is the current gold-standard investigation. If surgery is planned, the optimal timing is unclear given that some CTMs regress in the first one to two years of life. The uncertainties as to what best to do must be shared honestly with the family. There is no one right answer in the asymptomatic child, and this needs to be acknowledged. Follow up to obtain natural history data is recommended, whatever therapeutic decisions are made. The facts in the published literature are indisputable; their interpretation is contentious. The facts are:

1. Infection, air leak, bleeding and other complications. A large meta-analysis reported on 41 series published between 1996 and 2008 describing 1070 patients, nearly 80% of whom had an antenatal diagnosis of CTM [1]. 505 reached infancy without surgery of whom only 16 (2.3%) became symptomatic. Complications were significantly less likely after elective surgery, but whether this merely reflected that elective surgery was performed in older, bigger children is unclear. A more recent meta-analysis [2] of studies comparing elective resection with expectant management identified only one prospective and eight retrospective studies. Seventy of 168 (42%) patients underwent elective surgery when asymptomatic, with a 10% surgical complication rate; 63 of 98 (64%) patients managed conservatively developed symptoms with a 32% complication rate, which seems very high and suggests a selection bias. Hence overall there is about a 3% risk of complications such as infection, bleeding and air leak in

childhood, but whether the risk increases with age is not known; certainly the lifetime risk of complications in a baby with an asymptomatic CTM cannot currently be computed.

2. Risk of malignancy: We know that primary intrathoracic malignancy is very rare in childhood, and occurs in association with a CTM, with a risk of around 4%. The largest community-based series of pleuropulmonary blastoma (PPB) showed that there are no reliable radiological features predictive of malignancy [3]. Over the period from 1998 to 2008, in a population of around five million with 1,187,484 live births during the study period, 129 children were diagnosed with a CTM (CPAM), the incidence being one in 12,000, and 74 underwent a resection. The reasons for resection were generally poorly documented. A total of five PPBs were diagnosed during this time period, giving an incidence of one in 250,000 live births. Three were initially diagnosed as a CPAM. Thus the incidence of PPB among apparently benign CTMs is 4%, and worryingly, there was no clinical or radiological feature which distinguished benign from malignant. One of the two patients, both of whom were late-presenting, who had a PPB without a pre-existing lung lesion, died. A worrying recent study of 69 resection specimens of asymptomatic CTMs of various sorts revealed 18 (26%) had microscopic disease; $n = 16$ infection (7 microabscesses, 9 with inflammatory cell infiltration), and $n = 2$ PPB [4]. The risk of malignant transformation can be reduced but not eliminated by surgery; PPB is described after complete resection of CTM [5]. Tumor markers are found in excised CTMs, and these may be associated with malignancy; these include Echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion-type oncoprotein, MUC5AC, CK20, erythroblastic leukemia viral oncogene homologue 2 and K-ras
3. Risk of rare, but devastating complications of air travel: There is a very small and unquantifiable risk of complications of air travel, but these can be devastating, and fatal cerebrovascular accident has been described in such patients [6].
4. Risks of treatment: Although resection of a CTM in an otherwise well child is safe, there is a small risk of surgical complications.

Taken together, in my view the above risks outweigh those of elective surgery in skilled hands, and my answer to the question posed in the title is yes. However, many would disagree, and until we have better means of assessing the risk of complications, the present unsatisfactory state of affairs will likely continue. Placing CTM patients into high and low risk categories may be feasible with an algorithm incorporating radiological features and DICER1 mutation analysis [7]. Radiological features suggestive of uncomplicated CTM include antenatal detection and the presence of a systemic feeding vessel and hyperinflated lung. Features suggestive of PPB included bilateral or multisegment involvement. Although this is a large study (more than 100 patients in each group), this algorithm should be used with caution until prospectively validated in another cohort. CT features overlap

between CTM/sequestration and PPB, although the presence of a feeding vessel and hyperinflated lung (CTM/sequestration) and bilateral or multisegment involvement (PPB) have been reported as helpful distinguishing features [8]. A family history of other tumors such as PPB, lung cysts or renal anomalies, or a close relative with a childhood malignancy, especially Wilm's tumor and medulloblastoma, suggests an enhanced likelihood of the mass being a PPB [9]. Hopefully future work including molecular testing for tumor markers will allow risk stratification and targeting of surgery only to high-risk children.

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#3. Diagnosis and Management of Plastic Bronchitis

Bruce K Rubin

Virginia Commonwealth University Department of Pediatrics and The Children's Hospital of Richmond at VCU, Richmond, VA, USA
Email: bruce.rubin@vcuhealth.org

Plastic bronchitis is a rare disorder characterized the formation of firm branching casts that fill the airway. These firm and branching casts are different from the sputum plugs that can be seen in patients with

bronchiectasis and that rarely form branches. The casts are usually firm and white to grey in color except in patients with sickle cell and acute chest syndrome where they are often stained yellow.

Inflammatory cells are associated with all types of plastic bronchitis, so an arbitrary distinction of inflammatory casts and non-inflammatory does not relate to underlying etiology or prognosis. A better classification system is lymphatic or non-lymphatic plastic bronchitis. Children with a congenital heart disease, particularly those with single ventricle physiology, always have the lymphatic form of plastic bronchitis; however fewer than 10% of patients with single ventricle physiology are diagnosed as having PB. Itkin and Dori, at the University of Pennsylvania, have demonstrated that these patients all have characteristic abnormal pulmonary lymphatic drainage and thoracic ducts. Similar abnormalities may be seen in patients who have underlying lymphatic disorders, sickle cell acute chest and plastic bronchitis, and some patients who develop plastic bronchitis following a viral infection. It is unknown the extent of aberrant pulmonary lymphatics in the general population without plastic bronchitis. A second form is eosinophilic plastic bronchitis; most of these casts are greenish with few branches. Staining shows Charcot-Leyden crystals and eosinophils with eosinophil degradation. This form of plastic bronchitis is associated with asthma and appears to respond to high dose corticosteroids and inhaled heparin, presumably by inhibiting Tissue Factor.

Low dose macrolides are reported to be effective in a few patients, although the response is inconsistent. Inhalation of tissue plasminogen activator (tPA) can breakdown cast formation but also causes airway inflammation and is not recommended as regular therapy. There is no proven role for acetylcysteine, dornase alfa, hypertonic saline, bronchodilators, or asthma medications for treating plastic bronchitis.

Definitive therapy for patients with lymphatic plastic bronchitis consists of pulmonary lymphatic mapping and ablation of aberrant vessels. This produces significant relief and often appears to cure plastic bronchitis. In centers where lymphatic mapping and ablation are not readily available, the more aggressive, thoracic duct ligation has also proven to be helpful in many cases.

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Obesity, Growth and the Airways

#1. The Impact of Obesity and Infant Growth Patterns on Childhood Wheezing

John Henderson

School of Social and Community Medicine, Faculty of Health Sciences, University of Bristol UK

Email: A.J.Henderson@bristol.ac.uk

Asthma and obesity have both increased in prevalence in comparable settings and over a similar period of time. It is tempting to speculate that there must be a direct link between the two. However, the association between two phenomena in no way implies that they are in any way related, far less that one causes the other. However, there have been a number of cross sectional and longitudinal studies that have established a positive association between asthma/wheezing and high body mass (usually expressed as body mass index (BMI kg/m²) either as a continuum or more usually using accepted categorical thresholds of overweight and obesity). There are several possible explanations for such an association; they include reverse causation of respiratory symptoms by overweight, confounding by one or more independent variables, including shared genetic factors, associated with both high body mass and wheezing illness, mechanical effects of body fat distribution on respiratory function, and the play of chance. Infant growth could play into this relationship either through direct links between early body size and growth and later obesity¹ or through other mechanisms, such as the association between rapid growth in early childhood and lung function development. This raises a further question about the significance of rapid early growth; it could be a marker of intrauterine adversity even if birth weight is nominally in the normal range, i.e. not all growth retarded infants will have a birth weight <2500g, or it could be a feature of variations in infant nutritional practices.

Obesity and Asthma: The Observational Evidence

Cross sectional studies: The majority of cross sectional studies of obesity and asthma have reported a positive association overall with a suggestion that obese girls have a stronger association with asthma than their male counterparts. However, there is considerable heterogeneity in the sex-stratified risks between individual studies and a systematic review of sex modification of the association between obesity and incident asthma in children reported a stronger effect in boys than girls. Recent cross sectional evidence suggested that fat distribution played a role in the association, with central obesity being associated with asthma. It has also been reported that the association with obesity is stronger for nonallergic compared with allergic asthma. However, there is also a suggested link between high body mass in children and atopic sensitization. Therefore, although the cross sectional evidence supports an association, its potential mechanism is highly uncertain.

Longitudinal studies: Six longitudinal studies in children <18 years old met inclusion criteria in a recent systematic review² of the prospective association between obesity and asthma diagnosis, with at least 1 year

between measurement of BMI and diagnosis of asthma. Obesity/overweight was variously considered as BMI >85th centile for sex and age or BMI z-score. The majority described positive associations with some discordance in sex-stratified risk between individual studies. The combined effect estimates showed positive associations for both overweight (>85th centile BMI) and obesity (>95th centile BMI) with asthma. These results were consistent with earlier findings in adult men and women³.

Early Childhood Growth, Obesity and Asthma

We analyzed detailed growth data of over 9,000 children from birth to 10 years using linear splines to look at different parts of the growth trajectory. We found that rapid weight gain from birth to 3 months was associated with later asthma diagnosis and bronchial hyper-responsiveness⁴. The impact of early postnatal growth on asthma could be mediated through a causal association between obesity and asthma in later childhood. Both infant size and rate of weight gain during infancy have been associated with obesity at later ages¹. Infant obesity, measured by a variety of different metrics, including BMI >90th centile, in cohort and case-control studies showed consistent associations with obesity outcomes at a range of ages across the lifecourse from preschool to late adulthood. Also, the majority of studies of rapid weight gain in infancy measured over different periods showed positive associations with later childhood and adolescent obesity. Another possible explanation is the reported link between rapid postnatal growth and lower lung function in infancy and beyond. Small airways could predispose to wheezing symptoms that are misclassified as asthma in young children. Alternatively, rapid weight gain or feeding practices in infancy may have direct effects on immune development.

Causal Methods to Evaluate the Link Between Obesity and Asthma in Children

One of the major problems with making causal inferences from observational associations is that of confounding by both measured and unmeasured variables. We used a Mendelian randomization approach to test the unconfounded association between body mass and asthma in a birth cohort of children. Genetic risk for obesity was generated using a risk score based on 32 risk alleles, including FTO. On the assumption that these alleles are randomly assorted at meiosis, they can be used as an instrumental variable for high body mass. Although these 32 alleles explained only 2% of the variance of BMI in the population, we found evidence of a causal link between high body mass and asthma at age 7 years in this cohort⁵.

Possible Mechanisms to Explain the Link

If obesity is truly causal in the initiation of asthma in children, there have been a number of mechanisms advanced to explain this. A plausible explanation is that obesity is associated with systemic inflammation, which may give rise to airway inflammation and asthma. There is evidence that adipocytes are a source of pro-inflammatory cytokines but little evidence that systemic inflammation in obesity is directly associated with airway inflammation. Another possible link would be through promotion of allergic inflammation by adipokine effects on the immune system, but, like us, others have reported stronger associations

of obesity with non-atopic asthma, and we found no evidence that obesity is associated with atopy in mid-childhood in our cohort. A specific asthma-obesity phenotype has been suggested in both adults and children, which may be associated with increased asthma severity. There is evidence that obesity in established asthma is associated with poor asthma control, increased exacerbations, and suboptimal response to glucocorticoids. Poor response to steroids may be associated with neutrophil-predominant airway inflammation, consistent with our finding of a stronger association with non-atopic asthma. Other possibilities that have received recent attention are shared genetic loci underpinning both asthma and obesity, epigenetic effects and dietary influences on the microbiome promoting inflammatory responses.

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#2. Obesity, Systemic Inflammation and Respiratory Disease

Sejal Saglani

Professor of Paediatric Respiratory Medicine NHLI, Imperial College London and The Royal Brompton Hospital, London UK
Email: s.saglani@imperial.ac.uk

The intriguing aspect of the relationship between obesity and respiratory health is although obesity is an independent risk factor for conditions such as asthma, not all obese patients are affected by respiratory disease. It is therefore important to disentangle true causal relationships from mere associations when considering the triad of obesity, systemic inflammation and respiratory disease. As the majority of research to date that has investigated interactions between obesity, inflammation and respiratory disease in children has focused on asthma, this update will explore relationships in the context of asthma. One of the biggest conundrums that we are faced

with when considering obesity and asthma is that although more children with asthma are obese, it is not known whether asthmatic children are at increased risk of weight gain due to modifiable lifestyle factors. A cross-sectional study that aimed to investigate the impact of asthma on lifestyle factors also associated with obesity has shown non-obese children with asthma had greater sleep latency and plasma triglycerides compared to non-obese, non-asthmatic children,¹ suggesting asthma per se is a risk factor for obesity.

Although a specific phenotype of asthma associated with obesity has been accepted and described in adult patients, specifically those with severe disease (adult onset, predominantly females with little evidence of airway inflammation), there is now increasing evidence of an obese asthma phenotype in children. Obese asthma is complex and influenced by numerous factors including nutrition and its impact on the gut and lung microbiome, metabolism, airway wall mechanics, genetic susceptibility, and systemic inflammation.²

Th2 Low Inflammation and Systemic IL-6 Levels in Obese Asthma

A key difference between adult onset and the pediatric obese asthma phenotype is the role of maternal weight during pregnancy and the rate of the child's weight gain in early postnatal life. Maternal obesity has been associated with childhood asthma, and has been associated with altered immune profiles in cord blood including a switch towards pro-inflammatory cytokines including IL-6 and TNF- α .³ Interestingly, the pro-inflammatory state was not associated with an increase in the expected allergic inflammatory mediators such as IL-4 or IL-5. Indeed, numbers of eosinophils and CD4+ T helper2 cells were lower in babies born to obese mothers. This underscores a likely fundamental difference in the pathophysiology of childhood onset obese asthma from allergic asthma. A specific systemic inflammatory profile has recently been described in adult obese patients with a non-Th2 high phenotype. Systemic IL-6 inflammation and clinical features of metabolic dysfunction occurred most commonly in a subset of obese asthma patients, and were associated with more severe asthma.⁴ These data, together with the cord blood data from maternal obesity, suggest the mechanisms underpinning obese asthma in both adults and children may be very similar with IL-6 as a potential central mediator driving the disease. Furthermore, the absence of a Th2 inflammatory profile may explain why obese asthma is a relatively steroid resistant phenotype. Experimental studies have also shown that although steroids may help to reduce the allergen-induced component of airway inflammation in mice fed a high fat diet and exposed to house dust mite, a second Th2 independent inflammatory component including macrophage markers and type 1 inflammation persisted.⁵

An important point to consider when assessing inflammation associated with asthma is the relevance of tissue specific inflammation versus systemic inflammation. The cross-talk between airway structural cells and inflammatory cells is key to determining protective or pathological consequences.⁶ This may be of relevance in the context of obese asthma, since evidence suggests the location of eosinophils in different tissues is crucial in determining their effect. When in the lung (specifically the airway wall), they cause

inflammation, yet when located in visceral fat, they improve glucose homeostasis.⁷ Clinical data that correlate lung tissue eosinophilia with obesity may therefore shed light on the role of eosinophils in obese individuals with asthma and on how to improve treatments in these patients.

Nutrition, the Gut and Airway Microbiome and Downstream Immune Responses

A critical component of the growing prevalence of obesity in the Western world is the shift towards a diet that is high in fat content, but low in fiber. The direct impact of a low fiber diet, specifically low in short chain fatty acids (SCFA) on the composition of the gut microbiome and metabolites from the microbiota has been shown to influence the development of allergic airways disease. Dietary fiber content changed the composition of both the gut and lung microbiota. The gut microbiota metabolized the fiber, with an increasing concentration of circulating SCFAs. Therefore, mice that were fed a high-fiber diet had increased circulating levels of SCFAs and were protected against allergic inflammation in the lung, whereas a low-fiber diet decreased levels of SCFAs and increased allergic airway disease.⁸

Airway Mechanics and Dysanapsis in Obese Asthma

In addition to the low Th2 inflammation, an additional explanation for a relatively poor response of obese asthma to steroids may be the presence of altered airway mechanics. Obese children have been consistently shown to have a low FEV1/FVC ratio, and this obstructive picture may explain why they are more susceptible to the development of more severe asthma. A recent finding that has been reported in relation to lung structure in obese children is the presence of airway dysanapsis.² Airway dysanapsis describes a physiological incongruence (mismatch) between the development of the lung parenchyma and size, specifically the caliber (not length) of the airways and is reflected by the presence of an abnormal FEV1/FVC ratio despite the presence of normal values for both FEV1 and FVC. Airway dysanapsis was present in obese children with and without asthma, and was consistent in longitudinal measurements if obesity was present. However, in children with obese asthma, the presence of dysanapsis had a clinical impact manifested as more severe exacerbations and increased use of systemic steroids.⁹

The Impact of Weight Loss on Respiratory Health and Inflammatory Status

Sustained weight loss using dietary and lifestyle modification is difficult and has not revealed conclusive results about impact on asthma control or inflammatory status to date in children, primarily because of an inability to sustain the weight loss. However, the impact of bariatric surgery on asthma and systemic inflammation has been investigated in adults with obese asthma.¹⁰ This has highlighted the complexity of the relationship between obesity, systemic inflammation and asthma. Adults with obese asthma and low IgE had improved airway hyperresponsiveness (AHR) after weight loss, but they did not have a change in resting airway resistance. In contrast, obese asthma with high IgE had improved airway mechanics (resistance) but no change in AHR after weight loss. These data suggest at least 2

phenotypes of obese asthma, with distinct pathophysiology and contribution from both allergy and obesity, exist. The challenge in children is to disentangle the 2 phenotypes and target treatment accordingly. Those with the allergic obese asthma phenotype (perhaps they have an acquired phenotype related predominantly to diet and lifestyle) may benefit from aggressive weight loss measures as they may become more responsive to steroids once the impact of altered airway mechanics has been removed. But the second group, who have a non-allergic, predominantly systemic non-Th2 inflammatory phenotype, which may be driven by IL-6, are likely those with a predominant genetic susceptibility to obesity and asthma, and may not benefit from aggressive weight loss measures, but from systemic anti-inflammatory agents, such as anti-IL-6 antibody.

Summary

There is mounting evidence for the association between obesity and asthma in children, and both are increasing in prevalence. However, the pathogenesis linking the two conditions is complex and multifactorial. Obesity causes a variety of mechanical, metabolic and immunological changes in the airways and systemic circulation which significantly impact clinical asthma control. The pathways that can lead to reduced sensitivity to steroids and the molecular mechanisms driving obese asthma are being uncovered and suggest the presence of two pathophysiological phenotypes within obese asthma. A Th2 high, allergic phenotype that likely reflects an inherent susceptibility to AHR with the added acquisition of obesity, and a Th2 low, non-allergic phenotype that may reflect a susceptibility to obesity and is associated with airway dyspnea and obstructive airways disease. Studies confirming these phenotypes in children and investigating the efficacy of phenotype specific treatment approaches are needed to help tackle the challenge of obesity, inflammation and asthma.

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#3. Sleep-Disordered Breathing in Obese Children

Jean-Paul Praud

Pediatric Pulmonology Division University of Sherbrooke, QC – Canada
Email: Jean-Paul.Praud@USherbrooke.ca

The worldwide obesity epidemic is responsible for very significant respiratory problems in children and adults. As typically observed for chronic respiratory problems, consequences of obesity on respiration are more pronounced during sleep. The present short update focuses on the respiratory consequences of obesity during sleep in children and adolescents. Nevertheless, I will first briefly summarize the overall consequences of obesity on lung function, which is necessary for a complete understanding of sleep disordered breathing in obese children.

Overall Effects of Obesity on Lung Function

The most consistent effect of obesity on lung function is decreased functional residual capacity which, in morbid obesity, approaches residual volume. The decrease in functional residual capacity is due to the mass load on the lung of adipose tissue in the abdomen, as well as in the thoracic cavity and around the rib cage. Consequently, resting ventilation takes place at lower lung volumes while the tethering action of the elastic parenchyma on the alveoli and the intrapulmonary bronchi is reduced, leading in turn to deleterious consequences as follows. First, low lung volumes decrease lung compliance and increase work of breathing. Secondly, decreased functional residual capacity decreases pulmonary oxygen stores and increases the risk of bronchial closure during tidal breathing, especially in the lower pulmonary regions. Consequently, ventilation-perfusion mismatch is frequent in these regions, where perfusion is predominant, which explains the frequent mild hypoxemia observed with obesity. In summary, the bronchopulmonary consequences of obesity increase the work of breathing and favor mild hypoxemia, even at rest during wakefulness.

Sleep-Disordered Breathing in Obese Children

Even in the absence of significant sleep-related upper airway obstruction, the deleterious effects of obesity on lung function tend to be more pronounced at night. Indeed, in the recumbent position, the hyperpression on the diaphragm and the lower pulmonary regions due to the increased abdominal fat mass is the highest. In addition, sleep is normally associated with alterations in breathing, such as the loss of

the “wakefulness stimulus” to breathe and a decrease in upper airway and thoracic respiratory muscle activity, especially during REM sleep. Obesity is an important risk factor (4.5-fold) for sleep-disordered breathing (SDB), with at least 30% of obese children potentially having SDB. In addition, the severity of SDB is proportional to the degree of obesity in children, such that every body mass index (BMI) increment of one leads to a 12% increase in the risk of SDB.

The Mechanisms of Sleep-Disordered Breathing in obese children have been found to be multiple. First, as described above, the mechanical effects of the adipose tissue mass on lung function are more pronounced in the supine position. Secondly, a number of mechanisms tend to promote upper airway obstruction, explaining the high frequency of obstructive sleep-disordered breathing (OSDB):

- Fatty infiltration of the upper airways, especially at the level of the tongue and parapharyngeal pads, is often considered to be the primary causal factor for upper airway obstruction. However, a magnetic resonance imaging study performed in obese adolescents found that, even at this age, adenotonsillar hypertrophy remains the main factor for explaining upper airway obstruction (1).
- A higher frequency of malocclusions has been recently reported in obese vs. non-obese children with OSDB (2).
- The obesity-related decrease in lung volumes is responsible for a reduced tension on the trachea and upper airways. In turn, the consequent increase in upper airway compliance promotes upper airway collapse.
- Visceral adiposity is now held responsible for upper airway obstruction via inflammation. The high metabolic activity of visceral adipocytes produces pro-inflammatory mediators, which would lead, among others, to upper airway inflammation. In the same vein, OSDB is considered to be one manifestation of the metabolic syndrome, secondary to visceral adiposity (3).
- The release of growth factors secondary to the obesity/insulin resistance state may lead to soft tissue edema in the upper airways.
- Finally, blunted respiratory reflexes, such as the ventilatory response to CO₂, and reduced ventilatory drive, especially to the upper airway dilator muscles, are observed in some patients. Such reduction in ventilatory drive is seemingly related, among others, to a resistance to leptin, a cytokine and hormone secreted in large amount by adipocytes.

The Diagnosis of Obstructive Sleep-Disordered Breathing must be made with a high index of suspicion in obese children. Snoring, apneas and breathing difficulties at night are frequently reported at history taking, as well as nocturnal enuresis, excessive daytime sleepiness, hyperactivity, behavioral problems and/or academic difficulties. At clinical examination, in addition to systematically investigating for systemic arterial hypertension, the presence of risk factors for OSDB such as nasal obstruction, orthodontic anomaly, adenotonsillar hypertrophy should be noted. The neck-to-waist ratio independently predicts

obstructive sleep apnea syndrome (OSAS) (RR>2.16 per 0.1 unit) and a value>0.41 has been proposed as a screening test to help prioritize overweight and obese children for polysomnography (4).

Usual laboratory tests investigating for metabolic syndrome are especially important in the diagnostic workup in obese children.

As usual in children, diagnosing the severity of OSDB is strongly advised and an overnight, attended polysomnography is the preferred test to establish the diagnosis of OSAS. However, long waiting lists are the rule, and the higher severity of OSDB in obese children requires an early diagnosis and treatment. Although home sleep apnea testing has been reported as a viable alternative for diagnosing pediatric OSAS, the frequency of nocturnal hypoventilation in obese children necessitates performing CO₂ monitoring (5). In addition, recent results suggest that an overnight pulse oximetry + clinical examination can help to predict OSAS in obese children in a suggestive clinical context (2).

Beyond the above tests seeking to establish the diagnosis of OSAS, drug-induced sleep sedation is gaining popularity to substantiate the site of upper airway obstruction and guide surgical treatment, including in the presence of obesity (6). Whether the test is indicated in all surgical-naïve patients or only when OSDB persists following adenotonsillectomy remains a matter of debate.

Complications of OSDB

Overall, OSDB and obesity potentiate each other to yield more frequent and severe complications compared to OSDB in non-obese children.

Cardiovascular Complications. Childhood obesity is a leading cause of arterial hypertension, and OSDB is accompanied by higher sympathetic activity and reactivity, as well as increased arterial stiffness (7). In addition, both childhood obesity and OSDB are responsible for endothelial inflammation and dysfunction. Consequently, both obesity and OSDB favor cardiovascular complications, especially systemic arterial hypertension.

Metabolic Syndrome. Both OSDB and obesity interact to provoke metabolic dysfunction, especially via chronic low-grade systemic inflammation. One current hypothesis states that the gut microbiome is the inflammatory connection between obesity and OSDB. Disrupted sleep and other factors facilitating obesity (e.g., a high-fat diet) would alter the gut microbiome and increase the passage of lipopolysaccharides into the systemic circulation, leading in turn to systemic inflammation.

Neurobehavioral Consequences. Both OSDB and obesity lead to neurodevelopmental and behavioral consequences, especially hyperactivity/attention disorder (8) and lower school performance. Hence, obesity and SDB again have an additive effect on neurobehavioral consequences.

Quality of Life and Depression. Obesity is associated with lower self-esteem, anxiety disorders and depressive symptoms (9). An extreme reduction in health-related quality of life, similar to children with cancer, has been reported with morbid obesity. A decreased quality of life has also been shown with OSDB. Again, OSDB and obesity potentiate each other to reduce quality of life in affected children.

Treatment of Obstructive Sleep-Disordered Breathing in Obese Children

Adenotonsillectomy must remain the first line of treatment to consider. However, a recent meta-analysis has shown that, following adenotonsillectomy, OSAS is cured in only ~33% of obese children (10). Postoperative follow-up is thus important to detect residual OSAS, ideally with overnight polysomnography. In addition, obesity in children is a risk factor for postoperative cardiorespiratory complications (25% vs. 1%), such that overnight hospitalization and monitoring is mandatory following adenotonsillectomy. Further treatment options in obese children with OSDB include an intensive weight reduction program, CPAP, exercise as well as bariatric surgery in morbidly obese adolescents.

Obesity-Hypoventilation Syndrome

Obesity-hypoventilation syndrome (Pickwickian syndrome) is defined by the association of a body mass index >30 kg/m², arterial hypercapnia during wakefulness and SDB in the absence of other causes of alveolar hypoventilation. Children with obesity-hypoventilation syndrome are considered to be at the extreme of the OSDB spectrum. Their lung physiology is grossly impaired due to severe obesity, the marked mechanical loading of the respiratory system being responsible for increased work of breathing and gross ventilation/perfusion anomalies, leading in turn to chronic hypoxemia + hypercapnia. The consequent increase in bicarbonates and the resistance to leptin would be responsible for an abnormal ventilatory drive and response to hypoxia and hypercapnia.

Obesity-hypoventilation syndrome bears the risk of polycythemia, pulmonary hypertension and right ventricular failure and increases both morbidity and mortality.

With regard to treatment, although adenotonsillectomy should be considered, it is however usually insufficient. In addition, postoperative complications are frequent and severe, with a significant mortality risk. While CPAP can be efficient, BiPAP is most often necessary. Weight reduction is also of primary importance, bariatric surgery being often considered in adolescents.

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Grants and Publication**#1. How To Publish Your Research**

Bruce K Rubin

Virginia Commonwealth University Department of Pediatrics and The Children's Hospital of Richmond at VCU, Richmond, VA. The Children's Hospital of Richmond at VCU, Richmond, VA.
Email: bruce.rubin@vcuhealth.org

The Children's Hospital of Richmond at VCU, Richmond, VA. Publishing a completed research project as a manuscript in a peer reviewed journal can be a daunting prospect, even for seasoned investigators. Many years of service as editorial board member of pulmonary journals and published author (H-index 52), has allowed Dr. Rubin to collect a number of tips that will make it easier to have your manuscript eventually accepted and published. This presentation reviews these tips from manuscript preparation, targeting the appropriate journal, preparing an effective cover letter, choosing reviewers, and dealing with manuscript rejection and resubmission. Examples are given from the authors' own works.

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