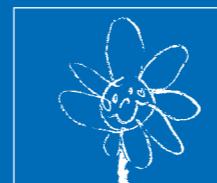


PEDIATRIC PULMONOLOGY

Volume 52 • Supplement 46 • June 2017

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PEDIATRIC

PULMONOLOGY



16th International Congress of Pediatric Pulmonology
Lisbon Portugal, June 22–25, 2017

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ISSN 8755-6863 (Print)

ISSN 1099-0496 (Online)

Cover image design by Gustavo Rymberg.

Printed in Singapore by C.O.S. Printers Pte Ltd

This Journal is printed on acid-free paper.

Foreword

The International Congress of Pediatric Pulmonology (CIPP) is the only international meeting devoted exclusively to paediatric respiratory medicine. Over the period of more than two decades, CIPP has acquired a reputation among practicing paediatricians and clinical academics as the premiere forum for sharing the new information in all areas of paediatric pulmonology. Through our continuing partnership with Pediatric Pulmonology, the abstracts of important research that will be presented in the 16th International Congress of Pediatric Pulmonology (CIPP XVI) in Lisbon, Portugal (June 2017) will reach a wider audience. The presentations cover a broad range of paediatric respiratory disorders, such as asthma and respiratory allergies, respiratory infections and their complications, neonatal lung diseases and their outcomes, cystic fibrosis, sleep disorders, critical care, rare

lung diseases etc., with cutting edge information which is relevant to both clinical and academic communities.



Professor Adnan Custovic MD PhD

President, CIPP XVI

How to cite this article: Foreword. *Pediatric Pulmonology*. 2017;52:S1. <https://doi.org/10.1002/ppul.23725>

ABSTRACT

Keynote Speaker

E-Cigarettes – The New Smoking

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Smoking is not safe at any age, and prevention in children and adolescents has long been a public health priority. Tobacco use is started and established during adolescence, with 90% of combustible cigarette smokers in the United States beginning before age 18 years. Teen smoking prevention strategies have been successful. Combustible cigarette smoking among middle and high school students has dramatically declined over the past few decades. However, a new threat has emerged – electronic cigarettes (e-cigarettes). Indeed, e-cigarette use in children and adolescents has become a major public health concern worldwide.

E-cigarettes, or electronic nicotine-delivery systems, are devices that deliver aerosols of nicotine and other volatile chemicals to the lung. Also known as cigalikes, e-hookahs, mods, vape pens, vapes, and tank systems, hundreds of e-cigarette brands with thousands of unique flavors are now on the market. Sweet-flavored e-cigarette liquids are the most popular, and make these products appealing to youths. Among American high school students, e-cigarettes were the most common tobacco products used, and their use has grown dramatically. The United States Centers for Disease Control and Prevention reported that e-cigarette use doubled among high school students over a one-year period. More than 450,000 American middle school students currently use e-cigarettes, four times the number of reported users the previous year. Nearly two million American students had tried them by 2012, only six years after they were first introduced into the United States.

Historically, tobacco smokers were most likely to be current users of e-cigarettes. Eighty percent of adult smokers who reported using electronic cigarettes did so because they considered them less harmful than combustible cigarettes, and many used them to reduce or quit combustible smoking. E-cigarettes provide a user experience more similar to cigarette smoking than other forms of nicotine-replacement therapy. Peak serum nicotine concentrations can be achieved within five minutes of inhalation. However, a third of adult e-cigarette users never smoked tobacco or were former tobacco smokers. The most commonly cited reasons given by younger e-cigarette users are curiosity, taste, and perceived safety. Not smoking cessation. An estimated 160,000 American students who used electronic cigarettes had never smoked combustible cigarettes, and surveys of college students showed that they were not motivated by the desire to stop smoking cigarettes.

While e-cigarettes generate fewer toxicants than combustible cigarettes, the aerosols are not harmless. Some flavorings are airway irritants and have been associated with respiratory disease. In a recent study, adolescents who used e-cigarettes had more respiratory symptoms when compared to past or non-users. Nonetheless, many of the short- and long-term health consequences of e-cigarettes are still unknown.

More worrisome, data indicate that e-cigarette use by adolescents increases the risk of nonsmokers developing nicotine dependence, particularly in children and adolescents. Teen e-cigarette use has been linked with cigarette experimentation, and young people frequently use e-cigarettes together with other tobacco products, establishing patterns of dual use and not substitution. There are also concerns that nicotine adversely affects adolescent brain development and leads to addiction.

The health risks of e-cigarettes have not been adequately studied, and greater research, surveillance, and monitoring are needed. Until more is known about their “safety,” e-cigarettes must be treated like tobacco products, with prohibition of the sale and marketing to minors, and banning of sweet, candy-like flavorings. Some but not all countries have begun to regulate these products.

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How to cite this article: Keynote Speaker. *Pediatr Pulmonol*. 2017;52:S2-S3.
<https://doi.org/10.1002/ppul.23727>

ABSTRACT

Post-Graduate Courses

#1. PEDIATRIC LONG-TERM NON-INVASIVE VENTILATION DEFINITION AND SITUATION

PLTNIV: Definition and Situation

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Definition

Respiratory support can be distinguished as "invasive" and "non-invasive". The distinction depends on the interface used for patient-ventilator connection. For non-invasive ventilation (NIV), gases are conducted into the airways via an external interface. For invasive ventilation (IMV), gases are conducted into the airways through an endotracheal tube or tracheostomy [1,2].

Indications for and Goals of NIV

Non-invasive ventilation in children is indicated essentially for: 1) Diseases due to increased respiratory load (intrinsic cardiopulmonary disorders, abnormalities of the upper airways, chest wall deformities); 2) Disorders characterized by weakness of the respiratory muscles (neuromuscular diseases, spinal cord injuries); 3) Abnormal neurological control of ventilation (congenital or acquired alveolar hypoventilation syndrome) [1,2].

Non-invasive ventilation can alleviate chronic respiratory failure through the correction of hypoventilation, the improvement of respiratory muscle function and reducing the workload of the respiratory system [1,2]. Goals of NIV are the relief from symptoms, reduction of the work of breathing, improvement and stabilization of gas exchanges, patient-ventilator synchrony, improvement of duration and quality of sleep, improvement of the quality of life and functional status, and prolongation of survival [3].

Patients and Interface Selection

Long-term NIV is applicable to cooperative and stable patients with a certain degree of respiratory autonomy [1,2]. Usually, NIV is applied at night and/or during daytime naps [1–3].

The choice of interface depends on the characteristics of the patient (age, facial characteristics, degree of cooperation, and severity of respiratory impairment). In children, interface acceptance is the first

step for a successful NIV program [1,2]. Nasal masks are the most often used interfaces, although there are promising experiences with the use of oro-nasal and full-face masks, nasal pillows and mouthpieces [1,2].

Ventilation Mode

Pressure-targeted ventilation is the modality most often used for non-invasive ventilation [1–3].

Continuous positive airway pressure (CPAP) support is based on the delivery to the airways of a constant pressure for the whole respiratory cycle. With CPAP, the work of breathing is entirely up to the patient [1–3]. CPAP acts by elevating the intraluminal pressure of the upper airway at levels higher than those of the critical transmural pressure that determines the collapse of the upper airway. This pressure keeps the airways open, promotes relaxing of the upper airway dilator muscles, and reduces inspiratory muscle activity of the upper airways and diaphragm [1–3]. CPAP prevents alveolar collapse favoring alveolar recruitments and the increase in functional residual capacity. Through this mechanism, CPAP improves oxygenation and unloading the inspiratory muscles reduces the work of breathing.

Bi-level positive airway pressure (Bi-level PAP) provides respiratory support at two different levels. Using bi-level PAP is possible, therefore, to separately adjust a lower expiratory positive airway pressure (EPAP, CPAP) and a higher inspiratory positive airway pressure (IPAP, PIP). The inspiratory pressure enhances the patient's spontaneous inspiratory act [1–3]. The expiratory pressure allows eliminating more easily exhaled air and CO₂. The EPAP plays the same role discussed above for CPAP [1–3]. The tidal volume will be generated as the result of the delta between the inspiratory and expiratory pressures [1–3].

In Pressure Support Ventilation (PSV) mode, the ventilator ensures a maximum value of inspiratory pressure in the airways equal to that set by the operator. This pressure support allows the patient to achieve more effective breaths. The patient determines respiratory rate, inspiratory flow and inspiratory time by determining the onset of inspiration, muscle strength applied during the inspiration and the passage to expiration [1]. The use of the PSV mode allows preserving the patient's spontaneous breathing while ensuring the reduction of excessive work of breathing undergone by the patient. This mode is preferable in patients capable of spontaneous breathing and able to activate the ventilator cycles.

In Pressure Control Ventilation (PCV) mode, the operator sets the maximum level of pressure that is delivered by the ventilator during the inspiratory act, the respiratory rate and the inspiratory:expiratory ratio (I:E), in the absence of respiratory effort. Breaths delivered by the ventilator are determined by a pressure, duration of inspiration and

expiration default. This mode is preferable in severely ill patients with significant impairment of the muscle pump efficiency or ventilatory drive [1].

Training Program and Discharge Plan for Long-Term Use

If NIV can be established gradually, an accurate clinical training session aimed at the introduction of the patient and family to its practice must be planned [1,2]. Training should start by using very low pressures and when the patient tolerates pressures throughout the night, the pressures can be gradually increased [1,2].

The choice of pressures is the process by which the clinician searches for a compromise between defect correction (through the increase in pressures), and the limitation of the side effects (with the use of a pressure as low as possible, although still effective) [1,2]. Pressure requests depend on the individual patient's current clinical condition and must be obtained from the evaluation of its monitoring [1–3].

Before discharge, the patient's respiratory status should be stable on the same ventilator, circuit and interfaces that the child will use at home. A personalized follow-up plan must always be provided [1,2].

The optimal frequency for follow-up evaluations has not yet been readily determined. These evaluations should generally be scheduled more frequently in infants and younger children [1,2]. On such occasions, the history and a complete clinical and instrumental assessment (ventilator, circuits, humidification, interfaces) must be performed [1,2].

Compliance should be systematically evaluated through the internal memory of the instrument to verify the actual time of ventilator use. This check also allows assessing air leakages, pressures delivered and nocturnal SpO₂ values [1,2].

Polysomnographic evaluations are recommended before initiating NIV and discharging with the ventilator, and during each in-hospital follow-up admission [1–3].

Pulmonary function tests, blood gas analysis, chest x-ray and lateral projection of the skull, echocardiography should be periodically repeated [1,2].

Situation

An increasing number of children with chronic hypercapnic respiratory failure are currently treated with NIV [1,2]. Non-invasive ventilation allows preserving functions such as swallowing, feeding, speaking, coughing, heating/humidification of the inspired air [1].

The introduction of NIV has reduced the number of emergency room visits per year, tracheostomies, intubations and the length of stay in the pediatric intensive care units. Non-invasive ventilation has allowed early weaning from IMV and extubations. Non-invasive ventilation has also enabled preventing vocal cord or trachea damages, and reduce the risk of lower respiratory tract infections [1].

Convincing data have been reported from national surveys on long-term experiences with NIV performed especially in Western countries [4–7]. In the last years, new data have come out from developing and Eastern countries [8–10].

Neuromuscular disease such as Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA), and diseases of the central nervous system such as the congenital central alveolar hypoventilation

syndrome represent two main indications for NIV [4–7]. Among respiratory diseases, airway malacia and obstructive sleep apnea have been the most frequently treated with CPAP/NIV [4–7]. Children with severe physical and cognitive disabilities are also increasingly offered long-term ventilation to prolong life [4,6].

The survival is longer in patients treated with NIV than in those undergoing IMV [4–7]. Usually, the median age at the beginning of IVM ventilation is significantly lower than in those treated with NIV [4]. Non-invasive ventilation has been successfully started even in children under 1 year of age [6]. Data are available on the possible weaning from long-term NIV, as well as on deaths during NIV (for example in children in whom a palliative approach was taken) [4–10]. Children with neuromuscular and neurological disease are least likely to wean off from NIV. Children most likely to discontinue long-term NIV are those with chronic lung disease of prematurity, airway malacia, and upper-airways abnormalities [4–10]. Non-invasive ventilation failures and consequently tracheostomy and IVM have been reported for example in children with Cerebral Palsy [4–10]. A significant number of patients with NIV have transitioned to adult care [7].

Compliance with NIV is a major issue. Data downloaded from built-in software showed a wide range on mean nightly use [2]. Parental assessment of PAP use may overestimate actual home ventilator use. In this latter study, patients with greater improvement in apnea-hypopnea index were more likely to be adherent. Clinical parameters and nighttime and daytime symptoms improved after PAP therapy regardless of age or adherence. Treatment adherence was not correlated with age, type of underlying disease, interfaces used, nocturnal gas exchanges, and duration of PAP treatment. Children who attempted to use CPAP at least 6 nights a week were treated with CPAP for a longer time on the nights of use. Usage in the first week of treatment predicted longer term use over 2 to 3 months. A predictor of PAP use was maternal education. Adherence was demonstrated lower in African American children. Adherence did not correlate with severity of apnea, pressure levels, or psychosocial parameters other than a correlation between family social support and nights of PAP use in month-3 [2].

Complications and Contraindications

Serious complications with the use of NIV are not reported in children and adverse effects described are minor [1,2].

Mid-facial hypoplasia has been described mainly in patients who started NIV earlier in life. Monitoring of maxillo-mandibular growth is necessary in infants and younger children receiving long-term NIV [1,2].

Swallowing disorders, personal history of inhalation from gastro-esophageal reflux, paralysis of the vocal cords and absent tolerance to NIV will contraindicate its use. Failure of NIV or a high level of daily dependence from mechanical ventilation (≥ 16 –20 hours) are indications for IVM [1,2].

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Management of Complex OSA in Children.

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Sleep-disordered breathing (SDB) is a prevalent disease in pediatrics. It is not a distinct disease, but rather a syndrome of upper airway dysfunction during sleep characterized by snoring and/or increased respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility^{1,2}. SDB includes a spectrum of clinical entities with variable severity of intermittent upper airway obstruction ranging from habitual snoring to severe obstructive sleep apnea (OSA)^{3,4}. In 2016, the results of a European Respiratory Society Task Force on the diagnosis and management of pediatric OSA were published⁵. The main recommendations of this paper concerning severe OSA will be presented in this summary.

In a first step, it is important to recognize the child with possible severe OSA. Certain symptoms such as frequent loud snoring, witnessed apneas, restless sleep and oral breathing are associated

with the presence of SDB. Young children and children with underlying syndromes are especially at risk of severe OSA and its possible complications. In the context of SDB symptoms and underlying syndromes with an inherent risk of OSA, the presence of failure to thrive and pulmonary hypertension are certainly indicative for the presence of OSA. Polygraphy or polysomnography, which is still the gold standard for the diagnosis of OSA, should be performed to document the presence and severity of OSA. Polygraphy and polysomnography provides us with the number of obstructive events per hour of sleep (the obstructive apnea hypopnea index, oAHI). Moderate-to-severe OSA is defined as an oAHI>5. To date, there are no other screening tools that can substitute polysomnography. However, some of these tools, for instance nocturnal oximetry, have their value considering their inherent limitations.

Moderate-to-severe OSA is an indication for treatment irrespective of the presence of morbidity. Especially in patients with underlying syndromes, treatment is a priority because these children have a higher risk of developing serious complications including pulmonary hypertension. In the Task Force document, an algorithm is presented guiding treatment from the least invasive (pharmacological treatment) to the most invasive (tracheostomy). Especially in children with underlying conditions, it is important to identify the site(s) of upper airway obstruction. These children might benefit from adenotonsillectomy, although residual disease is highly prevalent with the need for additional treatment including orthodontics, maxillofacial surgery and non-invasive ventilation. Because of increasingly available devices and especially interfaces for non-invasive ventilation in children, this option is being increasingly used in specialized centers. It is important after each treatment and with increasing age to follow the child with moderate-to-severe OSA to objectify if OSA is still present.

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PLTNIV in Children with Neuromuscular Diseases

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Neuromuscular diseases (NMD) affect the muscle, the nerve or the neuromuscular junction.

Respiratory complications are frequent in children with neuromuscular diseases (NMD). The incidence, age of onset and severity depend on which disease we are talking about.

The respiratory "pump" includes the chest wall, respiratory muscles and respiratory control center. Although there is sometimes parenchymal disease, caused by frequent aspirations or infection, it is the failure of this pump that most commonly causes respiratory problems in NM patients¹.

Respiratory efficiency is dependent on the balance between respiratory load and respiratory muscle capacity, under the control of the respiratory center. In NM patients, as respiratory load overwhelms muscular strength, an imbalance occurs causing alveolar hypoventilation². Ineffective cough and reduction of ventilation leads to respiratory infections, atelectasis and acute and chronic respiratory failure, causing frequent hospital admissions and limited survival¹. Weakness of pharyngeal muscles can also contribute to sleep disordered breathing (SDB)^{1,3}.

Every child with neuromuscular disorders must have a respiratory assessment investigating for infection risk, cough capacity, sleep quality and the presence of SDB, the presence or progression of scoliosis, swallowing difficulties and somatic growth⁴.

Lung function should be obtained in all patients that can cooperate, including determination of breathing patterns and respiratory rate, lung volumes such as vital capacity (VC), total lung capacity (TLC) and residual volume (RV), measurement of maximal inspiratory (MIP) and expiratory pressures MEP), cough peak flow (CPF) and sniff nasal inspiratory pressure (SNIP)². In some centers, invasive tests which require esophageal or gastric pressure transducers, are also used.

Assessment of sleep disruption should be carried out regularly in NM children since sleep disordered breathing and sleep fragmentation are frequent. Patients with muscle weakness, moderate to severe limitation of lung function (VC < 60%), non-ambulant, with significant scoliosis, suspected diaphragmatic weakness or with nocturnal or daytime symptoms of sleep disturbance should have a polysomnography (PSG) if it is available in adequate time. If it is not possible, a nocturnal oximetry and capnography should be obtained at least annually⁴. When there are doubts regarding oximetry or capnography results, a PSG must be obtained.^{4,5}

Diurnal hypercapnia or SDB are clear indications to initiate ventilation, non-invasive (NIV) being the indicated modality. It can be continuous (CPAP) or bilevel positive airway pressure, according to the clinical situation. NIV reduces symptoms of SDB and morning headaches and improves appetite, concentration and quality of life and improves survival.^{7,8}

Ventilation should be initiated in patients in whom SDB is suspected or diagnosed or in an acute setting, during an infectious or atelectasis episode.⁶ In children with spinal muscular atrophy (SMA), NIV may be used prophylactically, even in small daytime periods, to increase lung growth and prevent chest wall deformities.⁷ NIV may also have a role in palliative care as it reduces respiratory distress and anguish.^{6,7}

In children with great dependence on NIV, when this is not tolerated or if there is bulbar compromise, a tracheostomy and invasive

ventilation may be considered but it should be carefully discussed with the family and the children, and their preferences taken into account.^{6,7}

Facial side-effects of masks, such as facial flattening, skin injury and air leaks, are particularly frequent in NMD children and may compromise the adherence to NIV⁹. It has to be promptly managed by changing masks, skin protection and considering alternative ventilation modes.

Airway clearance assessment is very important in the management of NM children. Whenever possible, it should be quantified by CPF. Manual cough assist, air-stacking maneuvers or mechanical assisted cough can be prescribed according to child and family preferences and disease stage.⁴ In children with recurrent atelectasis or great difficulty in mobilizing secretions, oscillatory techniques may be useful.⁴

Swallowing dysfunction and nutritional status evaluation are essential in the management of NM children. Caloric supplements or feeding by nasogastric tube or gastrostomy have to be considered in order to improve somatic growth and respiratory performance.^{4,7} In some diseases, such as Duchenne Muscular Dystrophy, overweight may also be a problem and specialized support by a nutritionist ought to be provided.¹⁰

Scoliosis and other orthopedic abnormalities are frequent and may compromise respiratory performance. Surgery may improve quality of life although respiratory function and SDB should be assessed beforehand.^{4,10}

As part of a global management, chronic and acute pain, social inclusion and school attendance are relevant aspects when considering these children's quality of life and management.

Technological evolution of ventilators, masks and cough equipment has eased respiratory management in increasingly younger children, in a more comfortable manner and with a better quality of life, significantly changing the prognosis of neuromuscular disorders, and allowing many patients to reach adulthood. Transition to adult care is now a reality in childhood NMD and has to be considered in each adolescent patient.⁸

The complexity of these patients justifies their referral and follow-up in specialized centers, where multidisciplinary support is optimized for the overall development and quality of life of the child and family.

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Central Congenital Hypoventilation Syndrome (CCHS) and Rapid-onset Obesity with Hypothalamic Dysregulation, Hypoventilation, and Autonomic Dysregulation (ROHHAD syndrome)

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Introduction

Central congenital hypoventilation syndrome (CCHS) is not an uncommon reason for long-term pediatric home ventilation. Although invasive mechanical ventilation through tracheostomy has commonly been recommended in patients younger than five years for safety issues, non-invasive ventilation (NIV) has also been reported as a safe approach in small infants (1). Nevertheless, attempting non-invasive ventilation in neonates and infants should be performed cautiously, especially in patients having severe breath-holding spells (2).

Increasing knowledge in genetics, specifically the phenotype/genotype relationship, enables identification of patients with milder respiratory hypoventilation who can potentially benefit from a less invasive approach from the neonatal period without life-threatening episodes. There is a confirmed correlation between the size of the PHOX2B expanded allele and the severity of both the respiratory phenotype and associated symptoms (3, 4).

The incidence of dependency on continuous ventilation is lower than 40% in patients with polyalanine repeat expansion mutations (PARMs) and continuous ventilation is rarely indicated in individuals with the 20/25 genotype. Only 10% of patients with a CCHS

phenotype will be heterozygous for a non-polyalanine repeat expansion mutation (NPARM) in the PHOX2B gene. Continuous ventilatory dependence is commonly observed in patients with genotypes from 20/27 to 20/33 and also in individuals with NPARMs, approximately 70–80% of them (3, 5).

Rapid-onset obesity, with hypothalamic dysregulation, hypoventilation and autonomic dysregulation (ROHHAD syndrome) is a rare cause of respiratory failure. Often reported as healthy prior to the appearance of symptoms, patients with ROHHAD syndrome usually present with hyperphagia and significant weight gain at around 3 years of age (15 kg or more in a single year). Months and years later, hypothalamic dysfunction disorders can be diagnosed: antidiuretic hormone secretion abnormalities, central hypothyroidism, growth hormone deficiency, autonomic dysfunction, etc. All children with ROHHAD develop alveolar hypoventilation with a shallow breathing pattern during sleep. An abnormal response to hypoxemia and hypercapnia occurs during wakefulness as well as sleep, with half of the children demonstrating abnormal breathing patterns when awake. Ventilatory needs may vary over time. On initial screening for ROHHAD, only 2/6 (33.3%) children had nocturnal hypoventilation (NH). All children had NH at follow-up and required non-invasive positive pressure ventilation (6).

Therefore, sooner or later all children with ROHHAD will require at least nocturnal respiratory support. Approximately half of the children with ROHHAD require round-the-clock mechanical ventilation, some of them via tracheostomy (5).

Ventilatory Support in Central Hypoventilation Syndromes

Invasive ventilation

The main objective of ventilator support for patients with central hypoventilation syndromes is adequate ventilation and oxygenation in order to prevent adverse events due to hypoxemia/hypercapnia, mainly during sleep. The ventilatory assistance required in central hypoventilation syndromes has tremendous variability. In CCHS, for example, although infants usually require continuous mechanical ventilation, there are several experiences published using NIV in patients with milder hypoventilation. Positive pressure ventilation via tracheostomy is the most effective means to ensure adequate ventilation when continuous ventilation is required. Other candidates for invasive ventilation are normally children who cannot tolerate or be properly fitted with a mask (such as young infants). Additionally, patients requiring very high ventilatory pressures, not very common in these patients except for episodes of acute deterioration, should be invasively ventilated. Difficulties with invasive ventilation are mainly related to the requirement for a constant presence of trained caregivers and the risk of death due to tracheostomy obstruction/decannulation, thus there is an increasing demand from parents to use non-invasive support in this population.

Transition from invasive to non-invasive

A few articles have reported recommendations on how to switch from invasive to non-invasive ventilation in patients with central hypoventilation syndromes (1, 7, 8).

These are some reasonable recommended preliminary steps: previous review of upper airway and removal of hypertrophic lymphoid tissue if present, close supervision with several polysomnographic studies during a one-month period on the non-invasive support ventilator and the tracheostomy corked to ensure adequate titration for the patient. The ventilation parameters for normal sleep architecture should be set to achieve a minimum hemoglobin saturation (SpO₂) of 96% and a maximum transcutaneous carbon dioxide (PtcCO₂) of 40 mmHg.

Obviously, ensuring patient collaboration is crucial as removal of the interface during nocturnal ventilation could lead to severe consequences. This tends to happen after puberty when the interests of teenagers center on social relationships.

Non-invasive ventilation

- Non-invasive positive pressure ventilation (NIPPV) allows ventilatory support to be delivered via interfaces/masks, avoids tracheostomy, and is especially appropriate for those who require only nocturnal ventilation.

Modes and Settings

Many children with central hypoventilation syndromes are not capable of triggering the ventilator adequately during sleep, hence the selected mode should guarantee a respiratory rate. A pressure-controlled mode is commonly used because it fulfills the aforementioned criteria. Unfortunately, if lung conditions change, the tidal volume delivered could no longer be appropriate, so minute volume alarms should be tightly set.

New modes which offer volume guarantee are available. Average Volume-Assured Pressure Support (AVAPS) (Philips Respironics®) and iVAPS (intelligent VAPS) (ResMed®) adjust the pressure support (PS) in order to maintain a target average ventilation over several breaths. AVAPS calculates the average PS provided to the patient during the preceding 2 minutes in order to achieve a particular tidal volume. During AVAPS titration in a CCHS patient, the inspiratory positive airway pressure (IPAP) level ranged between the expiratory positive airway pressure (EPAP) and 19cmH₂O to ensure adequate tidal volume, calculated around 8 mL per kilogram of predicted body weight under a constant rate of 16 breaths per minute (7). We also have an unpublished experience with the iVAPS mode in a 12-year-old teenager who successfully transitioned from invasive ventilation to this mode. Theoretically, the advantage of iVAPS is the setting of alveolar ventilation related to the patient's height, such that its value is adjusted and modified according to the patient's respiratory rate to compensate for anatomic dead space.

Nevertheless, these modes should be used cautiously because the algorithms to provide pressure and respond to leaks vary greatly between different types of devices. It has been shown that a 21–40% decrease in tidal volume is delivered when random leaks appear (9).

- Non-invasive negative pressure ventilation (NPV) generates a negative inspiratory pressure around the chest to support inspiratory effort. The use of NPV has been limited by obstructive sleep apnea due to the asynchrony between the

opening of vocal cords and inspiratory efforts. NPV is used infrequently since NIPPV is available. Nevertheless, a few Ondine's patients have been successfully switched from invasive ventilation to NPV to remove their tracheostomy or from NIPPV to treat midfacial hypoplasia (1).

- Diaphragmatic pacing electrically stimulates the phrenic nerve, generating breathing using the patient's own diaphragm. These pacers can be used for approximately 12 hours a day and offer day-time freedom from the ventilator. Diaphragmatic pacers are not free of complications which include equipment failure, infection and obstructive apnea. Usually, patients are on day-time diaphragmatic pacemaker and use NIPPV at night, although endotracheal intubation could be occasionally required during respiratory tract infections (10).

In summary, teams managing patients with central hypoventilation syndromes should be able to offer non-invasive ventilation support in those patients fulfilling the clinical criteria for safety from the beginning or during their evolution. Knowing the patient's genotype could help to make decisions regarding the respiratory support required. Finally, negative pressure ventilation and diaphragmatic pacing, in spite of not being available worldwide, should be considered as alternative options when facing complications with NIPPV or tracheostomy weaning.

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#2. PORTUGUESE-BRAZILIAN SESSION

Genetics of Tuberculosis

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Pulmonary tuberculosis develops through a complex interrelationship of environmental, immunological and socioeconomic factors and genetic susceptibility. The fact that nearly one-third of the world's population is believed to be affected with latent tuberculosis infection although only a small fraction of the population develops active TB disease during their lifetime, suggests that most individuals possess an immune response able to contain or eliminate the bacteria, even after exposure to *M. tuberculosis*.

The role of genetic factors in the susceptibility to tuberculosis has been suggested by several epidemiological studies, such as high inter-ethnic differences, showing in particular a higher prevalence of disease in populations of African origin than in those of Caucasian origin. In addition, studies of twins highlighted the importance of genetic factors by showing a higher rate of concordance for the disease in monozygotic (~60%) than in dizygotic (~35%) twins. Moreover, after a first association reported in a Gambian population, a meta-analysis showed that several polymorphisms of the *NRAMP1* gene were associated with pulmonary tuberculosis in African and Asian populations but not in European populations.

The imbalance in the production of cytokines responsible for the activation and deactivation of macrophages may be one of the possible mechanisms for this phenomenon. For instance, the presence of IL-10 at the site of infection by *M. tuberculosis* appears to facilitate the evolution to active disease, probably by the suppression of protective mechanisms against the development of tuberculosis. Furthermore, cases of active pulmonary tuberculosis showed significantly higher levels of mediators that impair the Th1 and innate immunity, including intracellular mediators, such as the suppressor of cytokine signaling (*SOCS1*) and interleukin-1 receptor-associated kinase M (*IRAK-M*) as well as extracellular mediators (IL-10, TGF- β RII, IL-1RN) and enzymes (indoleamine 2,3-dioxygenase).

Studies carried out in Brazilian populations showed that 1) the -871A>G and -336A>G single nucleotide polymorphisms (SNPs) were associated, the first with protection to both pulmonary and extra-pulmonary TB, the latter only with the pulmonary form; 2) an association between GGAG haplotypes showed protection to tuberculosis infection; 3) the 139G>A and -939G>A SNPs were associated with susceptibility to tuberculosis, and in particular with pulmonary and extra-pulmonary forms respectively, and 4) the -871A>G and -336A>G SNPs were associated, the first with protection to both pulmonary and extra-pulmonary TB, the latter only with the pulmonary form. Moreover, CD209 and CD209L polymorphisms were associated with tuberculosis infection in a Northeastern Brazilian population, also suggesting that variations in these genes may influence the protection and susceptibility to infection caused by *M. tuberculosis*.

The polymorphisms of the HLA system have also been the subject of numerous studies, the most interesting results having been

obtained with certain class II antigens. Polymorphisms related to HLA-DRB1, HLA-DQB1, HLA-DQB and HLA-DQA1 genes were associated with higher susceptibility to pulmonary TB. Conversely, the presence of HLA-DRB1, HLA-DQB1, HLA-DQA1 and HLA-DQA1 genes demonstrated protection against PTB.

The above-mentioned findings suggest that the human genetics of TB involves a continuous spectrum from Mendelian to complex predisposition with intermediate major gene involvement.

The understanding of the molecular genetic basis of TB will have fundamental immunological and medical implications, in particular for the development of new vaccines and treatments. For instance, recent advances showed that patients with IFN- γ production defects could benefit from treatment with recombinant IFN- γ .

Suggested Reading

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Difficult-to-Control Asthma: Diagnosis and Treatment.

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Asthma in children presents high prevalence in many countries, with important repercussions in school performance, leisure and emotional aspects. It is estimated that approximately 5-10% of children with

asthma have severe disease. Some children with severe asthma are difficult-to-control, and some are insensitive to conventional pharmacological therapy (corticosteroids, long-acting beta-2 agonists, and leukotriene receptor antagonists), representing one of the major challenges in the clinical management of severe asthma. This group of patients is classified as severe resistant-therapy asthma (STRA). Severe asthma in children is strongly associated with the atopic phenotype. Not all STRA children have a history of hospitalizations, although their daily life is severely compromised by continuous disabling symptoms. Specific questions with regard to disease control (GINA or ACT criteria) are essential for correct detection of disease control. Any child with uncontrolled asthma using high-dose inhaled corticosteroid, and long-acting beta-2 agonist (LABA), deserves to be carefully evaluated, with clinical follow-up of at least 6 months by a specialist in the area for adequate diagnosis and management. A systematic clinical evaluation to exclude the following causes is essential: 1) another disease; 2) inadequate inhalation technique; 3) adherence-to-treatment problems; 4) relevant environmental factors; 5) or treatable comorbidities (allergic rhinitis, obesity, severe gastroesophageal reflux, among others). In patients with the final diagnosis of STRA, the first choice for treatment (Step 5 of GINA), associated with inhaled corticosteroid and LABA, is anti-IgE (omalizumab). The second option, usually not effective in many children, would be the use of daily systemic corticosteroids, although many children have shown to be clinically resistant to this therapy in the diagnostic approach and their use is also associated with a number of serious adverse events. Omalizumab emerged a little over a decade ago as an alternative for this group of patients, showing reduced exacerbations and hospitalizations for asthma. However, all therapies for complex diseases such as asthma may present distinct clinical responses, and each patient should be evaluated individually. Although omalizumab is a high-cost medication, one recent real-life study has shown a greater impact on prevention of exacerbations and hospitalizations. In conclusion, difficult-to-control asthma in children requires a careful systematic clinical evaluation by well-trained multidisciplinary teams for reducing the burden of disease in this group of patients.

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Early CF Lung Disease: The Brazilian Experience

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Cystic fibrosis (CF) is a well-known genetic disease caused by CFTR (Cystic Fibrosis Transmembrane conductance Regulator) protein dysfunction¹. Previously recognized mainly as a pediatric entity, it is switching progressively to a substantial condition for adult pulmonologists, since many patients are living longer and becoming adults². The consequences of CFTR dysfunction to the respiratory tract include disturbances in mucociliary clearance, and increased susceptibility to acute and chronic respiratory infections, resulting in neutrophilic inflammation and airway damage (bronchiectasis)¹. These events may occur very early in life, which means that early therapeutic interventions have potential impact for long term prognosis.

Cystic fibrosis used to be relatively unknown by health professionals in Brazil, a situation that is changing rapidly in the last years. One of the reasons for this change is the dissemination of newborn screening (NBS) for several Brazilian States, which has resulted in earlier diagnosis. The increasing contribution of newborn screening to the diagnosis of CF in Brazil can be seen in Figure 1. From 2009 to 2014, 1,341 cases of CF were diagnosed, 602 (44.9%) through newborn screening. The increasing percentage of cases diagnosed through newborn screening every year is noticeable, reaching almost 70% of all cases diagnosed in 2014 (Figure 1).

While we observed this impressive impact of NBS in diagnosis, many caveats remain regarding adequate follow-up and treatment of CF in the country. Many CF Centers do not have adequate resources for CF care, and our National public health model (SUS) does not recognize many of the needs of CF patients. Therefore, access to drugs and resources is delegated to States, resulting in substantial heterogeneity throughout the country.

Cohort studies of CF patients diagnosed by newborn screening have shown that early diagnosis may impact nutrition^{3,4}, and may also facilitate the identification of lung disease signs such as bronchiectasis, air trapping, and airflow obstruction very early in life^{5,6}. However, there are few studies assessing therapeutic interventions in this setting, as well as indication and timing for radiological and functional assessments in infants and toddlers with CF remain highly controversial⁷.

Since 2010, NBS was started regularly for all newborns in the Brazilian State of São Paulo. A new outpatient clinic (ALAFIC) was created in our Center to follow these patients, adopting a specific protocol of clinical and laboratory procedures to maintain them as healthy as possible. The first encounter occurred usually at 2 months of age, and we found many patients presenting with significant nutritional deficits: 44% with a Weight/Height Z score lower than -1, 26% with hypoalbuminemia.

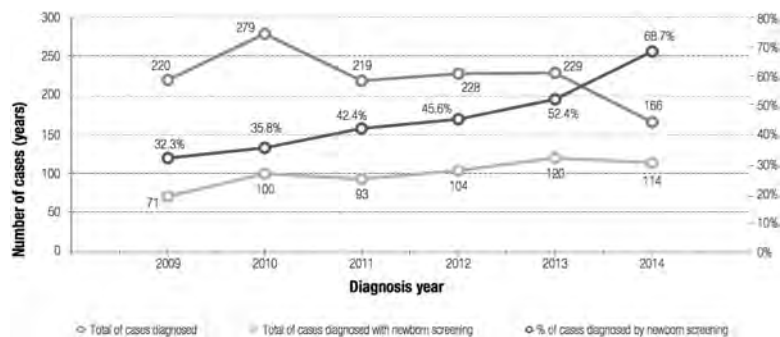


FIGURE 1 New cases diagnosed and the participation of newborn screening in the diagnosis of cystic fibrosis in Brazil, 2009–2014⁸.

While significant improvements in nutrition have been observed after pancreatic enzyme replacement and nutritional supplementation, many patients manifested respiratory symptoms very early, with significant clinical impact. At the first encounter, 20% of the patients attending our Center presented clinical respiratory manifestations such as cough or tachypnea. During the follow-up of the first five years, 80% had at least one hospital admission, mainly due to respiratory causes such as acute viral bronchiolitis. The mean age of the first acquisition of *Pseudomonas aeruginosa* was 11 months, and 54% of the patients had their first positive culture before their first anniversary.

The protocol for radiological examination in our Institution is an annual plain radiograph, and a chest CT scan is indicated when persistent radiographic abnormalities are identified, or when patients remain with persistent respiratory symptoms such as tachypnea or wet cough. A total of 60% of the patients had their first chest CT scan performed at three years of age (only one patient before one year of age), and this procedure resulted in the introduction of dornase alfa in 75% of instances. Therefore, a significant and very strong correlation was observed between the ages of the first chest CT scan and the introduction of dornase alfa ($r = 0.849$, $p < 0.001$). The need for at least one hospital admission due to a respiratory cause was associated with introduction of dornase alfa before the age of three years old ($p = 0.026$).

Expanding the view to the Brazilian CF Patient Registry data, it is possible to realize that the scenario for CF patients in the country has much to improve. The 2014 Annual Report⁸ depicts a proportion of 30% of children and adolescents (up to 17 years old) with signs of obstruction in lung function tests (forced expiratory volume at the first second – FEV1 – lower than 70% of predicted). Examining data only from patients younger than 12 years old show 22% of them in the same situation (FEV1 < 70%), illustrating a significant respiratory compromise very early in life. The mean FEV1 value of Brazilian patients in this age group was 86%, in contrast to the 2014 Cystic Fibrosis Foundation (CFF) Patient Registry Data (United States) that reports 96%⁹. Another marker of CF lung disease, pulmonary infection/colonization by mucoid *P. aeruginosa*, is reported for 10% of children up to 12 years old. While this report is based only on annual identification of this particular microorganism, it may be considered as a surrogate marker of chronic *P. aeruginosa* infection,

representing an elevated rate in the current era of routine *P. aeruginosa* eradication.

Fortunately, there are also some good news for the upcoming future. The Brazilian CF Patient Registry (REBRAFC) is expanding every year, and it now comprises more than 4,000 registered CF patients in the country, a condition that may help to improve knowledge about the disease among healthcare providers. The Brazilian Cystic Fibrosis Study Group (GBEFC), a non-profit organization composed of healthcare professionals involved in CF care and owner/manager of the REBRAFC, is also working hard to improve CF diagnosis through better sweat chloride testing (with financial aid from the CFF), and also by supporting the most extensive genotyping initiative ever carried out in the country for CF patients – aiming to sequence the CFTR gene of 3,000 patients without defined genotype (with a grant from Vertex Inc.).

In addition, the GBEFC is directing significant efforts to improve CF care, by organizing the first Brazilian Guidelines for the Diagnosis and Treatment of Cystic Fibrosis, a publication produced by more than 80 healthcare professionals involved in CF care, from several Centers throughout the country. These guidelines may help clinicians to standardize CF treatment in different Brazilian States, and possibly contribute to convince health authorities to expand treatment options available for CF in the country, aiming at a better quality of life and prognosis for Brazilian CF patients.

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Early CF Lung Disease – the Portuguese Experience

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In Portugal, cystic fibrosis was included in the newborn screening program in November 2013, enabling an early diagnosis and treatment, attempting to prevent/postpone its complications, thus improving the prognosis.

From this moment onward, the manner in which we looked at the children arriving at our CF clinic changed dramatically. The new patients are no longer very sick children with families desperately looking for a diagnosis and treatment, but generally healthy newborn babies and confused parents who, until that moment, had not thought that something was wrong with their children.

Health teams meet these “healthy” newborn babies and their goal is that they remain “healthy” as long as possible. Generally, during the following months, the main concerns are centered around pancreatic enzyme supplementation and nutrition whose adjustments turn out to be the major problem.

However, lung disease starts very early in the life of a CF patient and I will present our experience with the infants that we followed from the start of the newborn screening program.

From November 2013, 14 newborn patients started their follow-up at our CF Center, 12 identified by the screening program and 2 following a diagnosis of meconium ileus. Almost all patients have been diagnosed under the age of three weeks.

During their first year of life, 3 patients have been admitted for gastrointestinal problems – the two patients with meconium ileus and one with distal intestinal obstruction syndrome (DIOS) at the age of 5 months, who has been operated – while 7 patients have been admitted for respiratory / lung infection problems – including, at a different period, the child with DIOS. Only five patients have never been admitted during their first year of life (nor have they later).

Among the patients admitted for respiratory causes, all but one had respiratory symptoms, with or without troublesome infections, and only one was admitted strictly in an attempt to achieve MRSA eradication.

Excluding the two patients with meconium ileus who spend very long periods in the hospital including the first 3 months of their lives and could, because of this, have a different colonization pattern, we have reviewed all the respiratory cultures performed during the first 12 months of age:

A total of 114 sputum cultures were performed. The most frequently identified bacteria were *S. aureus* (10 patients, 31 samples), *E. coli* (7 patients, 23 samples), *P. aeruginosa* (5 patients, 7 samples) and *Haemophilus spp.* (5 patients, 17 samples). Of the 31 *S. aureus* isolates, 15 were methicillin-resistant (MRSA – 3 patients). Most *P. aeruginosa* isolates were sensitive to the antibiotics tested.

The first *S. aureus* isolate occurred in the first 3 months of life in 8 patients, while *P. aeruginosa* occurred in 2 patients.

No *S. maltophilia*, *A. xylosoxidans* or *B. cepacia* were identified.

At the present moment, 2 patients maintain MRSA colonization and one patient maintains *P. aeruginosa* colonization.

All of the patients are growing quite well and without major respiratory complaints. They follow physiotherapy programs continuously and antibiotic therapies according to infection. Dornase alfa is started only after three years of age.

Epidemiology, Clinical Features, Health Resources and Quality of Care for Community Acquired Pneumonia in Children

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Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality in children under five years of age. In low and middle income-countries (LMICs) pneumonia still accounts for the leading position as cause of mortality. In high-income countries, management guidelines and vaccination, including pneumococcal conjugate vaccines, have contributed to changes in epidemiology and clinical features, and pneumonia no longer accounts for relevant mortality.^{1,2}

Nevertheless and despite a significant body of relevant literature and guidelines, day-to-day practice is influenced by factors related to the child (age and clinical presentation), the etiology, the sociodemographic features, environmental exposures and geographies. The expansion of vaccine programs including vaccines against measles, pertussis and influenza as well as *Haemophilus influenzae* type b and pneumococcal conjugate vaccines associated with social improvements (exclusive breastfeeding for the first 6 months of life and improved environmental hygiene), have all contributed to the reduction of risk factors for the severity of pneumonia.^{3,4,5}

Pneumonia is also a leading indication for pediatric hospitalization where variation of management may account for ineffective care.⁶

The optimal management of community-acquired pneumonia (CAP) in children is controversial. Moreover, there is no single definition of pneumonia in childhood that is sensitive, specific, and can be widely implemented.⁷

Clinical practice guidelines (CPGs) are useful for summarizing evidence regarding a topic and for standardizing care, but assessing adherence to a CPG for a specific patient is often difficult, particularly if the guideline contains multiple branch points that depend on the results of clinical, laboratory, or radiographic data.⁸ However there is a strong body of evidence expressed in geographically different guidelines, emphasizing the clinical criteria for the diagnosis and for establishing severity both for the tackling of procedures (general, microbiological and radiological investigations) and for treatment. At the end of the day, the conclusion is that current measures underpin the heterogeneous approach and management of CAP in children, with the strength of recommendations being generally low, reflecting the paucity of literature studies in this area of pediatric medicine.⁵ Most of this heterogeneity is derived from differences in epidemiological data, prevalence of comorbidities, vaccination coverage, resource availability and health service accessibility.

Quality indicators (also referred to as quality measures or performance measures) are different from CPGs; they are specific measures that allow providers and external agencies to assess the quality of care provided for a given diagnosis. Achievement of these individual measures can easily be assessed for the management of a specific patient.⁸

As in other countries, Portugal has published a clinical orientation guideline for pneumonia in children and also a panel of evaluation criteria for CAP admitted to hospital, known as indicators that aim at assessing quality of care across the health system with the purpose of comparing results and providing access to informed health care.^{9,10}

Whether most of CAP in children is managed in the community there is a broad of evidence coming mainly from hospitalized children explained by the fact that both the clinical severity and the resources used are more considerable.

Children with CAP may present with a range of symptoms and signs: fever, tachypnoea, breathlessness, difficulty in breathing, cough, wheeze, headache, abdominal pain and chest pain. The spectrum of severity of CAP can be mild to severe.

The most important decision in the management of CAP is whether to treat the child in the community or progress through the hierarchy of the healthcare system from primary to secondary or tertiary care and refer and admit for hospital-based care. This decision is best informed by an accurate assessment of severity of illness at presentation and an assessment of a likely prognosis. Severity assessment will influence microbiological investigations, initial antimicrobial therapy, route of administration, and duration of treatment and level of nursing and medical care.⁷

The prediction of CAP severity is the relevant question to be asked and includes possible microbial etiology, the possibility of benefit from specific or supportive therapy, possible benefit from experimental therapies (i.e., for enrollment in clinical trials), and the probability of morbidity or mortality.¹¹ Most commonly, the question of location of

care (the major driver of the cost of treatment) has been the central problem of CAP severity. Moreover, prediction of severity may reduce broad-spectrum antibiotic use and decrease hospitalization among low-risk individuals.³

In many cases, the question of treatment or prognosis may depend more on chronic diseases, recent antibiotic exposures or individual susceptibility (respiratory risk factors or vaccination status) than acute physiology.

Although CAP is a well known entity, relevant questions such as quality of care and severity of disease remain to be answered mainly because of specific interaction with age and etiology of the acute lower respiratory infections in children.

The future should include targeting an approach of practice to the standards of care and to have precise indicators and models to predict etiology and severity and ultimately become relevant with regard to location of care and antibiotic selection.

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Reviewing the Guidelines: Management of Acute Viral Bronchiolitis

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Acute viral bronchiolitis is one of the most common reasons for hospital admission in childhood, with increasing incidence in the last decades¹. While the overall mortality is relatively low, its high incidence results in a very high burden, especially for low-income populations². The main etiologic agent is respiratory syncytial virus (RSV), although several other viruses, such as rhinovirus, influenza, parainfluenza, adenovirus and metapneumovirus are identified in these patients³. Risk factors for severe bronchiolitis include preterm delivery or chronic diseases such as congenital heart disease, Down syndrome, chronic lung diseases and neuromuscular diseases – all of which are associated with a higher risk of hospitalization, need of mechanical ventilation and death⁴.

Treatment of several diseases has changed dramatically in the last 50 years, but this is not the case for bronchiolitis. Although there have been hundreds of trials of drugs such as bronchodilators, steroids, antibiotics and other therapeutic strategies such as nebulized hypertonic saline and chest physiotherapy, they all lack evidence of significant benefit. Therefore, treatment of acute viral bronchiolitis remains mainly supportive⁵.

Treatment guidelines are published periodically, with the most recent being the 2014 North American Clinical Practice Guideline from the American Academy of Pediatrics⁶, and the 2015 British Clinical Guideline, commissioned by the National Institute for Health and Care Excellence (NICE)⁷. The AAP Guidelines designated recommendation levels to illustrate quality of evidence and balance for benefit and harm anticipated by its application in clinical practice. The NICE guidelines adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, incorporating health economics for some topics. The wording used in the recommendations (for example, words such as 'offer' and 'consider') denoted the certainty with which the recommendation was made (the strength of the recommendation).

Both guidelines had several recommendations of treatments to avoid, in a genuine attempt to reduce unnecessary interventions administered to children with bronchiolitis. The basic principle of "Primum non nocere" is prevailing. The AAP guideline is significantly shorter and more objective, focusing also on immunoprophylaxis and prevention of viral contamination between patients and caregivers. The NICE guidelines are much more extensive and detailed, containing details of the trials used for evidence-based recommendations, resulting in a document of more than 300 pages.

Main Recommendations and Comments:

- The diagnosis and assessment of severity of bronchiolitis is made by history and physical examination – assessment of risk must also take into account age, history of prematurity or other underlying conditions such as cardiopulmonary disease, immunodeficiency or neuromuscular diseases.
- Consider the diagnosis in children younger than 2 years of age with a history of upper respiratory tract symptoms (coryza), that get worse and affect the lower respiratory tract (persistent cough, wheeze and/or crackles on chest auscultation and signs of increased work of breathing (tachypnea and/or chest retractions).
- Radiographic or other laboratory studies are not routinely indicated.
- Hospital admission must be considered for children presenting:
 - apnea (observed or reported).
 - persistent oxygen saturation of less than 92% when breathing air.*
 - inadequate oral fluid intake.
 - persisting severe respiratory distress (grunting, marked chest retractions, or a respiratory rate >70 breaths/minute).

*The AAP Guidelines recommend 90% as the cutoff value for pulse oximetry (see below).

- Continuous pulse oximetry is not indicated for patients admitted to the Hospital
- **Do not use** any of the following to treat bronchiolitis in children:
 - salbutamol
 - ipratropium bromide
 - systemic or inhaled corticosteroids
 - adrenaline (nebulized)
 - a combination of systemic corticosteroids and nebulized adrenaline
 - nebulized hypertonic saline (AAP guidelines state that it may be used for patients admitted to the Hospital)
 - oral montelukast
 - antibiotics
- Do not perform chest physiotherapy on children with bronchiolitis (NICE guidelines state that it may be indicated for children with comorbidities such as spinal muscular atrophy).
- Regarding nasal (upper airway suctioning), only the NICE guidelines recommend:
 - "Do not routinely perform upper airway suctioning in children with bronchiolitis."
 - "Consider upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions."

- "Perform upper airway suctioning in children with bronchiolitis presenting with apnea even if there are no obvious upper airway secretions."
- Oxygen supplementation is indicated for children with hypoxemia, but the consensus state different cutoff values for oxyhemoglobin saturation:
 - AAP guidelines: "Clinicians may choose **not to** administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90% in infants and children with a diagnosis of bronchiolitis."
 - NICE guidelines: "**Give** oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently less than 92%."
- Nasogastric or intravenous fluids may be indicated for infants who cannot maintain hydration orally (less than 50–75% of the regular amount).
- Non-invasive ventilation (continuous positive airway pressure – CPAP) should be considered in children who have impending respiratory failure.

The inclusion of bronchodilators in the list of "Do not use drugs" was surprising and certainly very controversial among pediatricians and pediatric pulmonologists. The previous AAP guidelines published in 2006⁸ recommended a "carefully monitored trial" of bronchodilators for children with bronchiolitis, which seemed to be the breach for physicians to prescribe it. While bronchodilator use was definitely not associated with a reduction in hospital admission rates or length of stay, the belief that it could transiently improve respiratory mechanics may be the reason why it was prescribed to more than half of the admitted patients with bronchiolitis⁹.

Regarding oxygen supplementation, which is undoubtedly helpful and indicated for hypoxemic children, the new cutoff value of 90% of oxyhemoglobin saturation and the possibility of avoiding continuous pulse oximetry monitoring proposed in the AAP guidelines are both very impactful. While a slightly different value was recommended in the NICE guidelines (pulse oximetry of at least 92%), both guidelines support the idea of reducing pulse oximetry role as a decision making indicator for admission or discharge of the hospital. A very interesting study carried out recently by Dr. Schuh and colleagues from Toronto¹⁰ reinforces this view. They randomized children with moderate to severe bronchiolitis presenting to the emergency department to either having true oximetry values versus values that were artificially increased by 3 percentage points showed to the attending physician. Patients who had falsely elevated oximetry values were less likely to be hospitalized within 72 hours or receive active hospital care for more than 6 hours than those with unaltered oximetry readings. No difference was seen in the frequency of complications or unscheduled visits¹⁰.

Implementing these guidelines will be challenging in several parts of the world, but they signal a new attitude of minimizing interventions and reducing the role of pulse oximetry as the main indicator of severity. This could be of significant impact for admission rates and

length of stay, reducing costs and the burden of bronchiolitis for children and their families.

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How to cite this article: Post-Graduate Courses. *Pediatr Pulmonol*. 2017;52:S4–S16.

<https://doi.org/10.1002/ppul.23726>

ABSTRACT

Plenary Sessions

#1. Maintaining Respiratory Health in Resource Poor Populations

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The most vulnerable populations are those in developing countries. Pneumonia accounted for 16% of all deaths in children < 5 years of age – nearly 1 million – in 2015 alone. More than 95% were from developing countries, most prevalent in South Asia and sub-Saharan Africa (1,2). There were 0.29 pneumonic episodes per child per year with mortality of 1.3%-2.6% in developing compared to 0.05 episodes per child per year and low mortality in developed countries(3). Over time, the World Health Organization (WHO) has developed an algorithm pathway to health care – based on simplified premises tested and retested in appropriate settings(1). Respiratory illness in children < 5 years is determined with cough, and/or difficulty breathing, with or without fever, but pneumonia is diagnosed with tachypnea and lower chest indrawing(4). These two signs have a high sensitivity, reasonable specificity, and found to be a better predictor of pneumonia than auscultatory findings. Etiology is rarely identified, but *Streptococcal pneumoniae* and *Haemophilus influenzae* are the common infecting bacteria, then *Staphylococcus aureus*, with RSV accounting for 15–40% of those hospitalized for pneumonia or bronchiolitis(5). Epidemics of RSV and/or influenza coincide with epidemics of *Streptococcal pneumoniae*. In those with HIV, *Pneumocystis jiroveci* remains common, responsible for at least 25% of pneumonia deaths in this group. Pneumonia is classified into 3 categories; 'nonsevere', 'severe', and 'very severe'(1). Treatment is a compromise between that with the lowest risk of failure and the greatest simplicity of delivery.

Hypoxemia determined by pulse oximetry is observed in approximately 13% of children requiring hospitalization. A systematic review of 12 studies showed children with saturations <90% were at 5.4 times the risk of death(6). Even in low income countries, pulse oximetry is a relatively cheap and robust diagnostic tool. A recent study using pulse oximetry measured hypoxia as an indication for hospital referral and oxygen treatment resulted in a 35% reduction in pneumonia-related case fatality rates. Treatment failure occurs in 9–21% regardless of the antibiotic used and is associated with younger age, previous use of antibiotics, lack of breastfeeding, living in overcrowded home, higher respiratory rate on assessment and immunization status(7).

Pneumonia in the developed world is changing as a result of immunization, emerging pathogens and drug resistance, with profound differences between developing and developed countries in the organization and efficiency of their health systems(8). However, a significant burden of respiratory disease – bronchiolitis, pneumonia, bronchiectasis – also exists in populations within developed countries. Argentina, Australia, Alaska (USA), New Zealand and Turkey have published high rates of respiratory disease within sectors of the population, notably in indigenous children(9). While geography and potential isolation creates difficulties in accessing care for some (Australian Aboriginal, Alaskan First Nation communities) in others, such as our own Maori and Pasifika communities in New Zealand, other barriers occur. These populations also have more severe disease, and yet are less likely to receive preventative care with, for example, lower 'on time' immunization coverage, and less frequently given asthma action care plans. In a comparison of indigenous children with chronic respiratory disease to their national indigenous populations, and the national pediatric populations for 3 countries – those with disease experienced significant disparities in poverty indices; household crowding, tobacco exposure, poorer parental education resulting in early and repeated acute respiratory infections (10).

Effective interventions to improve respiratory health to poorly resourced populations are grouped by WHO into 'protection', 'prevention' and 'treatment' (1). **Protection** includes the promotion of exclusive breast-feeding for 6 months, adequate nutrition or complementary feeding, and vitamin A supplementation. Zinc supplementation is associated with a reduction in the incidence and prevalence of pneumonia (11). Vitamin D deficiency is associated with an increased risk of infections but supplementation to reduce infection rates is inconclusive with research ongoing (12).

Successful **prevention** includes immunizations (pertussis, measles, Hib, PCV, rotavirus), handwashing with soap, access to safe drinking & sanitation, reducing household pollution, and HIV prevention. The major success has been with immunizations. By 2015, 86% of the world's children received three doses of Diphtheria-Pertussis-Typhoid reducing the number who did not receive these routine vaccinations from 33.8 million in 2000 to 19.4 million(13). In the USA subsequent to pneumococcal vaccination (PCV 7) introduced in 2000, rates of invasive disease fell from 98.7/100,000 cases to 23.4/100,000. Pneumococcal vaccination is in 128 countries with 32% coverage contributing to a reduction in < 5 year age mortality from 12 million in 1990 to 6.9 million in 2011(13). Vaccine introduction is currently lagging in middle income countries as they are less able to finance national programs and have less access to external funding sources.

Indoor pollution associated with increased respiratory disease (wheezing and infections) are exposure to tobacco smoking, cooking and heating with biomass fuels. Cooking with kerosene, for example, was associated with higher rates of cough, bronchitis, sputum, and chest illness in adults and children relative to cooking with LPG(14). Respiratory infections have been associated with self-reported mould in the home in both developing and developed countries. Indeed the prevalence of respiratory symptoms was also higher in moisture-damaged schools in Spain, the Netherlands and Finland(15).

Treatment includes improved care seeking and referral with case management at health facility and community level, access to antibiotics and oxygen, and continued feeding (including breastfeeding). Trials continue to compare shorter versus longer courses of oral antibiotics, reduced doses per day to improve adherence, and look at bacteriostatic versus bactericidal antibiotics. First line drugs are simplified; benzylpenicillin, amoxicillin, and chloramphenicol, or amoxicillin plus gentamicin with severe disease. Shorter course, daily azithromycin has also been explored. A mortality reduction of 36% is attributed to this standardized management with the integrated community care including a 13% increase in seeking care for pneumonia in these communities(5).

Whole focusing on infection above, wheezing illnesses are even more common as seen in studies from India and Brazil – where bronchodilators were shown useful in children with a history of wheeze, recurrent episodes of respiratory distress or the presence of wheeze in the absence of fever. WHO defines **essential medications** as those that meet priority health care needs of the country. This list now includes two inhaled corticosteroids and one bronchodilator meter dose inhalers. The Global Asthma Network (GAN) is promoting that children (and adults) with asthma need a reliable, uninterrupted supply of quality-assured medicines, affordable over the long term(16). In a survey GAN conducted in 99 countries, 79 had an 'Essential Medicines List' with 62 including one or more inhaled corticosteroids, and 68 including a bronchodilator (GAN).

The future; a new 'WHO/UNICEF Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea' describes establishing healthy environments to protect children, and increasing access to cost-effective interventions for both prevention and treatment. Other initiatives include improvement in immunization coverage with the UN 'Global Vaccine Action Plan' working towards universal access to immunization by 2020, endorsed by all 194 WHO member states. The GAN are also setting targets for asthma treatment – recommending asthma medications are on essential medication lists with appropriate dosing for children. New interventions are being investigated including diagnostics, recognizing genetic predisposition for the development of severe or chronic disease and new immunizations. The final article in an excellent Lancet series in 2013 noted that ending preventable deaths (predominantly pneumonia and diarrhea) in young children within the next 12 years was "ambitious but achievable"(17). They suggested at a cost of \$USA 6–7 billion, significant further improvements could be made if coverage of the key evidence-based interventions were scaled up to at least 80% and immunizations to 90% for all countries – leading to 2/3rds reduction in deaths in children < 5 years age.

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#2. Respiratory Syncytial Virus Mortality

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Respiratory syncytial virus (RSV) is the most frequent cause of hospitalization and an important cause of death in infants in the developing world. The relative contribution of social, biological, and clinical risk factors to RSV mortality in low-income regions is unclear. In this presentation, we discuss the burden and risk factors for mortality due to RSV in low-income populations. Our findings stem from a prospective, population-based, cross-sectional, multicenter study conducted between 2011 and 2013. Hospitalizations and deaths due to severe lower respiratory tract illness (LRTI) were recorded during the RSV season. All-cause hospital deaths and community deaths were monitored. Risk factors for respiratory failure and mortality due to RSV were assessed using a hierarchical, logistic regression model.

Between 2011 and 2013, 2,588 (65.5% of population) infants with severe LRTI were infected with RSV. 157 infants (148 post-neonatal) experienced respiratory failure (RF) or died with RSV. RSV LRTI accounted for 57% fatal LRTI tested for the virus. A diagnosis of sepsis and pneumothorax were the main determinants of poor outcomes.

RSV was the most frequent cause of mortality in low-income post-neonatal infants. Respiratory failure and death due to RSV LRTI, almost exclusively associated with prematurity and cardiopulmonary diseases in industrialized countries, primarily affected term infants in a developing world environment. Poor outcomes at hospitals are frequent and associated with the co-occurrence of bacterial sepsis and clinically significant pneumothoraces.

#3. Food Allergy

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Around 4,500 hospital admissions in the UK per annum are attributed to food allergy, of which one third are due to severe, anaphylactic reactions. Peanut is one of the most potent allergenic foods, causing IgE-mediated reactions in at least 2% of UK school-age children¹. In young children, the most common food allergy is that to cow's milk, affecting up to 1 in 30 infants².

Allergic reactions to foods are unpredictable, and accidental exposures can result in severe allergic reactions, and in rare instances fatal reactions. Due to the potential for life-threatening allergic reactions (anaphylaxis) and the restrictions needed to mitigate this risk, food allergy has a major impact on the quality of life, since for both patients and their families the pressures of avoidance of implicated foods and the fear of a reaction due to accidental exposure significantly impair the quality of life.

Diagnosis of Food Allergy

Accurate diagnosis of food allergy is critically important. The double-blind placebo controlled food challenge (DBPCFC) remains the gold standard for diagnosing food allergy³, but the procedure is time-consuming, expensive and patients may be at risk of severe reaction. In daily clinical practice, diagnosis is usually based on a clinical history supported by positive allergy tests (skin prick test [SPT] or specific IgE in serum). However, these tests have low specificity, and while "positive" test confirms sensitization, it does not unequivocally confirm clinical reactivity upon exposure (i.e. allergy); as a consequence, the utility of SPTs and sIgE to whole allergen extracts in confirming the diagnosis of food allergy has been questioned. Cut-off points related to the size of skin test wheal and sIgE titer which confer high probability of clinical allergy have been proposed for some allergenic foods, but these decision points may differ between different populations or setting⁴.

In a population-based birth cohort study, using oral food challenge to confirm peanut allergy, we have shown that the majority of children sensitized to whole peanut extract do not have peanut allergy (~10% were sensitized to peanut using standard tests, but only ~2% had true peanut allergy)¹. By measuring IgE responses to individual peanut allergenic proteins (or components, so called component-resolved diagnostics), we demonstrated marked differences in the component sensitization profile between peanut-allergic and peanut-tolerant subjects, in that IgE to peanut protein Ara h 2 offered the best discrimination between peanut-allergic and peanut-tolerant subjects¹. In a follow-up study in which we compared the diagnostic performance of IgE titers to the whole extract with that to different peanut components (Ara h 1, 2, 3, 8 and 9) using standard ImmunoCAP™ method, we confirmed that sIgE to Ara h 2 had the highest accuracy in differentiating between peanut-allergic and peanut-tolerant children⁵. IgE to Ara h 2 >0.35 kU_A/L conferred 100% sensitivity and 96.1% specificity in diagnosing clinical peanut allergy. However, it is important to stress that this allergenic molecule may not be the best prognostic marker in other areas, were different allergenic components may be more relevant. It is also of note that none of the currently available tests accurately predicts the severity of allergic reactions⁶. Given the heterogeneity in the recognition patterns observed of different allergenic proteins in different populations

and geographical areas, further studies are of crucial importance to identify and confirm potentially clinically useful molecular diagnostic and prognostic markers of food allergy⁶.

Management of Food Allergy

There is no curative treatment available for food allergies in the routine clinical practice. The day-to-day management involves avoidance of implicated foods, and the availability of rescue medication (such as an adrenaline 'pen') in the event of an accidental reaction. One approach to treatment, used in some specialist centers in their continental Europe and USA, is oral food immunotherapy. Oral immunotherapy involves administering very small but increasing amounts of the allergenic food daily for several months. Oral food immunotherapy has been shown to be effective for peanut⁷ and milk allergy⁸, but causes frequent (and occasionally) severe reactions in some patients. Furthermore, milder reactions occur with up to 80% of administered doses, particularly in those with persisting milk allergy⁸.

Dietary avoidance remains the foundation of the management of food allergies. However, it has to be emphasized that dietary avoidance is not a treatment, but rather a management strategy which is dependent on appropriate food allergen labeling⁹. Food allergen labeling is mandatory for several allergenic foods, including peanut, when used as ingredients in manufactured foods. This requirement is now being extended to catered foods. However, despite mandatory labeling, accidental exposures remain common. In a study of ~1000 peanut-allergic children, nearly half of them experienced at least one reaction to peanut in the previous 12-month despite dietary avoidance¹⁰. Another major allergenic food (milk) is ubiquitous in human diet, and avoidance is very difficult, especially as children grow older. In one study, cow's milk was detected in 43% of the bakery products, with 21% containing sufficient amount to cause an allergic reaction in 10% of children with milk allergy¹¹. It is thus not surprising that 2 in 5 children with cow's milk allergy will have allergic reactions due to accidental reaction every year². While some children outgrow their milk allergy by school age, recent studies have shown that up to 50% will continue to remain allergic into their teens and beyond, and this group are at greater risk of severe reactions and death².

Epidemiological data from the UK, USA, Canada and Australia suggest that a considerable proportion of children with food allergy are not diagnosed (and appropriately managed) by their primary care physicians¹². This suggestion underpins the urgent need to tackle the problem of food allergies, and raise the awareness among health professionals involved in the care of children.

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#4. Invasive and Non-invasive Methods to Assess Responses to Respiratory Treatments in Early Childhood

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The importance of early childhood:

Respiratory disease in early childhood poses a huge burden to patients/families and to healthcare systems. In addition to the immediate impacts of time away from school and parental missed work, there are the well-described longer term clinical impacts extending into adulthood and in some diseases, significantly impacting health and prognosis.

Response to Treatment Varies

A number of factors, both known and unidentified, may influence response to prescribed treatments including, but not limited to:

accuracy of the diagnosis; severity of underlying disease; technique (e.g. inhaled medication); adherence and environmental influences such as second-hand tobacco smoke, pollution, exposure to infection. The ability to reliably assess response will allow individualized care to be delivered: optimal therapies at required doses (but not higher) for the necessary period of time (but not longer). It can also provide a useful demonstration to caregivers that persisting with the therapy is useful, thereby aiding adherence. Conversely, failure or an inability to assess response can result in the wrong treatments, persisting ill-health, drug side-effects, antimicrobial resistance and adverse long term consequences.

What Are the Issues with Current Monitoring Techniques?

Disease may begin early in life, but remain 'silent'; in contrast to the ease with which airway health can be monitored in older children and adults, there are few useful tools for very young children

- We rely heavily on **symptom** reporting, which is subject both to under- and over-estimation.
- **Clinical examination** is extremely insensitive: in cystic fibrosis (CF) for example, a young child needs to be quite sick before signs are abnormal.
- **Infection** can go undetected leading to chronic modes of growth less susceptible to treatment: sputum cannot be expectorated spontaneously; alternative non-invasive culture samples such as cough and throat swabs lack sensitivity and specificity. The gold standard of bronchoalveolar lavage is invasive and cannot be undertaken repeatedly. Indeed, although useful at periods of clinical concern, regular use has not shown benefit in children with CF¹. The limitations of sample collection also restrict any ability to monitor airway **inflammation** frequently in this age group.
- **Imaging**: radiographs are blunt, whereas CT scans possess more sensitivity. Although they are used relatively frequently in some centers, concerns over radiation limit their use in others.
- **Physiology**: lung function testing, the mainstay of monitoring for older children and adults with lung disease is not easy in very young children. Lung clearance index, which seems in fact most useful in the early stages of disease², requires significant expertise and sufficient time to be performed well, so is currently only available in a small number of centers, most commonly on a research basis.

How Might We Do Better?

Consider doing easy things more frequently:

- an example of this would be sputum induction in young children with CF or PCD; we and others have reported a significant reduction in the need for BAL
- monitor drug pick-up rates. Although not absolute of drug administration, this is a useful and easy surrogate
- further, the development of smart technology coupled with inhaler/ nebulizer devices provides a real opportunity for us to

assess adherence to prescribed medicines and to tailor interventions to best suit the patients and their family³

Alternatives to potentially useful tests which may be limited by their acceptability:

- ultralow dose CT scanning protocols are being developed which may reduce concerns over radiation; as an alternative, there is increasing interest in non-radiation forms of imaging such as MRI⁴. Protocols are being investigated both with and without the administration of gases (hyperpolarized or simple oxygen), which are likely to demonstrate utility in chronic airways diseases

Novel approaches:

- breath monitoring for airways disease is beginning to show promise. Initiatives such as BreathCloud (<https://www.breathcloud.org/en/>) may add substantially to knowledge around utility of these novel approaches, which may ultimately prove useful for even the youngest patients; we and others are exploring the potential for breath and other non-invasively obtained samples to aid in the detection of lower airway infection⁵.
- CFTR modulator drugs have arrived, targeting the root cause of cystic fibrosis at the molecular level. With the first of these, ivacaftor, significant benefits on lung function and exacerbations was shown. Both of these outcomes are impractical in very young children but as the drugs are administered systemically, there are opportunities to assess the impact on other organs: sweat chloride, weight and height, markers of pancreatic disease such as fecal elastase-1⁶. Indeed, these assays are mandated in some countries as evidence of adherence to this high-cost treatment.

In Summary

Childhood lung disease is of major importance not only because of the burden to the child and family at the time, but also as it provides the foundation for later, adult disease. It is therefore crucial that the *right treatments* at the *right dose* are provided to the *right patients* at the *right time*. Personalized therapy, as opposed to a 'one-size-fits-all' approach is only possible when treatment response can be assessed accurately underscoring the importance of efforts to further develop and refine these in our youngest patients.

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#5. Changing the Natural History of Asthma through Early interventions: A Summary

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Two major factors emerging during the first years of life have been consistently associated with the development of asthma: wheezing lower respiratory illnesses (WLRI) and early sensitization to aeroallergens (1). Many young children present with WLRI before age 3, but only a fraction go on to develop persistent wheezing and asthma by the school years (2).

WLRI caused by both human rhinovirus (HRV) and respiratory syncytial virus (RSV) increase the risk for subsequent asthma, but the strongest link has been reported with HRV, especially among infants at high risk for asthma (3,4). Whether the association between WLRI and asthma is causal is currently debated. However, genome-wide association studies have identified polymorphisms in a gene cluster in chromosome 17q (5) and in the gene coding for CDHR3 (6), which interact with WLRI to increase the risk for subsequent asthma. The specific gene (or genes) responsible for the signal reported in chromosome 17q has not been identified, but CDHR3 appears to play an important role in the receptor system for HRV-C, an HRV species that has been found to trigger severe asthma exacerbations (7). Thus, genetic susceptibility to WLRI may be a potential link between these illnesses and subsequent asthma.

Complex analyses of patterns of sensitization to aeroallergens in early life have shown that a subclass of young children that tested positive for specific IgE against multiple such allergens in early life were at the highest risk for the subsequent development of asthma associated with airflow limitation (8,9). It is plausible to surmise that the persistent allergic inflammation, especially when it has its origins before the age of 3 years, may be associated with airway remodeling and may thus predispose for the development of atopic asthma later in life. The combination of WLRI with early sensitization identifies the young children at the highest risk for persistent asthma during the

school years (10). These findings have suggested that opportunities for asthma prevention could arise from interventions that prevent either (or both) WLRI and early allergic sensitization and their consequences.

Studies of children raised in rural communities, and especially on animal farms, have provided solid evidence indicating that increased exposure to environmental microbes and microbial products during early childhood has a protective effect on the development of asthma (11). Of particular interest is the finding that these exposures do not only prevent atopic asthma, but also transient WLRI occurring before the age of 3 years, which is known to be unrelated to allergic sensitization (12). The mechanisms through which microbial exposure may prevent viral-induced WLRI are not known. However, a gene expression analysis comparing peripheral blood of Hutterite and Amish children showed activation of antiviral gene pathways in the latter, who were also shown to be exposed to dramatically higher home microbial loads than Hutterite children (13). Of interest, oral lyophilisates of bacterial extracts have been used empirically for decades in Europe and Latin American for the prevention of viral respiratory infections. A recent clinical trial found significantly decreased incidence and duration of WLRI among preschool children with a history of recurrent WLRI treated with Bronchovaxom, a bacterial extract, as compared with those treated with placebo (14). A large clinical trial is now underway in the United States to test the hypothesis that bacterial extracts can prevent the development of persistent wheezing in children aged 6 to 18 months at high risk for the development of asthma (clinicaltrials.gov NCT02148796).

Monoclonal antibodies against IgE (omalizumab) have been widely used for the treatment of asthma, and have been shown to decrease the incidence of acute asthma exacerbations, especially among individuals with a history of recurrent exacerbations (15). In children, administration of omalizumab has been associated with a significant decrease of markers of airway inflammation such as exhaled nitric oxide (16). These results have suggested the possibility that omalizumab may play a role in the progression from early allergic sensitization to the development of asthma by blocking the effects of allergic inflammation on lung remodeling during the preschool years. A clinical trial using omalizumab in preschool children with early allergic sensitization is also ongoing in the United States (clinicaltrials.gov NCT02570984).

In conclusion, advances in our understanding of the early origins of asthma have opened novel and promising strategies for the primary and secondary prevention of the disease.

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#6. New CF Therapies: Is this the Light at the End of the Tunnel?

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CF is a life-shortening hereditary disease with relentless pulmonary infection and malabsorption as the main symptoms. The disease is caused by mutations in the *CFTR* gene coding for the CFTR protein that mainly functions as an epithelial chloride channel. The ultimate therapy for CF would be gene therapy, replacing the mutated CFTR with normal CFTR copies. The large UK gene transfer study did not show clinical efficacy, therefore, most efforts are directed towards development of mutation specific therapies. The current CF drug development landscape has expanded to include therapies that enhance CFTR protein function by either restoring wild-type CFTR expression or increasing (modulating) the function of mutant CFTR proteins in cells. Grouping *CFTR* mutations into classes according to the molecular mechanism by which the mutation disrupts normal protein synthesis or function is useful, especially in view of developing CFTR repair therapies. *CFTR* mutations are generally divided into 5 classes: Class I mutations are nonsense mutations resulting in incomplete mRNA transcripts and protein production. For this class of mutations, molecules causing 'read-through' agents allow ribosomes to continue translation through the premature stop codon to produce full-length CFTR protein resulting in increased normal CFTR copies. Recently a large, international, double blind placebo controlled study with ataluren failed to show clinical efficacy. Other drugs are in the process of development. Class II mutations cause defected processing causing a production of a protein which is incorrectly processed and fails to reach the cell surface. For this class of mutations, 'correctors' facilitate Class II mutant CFTR protein processing and increase the quantity of CFTR protein at the plasma membrane. Orkambi shows modest

improvement in FEV1, reduced pulmonary exacerbations in patients homozygous for the F508del mutation. Class III are gating mutations in which altered protein at the membrane surface has reduced ability to support anion transit. Ivacaftor is a novel CFTR potentiator that increases chloride transport by potentiating the channel open probability of the CFTR protein. Ivacaftor has shown improved lung function, weight, and patient-reported respiratory symptoms, reduced frequency of pulmonary exacerbations, and reduced sweat chloride levels to below the diagnostic threshold. In Class IV, CFTR reaches the cell surface, however with reduced function, and Class V is characterized by a reduced amount of normally functional CFTR. Ivacaftor may increase the function of Class IV and V mutant CFTR proteins residing at the plasma membrane. Thus, CFTR repair therapies that are mutation class-specific can be positioned as an advanced type of individualized personalized treatment, geared for correcting the basic molecular defect in a specific CF individual.

#7. Preventing Food Allergy: Early Consumption or Avoidance

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Food allergy has been considered as the second wave in the increase in allergic disorders around the world following the first wave of increase in asthma and allergic rhinitis (1). It is well known that the prevalence of allergic conditions would follow the economic development in many countries or regions. In the developed countries, one in three children suffers from at least one allergic disorder and these include food allergy, eczema, allergic rhinitis and asthma. Food allergy is very often the first allergic disease affecting children. It has been divided into two main categories – the IgE mediated and non-IgE mediated food allergies. The exact etiologies are not known. It is interesting to note that the natural history of different types of food allergies vary dramatically. Egg and milk allergy in children tend to remit while peanut allergy tends to stay with the subjects for a long time. Exposure to microbes early on in life may affect maturation of the immune system resulting in protection against allergies and may include the protection against food allergies. The common allergens resulting in food allergies in developed countries include egg, milk, fish, wheat, peanuts and tree nuts (2). Anaphylaxis is the most severe form of food allergy and can be fatal. There have been several clinical trials investigating early exposure as the primary preventive strategies with some success in high risk and general populations. The LEAP study clearly demonstrated that early exposure to peanuts in high risk infants dramatically reduced the subsequent risk of peanut allergy (3). The PETIT study demonstrated that the combination of meticulous management of eczema and a step-wise increase in the consumption of cooked eggs could reduce egg allergy by one year of age (4). The EAT study attempted to apply the same strategy in the general population but it was rather difficult to introduce so many foods in young infants such that the results in the intention-to-treat analyses

were negative (5). With the increasing use of genetic engineering techniques, one may be able to genetically modify foods to reduce their antigenicity but such techniques may also possibly generate new food allergens (6). Further research is needed to develop primary preventive strategies on a population level in order to maximize food safety in order to reduce the morbidity and mortality related to food allergies.

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#8. Interstitial Lung Disease in Childhood: Current Status of Diagnosis and Management

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Childhood interstitial lung diseases (ILD), also called "diffuse parenchymal lung diseases" (DPLD) comprise more than 200 different entities. For a pediatric pneumologist, it is very useful to have a clear and comprehensive classification system in mind. This helps to keep the various entities in order and to accommodate rapidly novel entities.

Disorders which preferentially manifest in infancy and childhood (groups labeled "A") need to be recognized every now and then, and the pediatric pneumologist is expert for this. For the developmental disorders (A1), novel molecular entities such as mesenchyme homeobox 2 (MEOX2), T-box transcription factor 4 (TBX4) mutations, have been described in addition to filamin A and FOXF1 deficiency. Progress has been made in the group of children with chronic tachypnea of infancy (A3), allowing differentiation in usual and aberrant cases. Interstitial lung diseases related to the alveolar surfactant region (A4) will be presented with respect to ABCA3, SFPTC and MARS.

Disorders manifesting at all ages (groups labeled "B") include Hermansky Pudlak syndrome 2, mutations in stimulator of interferon genes (STING), integrin $\alpha 3$ mutations and COPA mutations. Several of such entities are more frequent in adulthood.

A brief algorithm how to use this classification and the European management chILD platform where further help is available, are demonstrated.

#9. Personalized Medicine for Lung Disease

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Cystic fibrosis (CF) is a major life-shortening genetic disease leading to severe respiratory symptoms caused by mutations in CF transmembrane conductance regulator (CFTR), a chloride/bicarbonate channel expressed at the apical membrane of epithelial cells. Absence of functional CFTR from the surface of respiratory cells reduces mucociliary clearance, promoting airways obstruction, chronic infections and ultimately lung failure [1]. To date ~2,000 CFTR mutations have been reported [2] but one single mutation – F508del – occurring in ~85% of CF patients worldwide, is associated with intracellular CFTR protein retention and a severe clinical phenotype.

Major clinical advances in treating CF symptoms (with mucolytics, antibiotics, etc.) have significantly increased survival beyond the second decade (~25 years in Europe). However, to further increase CF patients' life expectancy, CF needs to be treated beyond its symptoms i.e., through treatments addressing the basic defect associated with each CFTR gene mutation [3,4]. One new drug, potentiator VX-770 (ivacaftor/Kalydeco) has reached the clinical setting but only for ~5% of all CF patients, i.e., those bearing G551D and 8 other mutations causing a similar defect in the channel [5]. More recently, a new drug (Orkambi), which combines corrector VX-809 (lumacaftor) rescuing F508del-CFTR to the cell surface with potentiator ivacaftor, went into the clinic, following proven efficacy, albeit modest, in a phase III clinical trial for F508del/ F508del patients [6].

As these therapies correcting defective CFTR become available, we should quickly pre-assess how other CFTR mutations respond to such new drugs. This is the way forward to extend them to more CF patients, namely to those with ultra-rare ("orphan") mutations in an

effective and expedite way. Indeed, for such mutations, "classical" clinical trials are not possible due to low numbers of patients and their geographic dispersion. It is thus crucial to use the above novel methods to pre-assess directly on patient's cells/tissues how each individual responds to these novel drugs. These can include a swelling assay in intestinal organoids [7] or measurement of CFTR Cl^- currents in polarized primary cultures of nasal cells [8]. Such pre-assessment may become a standard basis for a drug clinical use in a precision medicine approach.

Work in the author's lab is supported by strategic grant PEst-OE/BIA/UI4046/2011 centre grant (to BiolsI) from FCT/MCTES, Portugal; and by research grants (to MDA): "INOVCF" from CF Trust, UK (SRC Award No. 003), Gilead GÉNESE (Ref PGG/008/2015) and AMARAL15XX0, AMARAL15XX1, AMARAL16I0 from CFF-Cystic Fibrosis Foundation, USA.

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#10. Novel Treatments for Acute Asthma

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Asthma is characterized by variable symptoms, usually incorporating periods of relatively stable disease interspersed with acute episodes. The predominant aim of asthma management is to minimize these exacerbations, or "lung attacks" as they can be lethal, impair quality of life, and are associated with accelerated decline in lung function. Although maintenance inhaled steroids can control disease and prevent exacerbations in the majority of children, adherence to maintenance therapy is poor (National Review of Asthma Deaths, UK). Children do not want to / do not remember to take medicines if they are feeling well, and so exacerbations on a background of poor adherence can be even more severe. Before discussing novel treatments for acute asthma, it is therefore important to emphasize the need to optimize maintenance therapies for all patients and to assure good quality patient and parent education so that optimal adherence is achieved and asthma attacks are prevented.

Diagnosis of Acute Asthma

Asthma attacks may be very variable in both their presentation and response to treatment. Although not novel, the importance of ensuring

an accurate diagnosis of acute wheezing and an asthma attack is essential. One of the known factors for a "high risk" patient with acute asthma is the presence of previous severe asthma and / or psychological factors and non-adherence to maintenance therapy.¹ But, those with difficult asthma may also have a significant overlay of dysfunctional breathing and this will become worse during periods of worsening control and more symptoms.² An important feature is to question a diagnosis of acute severe asthma in the presence of normoxia. A severe asthma attack in the absence of hypoxia may not be an asthma attack at all. Acute asthma severity scores that can be applied at the bedside and incorporate simple clinical parameters such as respiratory rate, use of accessory muscles, heart rate and oxygen saturations are reliable and reproducible between observers and should be used both to make an initial assessment of the severity of the acute episode, but also to assess response to therapy.³

Administration of Bronchodilators: Route and Device

Rapid initiation of bronchodilator therapy is a key component of managing acute asthma.¹ However, the route of administration and use of the most appropriate device is also critical. If children are not hypoxic at presentation, the most effective and cost saving mode of delivery is without a doubt the use of a metered dose inhaler with valve holding chamber (spacer). If nebulizers are used initially to administer bronchodilators, prompt switching to metered dose inhaler (MDI) with a spacer is essential. Thirty-two percent of children hospitalized with acute asthma were not switched to MDI and spacer, and this was associated with significantly less being issued with asthma action plans and education at discharge.⁴ Child and parental education, checking inhaler technique and administration of asthma action plans for each child at discharge is essential as the only way to prevent future attacks, and are as important in the care pathway for an acute attack as the treatment at presentation.

Short-acting beta2 agonists (SABA) are the first choice bronchodilators and are often administered with the anticholinergic ipratropium bromide. However, if additional bronchodilator therapy is required, it remains uncertain whether this should be the addition of inhaled magnesium sulphate (MgSO₄), intravenous MgSO₄, or a switch to intravenous SABA. Current evidence from pediatric trials does not allow firm conclusions to be drawn about the added benefit of either intravenous MgSO₄⁵ or nebulized MgSO₄⁶ for acute asthma. However, despite this lack of evidence both are widely used as part of the management of acute asthma in children.¹

Failure of Response to Therapy

It is important to consider why children may not respond to bronchodilators during an acute asthma attack. A prospective multi-center study that included children aged 1–17 years presenting with acute asthma has investigated reasons for failed emergency department management (oral steroids and prompt administration of bronchodilators) and requirement for hospitalization or prolonged emergency assessment unit stay (>8 hours). 165/965 children (17%) failed emergency department management. Interestingly, in addition to exacerbation severity (oxygen saturation <92%), detection of virus on nasopharyngeal secretions during the acute episode was most strongly associated with failed therapy, and contrary to expectation, young age was not associated with failed management.⁷

A particular phenotype for which we are yet to find effective therapies for exacerbations is wheezing in preschool children. Children under 5 years account for the majority (approx. 75%) of hospital admissions for acute wheezing in the pediatric population, and this figure has remained unchanged in the UK for over a decade. However, we still have little to offer for either prevention of attacks, or the treatment of the acute attack in these patients. The most likely reason for failed response to therapy in this age group is that most, if not all, acute attacks are caused by respiratory infection, most commonly viruses⁷ which are known to be associated with steroid resistance.⁸ Therapies that have recently been investigated specifically for the preschool child with acute wheezing include the use of leukotriene receptor antagonists (LTRA). A large clinical trial has shown that there was no significant reduction in unscheduled healthcare visits between children that received montelukast or placebo when the treatment was initiated at home by parents.⁹ However, as with all aspects of asthma management, disease heterogeneity must be considered, and there was a sub-group, those with the ALOX5 promoter genotype, who did respond to montelukast during an acute attack, and reduced oral steroids were prescribed for the montelukast group, but that was a secondary outcome.⁹ LTRA cannot therefore be dismissed for the management of acute preschool wheezing attacks, however they will only be effective in a proportion of children.

As it has become increasingly apparent, a similar number of acute wheezing attacks in preschool children may be caused by bacterial infection, as viral infections, the use of antibiotics to treat acute preschool wheeze has been investigated. However, the choice of antibiotic (azithromycin) that was used in the two large recent clinical trials that have been undertaken, suggests the mode of action was predominantly anti-inflammatory, not anti-bacterial. The data from the trials have been summarized elsewhere,¹⁰ but it is accepted that currently the data are too preliminary to promote the routine use of a macrolide for the management of acute preschool wheeze attacks. The data showed development of macrolide-resistant organisms, very narrow patient populations were included, not necessarily reflective of those in whom effective therapies are needed, and there was no impact in either trial on prevention of progression to a severe attack requiring hospitalization, unscheduled healthcare visits, or on use of oral steroids.

Summary

The most important aspect of management of acute asthma in any child is to review regularly and assess response to therapy. Severe attacks should be treated with early use of intravenous bronchodilators, although the added benefit of MgSO₄ remains uncertain. Finally, if there is further deterioration, then the institution of non-invasive ventilation, or high flow oxygen via nasal cannula are options that can be tried to avoid the need for ventilation, but the evidence for their efficacy is very limited.

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#11. Immunomodulatory Therapy by Macrolides: More than Killing Bugs

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

The effects of macrolides in patients with chronic inflammatory airway disease are independent of antimicrobial properties and have also been demonstrated in macrolides that are devoid of antimicrobial activity. Immunomodulation, which differs from immunosuppression or anti-inflammation, is a nonlinear resetting of the immune response by modifying or regulating one or more function of the immune system. We use the term immunomodulation to describe the down regulation of a hyperimmunity or hyperinflammation without impairing the normal immune or inflammatory response to defend against infection. Macrolides accumulate within cells, suggesting that they may associate with receptors or carriers responsible for the regulation of immune cell activities.

Macrolides initially decrease, then increase, and have finally a sustained suppression of cytokine secretions from normal human bronchial epithelial cells through inhibition and activation of extracellular signal-regulated kinases (ERK) and then reversibly retard cell proliferation probably through ERK. Consistent with this, macrolide antibiotics possibly reduce mucin production as well as neutrophil migration by interfering with ERK signal transduction.

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#12. Current Status of Pediatric Lung Transplantation

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Word count: 1544 (excluding title page and references)

Keywords: lung transplantation, immunosuppression, bronchiolitis obliterans,

Introduction

This review summarizes our current state of knowledge on pediatric lung transplantation, with particular emphasis on information that is useful to referring pediatricians.

The availability of lung transplantation has improved in recent times. It is assumed that most – though not all – lung transplant procedures performed worldwide are reported to the data Registry of the International Society of Heart and Lung Transplantation (ISHLT). Currently almost 4000 LTx procedures are reported in adult recipients every year, which represents a two-fold increase in activity over a decade¹. In contrast, only 100 procedures are performed each year in children. The commonest indications in childhood are cystic fibrosis, idiopathic pulmonary arterial hypertension (IPAH) and obliterative bronchiolitis².

Long-term survival of lung transplant patients remains disappointing with five-year survival approximately 50%. Outcomes following lung transplantation are worse than for any other solid-organ transplant with the exception of small bowel transplantation, due to the lung having a) a large surface area exposed to the external environment, predisposing to opportunistic infection; b) a high-blood flow with increased exposure to circulating immune cells; and c) large numbers of antigen-presenting cells and numerous aggregates of lymphoid tissue. These factors all predispose to graft rejection. In early post-transplantation, the greatest risks are graft failure and overwhelming infection, whereas the commonest cause of poor long-term outcome is chronic graft dysfunction manifesting as bronchiolitis obliterans syndrome (BOS)^{1,2}.

Which Children Should Be Referred?

Lung transplantation is indicated for patients with end-stage lung disease when – despite maximal medical therapy – the quality of life is impaired by severe respiratory symptoms and life expectancy is limited. Waiting times are longer for small adults and children and especially those with blood groups O or B. Many children who could potentially benefit from transplantation will die whilst waiting for donor organs. It is therefore important for the referring center to discuss possible transplantation early in the course of the child's deterioration, and to refer early to the transplant center so the child can be assessed many months before listing is required. The assessment process involves a careful review of the child's history and physiological status, and also extensive discussion with the child and family regarding process, risks, and long-term complications and obligations. Early referral will allow the transplant center to arrange additional investigations if necessary, and allow the child and family to make a truly informed decision.

Contraindications to transplantation vary between centers. In our center and most others, absolute contraindications are chronic infection with *Mycobacterium abscessus abscessus* or *Burkholderia cenocepacia*; recent malignancy; major dysfunction of other organs (e.g. severe cardiac, renal or hepatic disease); active viral hepatitis; severe acute illness; untreatable psychiatric or psychological conditions interfering with adherence to medical advice; and full invasive ventilator-dependent respiratory failure. Many other issues such as

(but not limited to) poor family support; long-term high dose corticosteroid therapy; poor nutritional status or severe obesity; or thoracic deformity such as scoliosis will be considered relative contraindications.

Most children are now listed for double (also termed bilateral) lung transplantation. Single lung transplantation is not recommended for suppurative lung disease such as CF, and is challenging in children with pulmonary hypertension. Heart-lung transplantation is now rare due to donor shortage^{1,2}, but may be the only option for a child with severe cardiac disease and secondary pulmonary hypertension.

Timing of Listing, and Organ Allocation

The ideal time to perform lung transplantation is as late as possible in a child's disease, but whilst they are still strong enough to survive the procedure without unacceptable risk. In practice, the need for cadaveric donors makes exact timing impossible, and different centers have adopted different approaches to this dilemma. Our own center policy, shared by most large centers in Europe³, is to list the child when they have a predicted life expectancy without transplantation of two years or less. Once the child is on the list, there is a further challenge of organ allocation. A simple wait list seniority system – where the child waiting the longest gets the donor organ – sounds appealingly fair. Unfortunately in practice such a system can lead to children being listed and subsequently transplanted earlier than would be ideal^{4,5}. Many countries have followed the lead of North America in employing scoring systems where adults are allocated donor lungs according to their predicted survival benefit. These models are based on *pre* and *post* transplantation survival data from large numbers of adults with severe lung disease⁶. Such data are not available for children, and the use of allocation scoring in pediatrics is still limited⁷. Most pediatric centers will employ a similar but informal approach of identifying the sickest children on their lists and prioritizing them for organs.

Optimizing a Child for Transplantation

Whilst listed for transplantation, the child remains the responsibility of the referring center, but the transplant center may have some management recommendations. In general, the transplant center will ask the referring center to maintain the child's cardiorespiratory fitness, nutrition, and bone mineral density as best possible. Centers have widely differing policies on use of 3rd or 4th line antimicrobial agents whilst a child is listed, balancing the need to reduce infective load against the risk of developing further antimicrobial resistance. Supplemental oxygen and non-invasive ventilation are often helpful, and tracheostomy ventilation – provided the child remains ambulant – is only considered a relative contraindication by most centers. Bridging to transplantation via invasive ventilation or ECMO is more controversial. There is strong evidence that adults and children who are invasively ventilated in intensive care have poor post-transplant outcomes¹, whilst reports of excellent outcome post-ECMO bridging are largely confined to adults who remain ambulatory whilst on ECMO⁸.

Peri- and Post-Transplant Care

Matching of organ to recipient is based upon body size and ABO group. Full HLA matching is not practical, but antibody testing for anti-HLA antibodies is performed at time of listing, and identifies individuals for whom further compatibility testing at time of organ offer is required. Minor to moderate surgical trimming may allow donor lungs from an adult to be transplanted into a child with acceptable outcomes. Bilateral sequential lung transplantation is usually performed via a clamshell incision with a sternotomy, although bilateral thoracotomies without sternotomy can be used. Cardiac bypass is not mandatory in adult patients who are hemodynamically stable, but commonly employed in children. Either way, the operation requires mobilization of a large surgical, anesthetic and intensive care team, lasts several hours and usually happens in the middle of the night, due to timing of donation and need for short organ ischemia time.

Mobilization and airway clearance are crucial in the early post-operative period. In our practice, most children will spend three to four weeks in hospital following lung transplantation, but this can be shorter if there is low risk of post-operative infection.

Substantial immunosuppression should be instituted immediately prior to the operation. More than 50% of pediatric lung transplant centers now use induction therapy with either polyclonal (anti-thymocyte globulin) or monoclonal antibodies (such as basilixumab) to induce immunosuppression at the time of transplant². Immunosuppression then continues with three agents:

1. A calcineurin inhibitor (CNI) such as tacrolimus or cyclosporine which downregulates cell-mediated immunity
2. A cell-cycle inhibitor such as mycophenolate mofetil (MMF) or azathioprine with a more general immunosuppressive action including against antibody-mediated reactions
3. Corticosteroids, which also have a general immunosuppressive effect.

Each of the immunosuppressive agents also has its own spectrum of side-effects. Tacrolimus has reduced the incidence of rejection but it is profoundly nephrotoxic, and has neurological and diabetogenic side-effects. The pharmacokinetics of tacrolimus are complicated and require careful monitoring with frequent trough levels. Many drugs with effects on the cytochrome P450 system can profoundly influence tacrolimus blood levels.

Rejection was a common cause of death in the early years of lung transplantation. With the advent of more effective immunosuppression, severe rejection has become less common, and is normally treated effectively with high-dose corticosteroids. A drop in spirometry may be the earliest indicator of rejection. Children are encouraged to perform and record spirometry each day with a home spirometer and report an unexplained drop of 10% or more.

Obliterative bronchiolitis is seen in many children on lung biopsy or autopsy in the years following transplant and is the commonest cause of post-transplant death long-term. The clinical manifestation of this pathology is termed BOS, which is defined and graded as an irreversible fall in FEV₁. It is assumed that BOS results from a

combination of lung injury and chronic immune rejection of the graft. Our understanding of the origin of BOS has developed in the last decade, and treatment of gastroesophageal reflux by fundoplication or neutrophilic inflammation by azithromycin appears to reduce some forms of BOS incidence⁹. In addition, many centers including our own are now much more aggressive with treatment of bacterial airway infection to reduce endobronchial inflammation. These interventions have thus far made only minor improvements to international survival figures, but individual centers following such policies are reporting favorable results.

Conclusion

Lung transplantation should no longer be considered experimental, but is now an accepted treatment for end-stage lung disease in children. Outcomes are less good than for other solid organ transplants, and management is complex. A better understanding of the development of BOS is the key to improving outcomes further.

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#13. Is there a Way to Prevent Adult COPD during Childhood? A Summary

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A major change has occurred lately in our understanding of the natural history and risk factors for COPD. For decades, COPD was considered a disease that started almost exclusively in the sixth and seventh decade of life, and which was confined to individuals who were particularly susceptible to cigarette smoking or exposed to biomass smoke in poor countries. These noxious factors are known to accelerate the normal rate of decline with age (approximately 25 ml/year) of parameters of lung function such as FEV1 and, as a consequence, the affected patients eventually reach a degree of airflow limitation that is associated with dyspnea and hypoxemia. The corollary of this conceptual framework was that all patients with COPD would show progressive deterioration in lung function with aging. Recent longitudinal studies of individuals with COPD strongly challenge this framework. It was first observed that only approximately half of all patients with COPD showed excessive lung function decline when followed prospectively (1). Furthermore, among subjects with COPD, two distinct groups were identified(2): one group showed the "classical" pattern of excessive lung function decline associated with cigarette smoking and these subjects had reached an FEV1 plateau in early adult life that was similar to that of subjects without lung disease. A second group showed no excessive FEV1 decline with aging, but was shown to have reached an FEV1 plateau that was significantly reduced with respect to subjects without lung disease and to those with "classical" COPD. These results suggested the existence of a new pathway for the development of COPD, one that was characterized by insufficient growth of airway function during childhood as a major predisposing factor. Prevention of risk factors that may hamper the development of airway function, starting *in utero*, thus becomes a major new avenue for the prevention of COPD, the third cause of death among adults in developed countries.

Thorough descriptions of these risk factors have been recently published (3, 4). In summary, six major determinants of lung function growth have been identified. A large number of genetic variants that influence lung function in older children and adults have been identified by use of genome wide association studies (5). Unfortunately, all these variants have small effects on the outcome and therefore, it is unclear if they will be useful in a future preventive strategy. Prematurity, and especially bronchopulmonary dysplasia (BPD), induce significant deficits in lung function that persist into adult life (6). Prevention of BPD will not only decrease morbidity and mortality during childhood but also extend its beneficial effects to the

long term well-being of adults. Exposure to tobacco smoke *in utero* is also associated with subsequent deficits in airway function that persist into adult life (7). Deficits in maternal micronutrient such as vitamin A during pregnancy and early life have also been associated with deficits in lung function growth (8). Lower respiratory illnesses in early life, and especially pneumonia before age 3, are associated with persistent deficits of lung function (9), and these deficits are in part related to pre-existing lung function abnormalities (10) and to the direct damaging effects on the airways triggered by the infectious agent causing the acute illness(11). Asthma, especially when starting during the first years of life, is often associated with airway remodeling and chronic airflow limitation, and many patients with COPD have a history of asthma starting during childhood (12). Finally air pollution has been unequivocally shown to induce deficits in lung function growth: a recent study of the effects of improvements in air quality in California demonstrated significant increases in lung function in children living in the areas in which efforts to improve air quality were the most successful (13).

In conclusion, prevention of bronchopulmonary dysplasia, early life pneumonia, asthma, and maternal smoking during pregnancy; appropriate supplementation with micronutrients during pregnancy; and improvements in air quality are all attainable goals that may markedly decrease the prevalence of and morbidity and mortality associated with COPD in adult life.

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How to cite this article: Plenary Sessions. *Pediatric Pulmonology.* 2017;52:S17-S31.
<https://doi.org/10.1002/ppul.23728>

ABSTRACT

Topic Sessions

The Impact of the Environment on Respiratory Outcome

#1. Indoor Pollution in LMICs

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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 (NO₂) is an important component for both indoor and outdoor air pollution. Indoor sources of NO₂ include gas-fueled cookers, fires and water heaters; paraffin heaters also emit NO₂, and small amounts occur in tobacco smoke. Research suggests NO₂ contributes to respiratory symptoms in children, particularly asthmatic children. Other studies suggested a 20% increased risk of LRTI in children exposed to long-term NO₂. Yet, exposure to NO₂ 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

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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.

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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

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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 (FEV_{1,2} 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

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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 be 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?

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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

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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

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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

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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?

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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

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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

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

signaling. In a trial with the IL-4 receptor-a 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

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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.

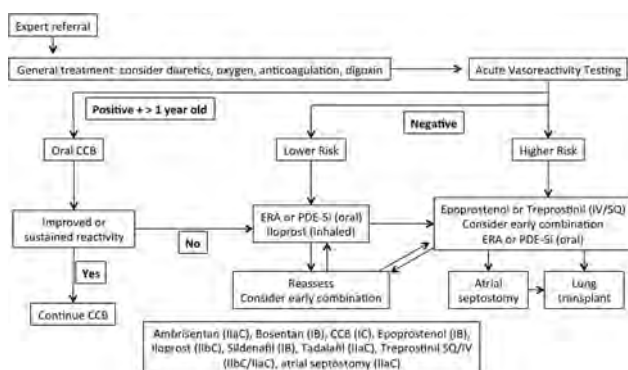
Prognosis

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

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Word count: 1516 (excluding title page and References)

Keywords: Congenital heart disease, Lung disease, children

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

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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 (AIPHI)

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

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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 transplantation¹⁻³.

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 controversial⁴⁻⁶. 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

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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 amoxicillin-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

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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

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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 neurokinin A and Substance P [7]. These mediators are involved in the pathogenesis of neurogenic inflammation and in bronchomotor tone dis-regulation [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 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

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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

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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

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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?

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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)

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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

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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-κB). 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 imparted 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

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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

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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

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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

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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

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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

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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

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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 pneumoniae* 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

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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

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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 reinstatement 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 cmH_2O) as this has been shown to be more effective than lower pressures (4 to 6 cmH_2O).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 reinstatement 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 $\text{PaO}_2 > 6.6 \text{ kPa}$) on $\text{FiO}_2 < 0.6$,
- rising pCO_2 of $> 8\text{-}9$ (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

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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

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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

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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?

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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

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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

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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

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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

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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

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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.

How to cite this article: Abstracts from CIPP XVI Meeting. *Pediatric Pulmonology*. 2017;52:S32-S93.
<https://doi.org/10.1002/ppul.23729>

ABSTRACT

Young Investigator's Oral Communications

#N12 – Clinical Profile and Outcome of Pediatric Sarcoidosis

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Objectives

Pediatric sarcoidosis is a rare disease with multisystem involvement. However, there is limited information in the published literature on childhood disease.

Methods

A chart review of children with diagnosis of sarcoidosis between 2006 and 2016 was performed. Diagnosis of sarcoidosis was based on clinical phenotype with documentation of non-caseating granuloma from body tissues, increased angiotensin converting enzyme (ACE) and increased calcium creatinine ratio in spot urine examination. All children were evaluated clinically, along with hematological investigations, liver and kidney function tests, and spirometry (in older children). The cases were followed up every 2–3 months for the course of the disease.

Results

A total of 18 children (mean age 108 months + 29.61) were diagnosed with sarcoidosis over 10 years. Clinical features at time of diagnosis with decreasing frequency were fever (83%), uveitis (50%), difficulty in breathing (44%), hepatosplenomegaly, weight loss, arthritis, and peripheral adenopathy. Imaging findings included: hilar adenopathy (94%), abdominal nodes (50%) and pulmonary infiltrates (44%). All children were treated with steroids (range 6–12 months), while weekly low-dose oral methotrexate (MTX) was the commonest second line therapy. Mean duration of follow up was 3.12 ± 0.88 years. All patients showed significant improvement as assessed by resolution of clinical symptoms, spirometry parameters, ESR and serum ACE levels. None of the patients had residual pulmonary disease. Two patients who had uveitis and complicated cataract did not show reversal of eye problems.

Conclusions

Pediatric sarcoidosis is a rare disease. Children with sarcoidosis respond well to systemic steroids and low-dose methotrexate. Pulmonary involvement of pediatric sarcoidosis has a good prognosis. Delayed diagnosis and ocular involvement have poor outcome.

Key words: Hilar lymphadenopathy, epithelioid granuloma, non-caseating, pediatric sarcoidosis, serum ACE level.

#C8 – TIPE2 negatively regulates MP-triggered immune response via the MAPK signaling pathway

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Objective

Recent studies have shown that Toll-like receptor (TLR) signaling pathways play an important role in inflammation induced by *Mycoplasma pneumoniae* (MP). Tumor necrosis factor- α -induced protein 8-like 2 (TIPE2) is a negative regulator of TLR, and could prevent hyper-responsiveness and maintain immune homeostasis. However, the effect and underlying mechanisms of TIPE2 on MP infection remain unclear. This study will investigate the influence of MP infection on the expression of TIPE2, and explore the role and underlying mechanisms of TIPE2 in human defense against MP infection.

Methods

Peripheral blood mononuclear cells were collected from 130 children with *Mycoplasma pneumoniae* pneumonia (MPP), which were divided into a general MPP group and a Refractory *Mycoplasma pneumoniae* pneumonia (RMPP) group according to clinical manifestation, and in which the expression of TIPE2 was detected. The levels of TIPE2 were also detected in macrophages *in vitro* after MP infection. In addition, we performed TIPE2 expression interference in macrophages, studied the production of cytokines and detected the MAPK signal pathway after MP infection.

Results

A significant decrease in TIPE2 mRNA was detected in peripheral blood mononuclear cells (PBMCs) from 130 cases of children infected with MP compared to that in PBMCs from control healthy children, which was correlated with the degree of severity of MPP. *In vitro*, the expression of TIPE2 was down-regulated after MP infection. This implied that TIPE2 might play a critical role in anti-MP immunity. Therefore, THP-1 cells were infected after silencing TIPE2, after which the production of TNF- α , IL-6 and IL-1 β was found to be up-regulated, and the MAPK signal pathway activated.

Conclusions

Taken together, our results have identified TIPE2 as having an important negative role for MP-triggered inflammatory cytokine production via the MAPK signaling pathway. These findings provide insights into the novel function of TIPE2 in anti-MP immunity and its related clinical significance.

#D16 – Correlation between Nasal Resistance and Pulmonary Arterial Pressure in Mouth Breathing Children and Adolescents.

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Objectives

To evaluate the correlation between nasal resistance and pulmonary arterial pressure in chronic mouth breathing (MB) children and adolescents aged 2 to 12 years old with adenotonsillar hypertrophy (ATH) and allergic rhinitis (AR) through rhinomanometry measurements and Doppler echocardiography.

Methods

This single-blinded, case-control study was approved by the Federal University of Minas Gerais (UFMG) ethics committee. Fifty-four patients with ATH and adenoidectomy and/or tonsillectomy indication (31 male, mean age 7.04 ± 2.24 , and mean body mass index (BMI) 16.57 ± 2.63), twenty-four patients with exclusive and persistent AR (14 male, mean age 7.42 ± 2.05 and mean BMI 16.08 ± 2.18), and twenty-five controls (with similar age, sex and body mass index distribution with the study groups) were selected. They underwent Doppler echocardiography in order to estimate systolic pulmonary arterial pressure (SPAP) through tricuspid regurgitation in a blinded manner. We also measured total nasal inspiratory flow and resistance (NIF) at a transnasal pressure of 150 Pascal (Pa) during quiet breathing with a closed mouth by using active anterior rhinomanometry. Correlations between NIF and SPAP were obtained from Spearman's method.

Results

Nasal patency was normal in the control group, while the majority of the MB patients (ATH – 59.1% and AR – 70.7%) presented a severe/very severe nasal obstruction. The ratio between the total measured flow and the total expected flow for height was significantly higher in controls than in the ATH and AR groups, without significant difference between the study groups (controls – $91.4\% \pm 14.5\%$; ATH – $48.2\% \pm 17.3\%$; AR – $45.5\% \pm 14.9\%$). The mean SPAP was significantly higher in MB groups than in the control group (SPAP – 25.61 ± 3.38 [ATH] and 25.33 ± 2.06 [AR] versus 21.64 ± 3.87 mmHg, $P < 0.005$). SPAP also presented a negative association with nasal flow (rho of Spearman = -0.34 ; $p < 0.001$).

Conclusions

MB children and adolescents with either ATH or AR showed evidence of increased pulmonary arterial pressure by Doppler echocardiography while the increased SPAP was correlated with increased nasal resistance.

Keywords: Children. Echocardiography, Doppler. Pulmonary Hypertension. Mouth Breathing. Rhinitis.

#E81 – Bronchopulmonary Dysplasia: An Assessment during Adolescence.

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Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung condition due to prematurity. Follow-up studies show that these children have an obstructive lung function. However, no correlations were found between lung function and radiological findings on computed tomography (CT). A new method in pulmonology is functional respiratory imaging (FRI), which is a technique to calculate flow patterns, lung volumes and resistances, to visualize blood vessels and emphysema. The aim of this study was to assess the lung damage of adolescents, diagnosed with BPD during infancy. This was achieved by comparison between FRI, CT findings and lung function tests.

Methods

35 children were included from an existing cohort of premature neonates. They were assessed by history, clinical examination, lung function tests and low-dose CT-thorax, which was evaluated by a scoring system (Aukland 2009). The scans were used to calculate the FRI parameters.

Results

In the present study, at adolescence (15 ± 0.9 years, 16M/19F), the total cohort was divided into three groups: 14 no BPD, 11 mild and 10 moderate-to-severe BPD.

BPD correlated with a more obstructive lung function; lower volume exhaled during the first second ($p = 0.03$), lower Tiffeneau index ($p = 0.03$), higher residual volume (RV) ($p = 0.04$) and lower diffusion capacity ($p = 0.03$). BPD correlated with more emphysema on CT-scan ($p = 0.01$). More severe BPD correlated with increased volume of the lobes (iVlobe) ($p = 0.01$) and more air trapping at functional residual capacity (FRC) ($p = 0.003$) at FRI.

Numerous significant correlations were found between lung function tests and FRI: negative correlations between airway resistance (siRaw) at total lung capacity (TLC) and forced expiratory volume during the first second (FEV1), Tiffeneau index, mid-expiratory flow, peak expiration flow and diffusion capacity. Conversely, these correlated positively with airway volume (siVaw) at TLC.

The CT score showed some correlations with lung function, mostly with vital capacity, specific airway resistance and diffusion.

Conclusion

The severity of BPD correlates with a more obstructive lung function, emphysema, air trapping and lobar volume at FRC. Previously, little was known regarding correlations between lung function and CT in children with a history of BPD. While this study did find some

correlations, FRI shows many more. It appears that iVlobe and air trapping at FRC and siRaw / siVaw at TLC matter the most in lung damage. These findings could not have been determined with classical lung function tests or CT alone, making FRI of great added value in the assessment of lung damage.

#F105 – Respiratory Viruses in Healthy Infants and Infants with Cystic Fibrosis. A Prospective Cohort study.

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Background

Acute respiratory tract infections in children with Cystic Fibrosis (CF) are known to cause exacerbation of disease; viral infections are reported as a frequent underlying cause. The role of virus infections during infancy is however not known, although early infancy is a crucial period of CF disease modification. The newborn screening for CF allows early diagnosis and opens new opportunities in preventative and therapeutic approaches. Before this can be done, a better understanding of respiratory health and viral colonization during infancy is needed. We prospectively assessed symptomatic and asymptomatic viral colonization in the first year of life in infants with CF and contemporary matched controls.

Methods

We included 31 infants with CF from the Swiss Cystic Fibrosis Infant Lung Development (SCILD) Cohort and 32 unselected, healthy infants from the Basel Bern Infant Lung Development (BILD) Cohort in this prospective longitudinal study within the first year of life. In weekly telephone interviews, respiratory symptoms were recorded. Biweekly nasal swabs were analyzed for 12 different viruses with Multiplex PCR (CF = 576, controls = 718).

Results

While viral colonization in general did not differ between the two groups (mean 41% vs. 44%), virus positive swabs were less often accompanied by respiratory symptoms in infants with CF (37% vs. 50%; $p = 0.022$). This finding was pronounced for Human Rhinovirus infections (6% vs. 10%; $p = 0.009$).

Conclusion

Viral colonization was not more frequent in infants with CF and respiratory symptoms during virus infection occurred even less often in infants with CF. While we can only speculate about underlying reasons, it is likely an interplay of different factors, such as local epithelial properties, immunological mechanisms and early treatment, that contribute to our findings. Further studies investigating the

interaction of viruses, bacteria, immune responses and genetics are thus needed, to help better understand respiratory health in infants with CF.

#F116 – Functional Magnetic Resonance Imaging and Lung Function Tests in Cystic Fibrosis.

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Background

Cystic fibrosis (CF) is characterized by chronic respiratory infections and functional impairment of the lung. Lung function tests such as nitrogen multiple breath washout (N2-MBW), are sensitive in detecting ventilation inhomogeneity, but cannot determine its exact origin. Novel magnetic resonance imaging (MRI) methods such as matrix pencil decomposition MRI can visualize functional changes in the lung without the administration of contrast agents and the need for breathing maneuvers.

Objectives

To examine the correlation between novel functional MRI and lung function tests in patients with CF.

Methods

Forty patients with CF (mean age 11.7 years, range 6–18) underwent MRI and lung function tests on the same day. Functional MRI provided semi-quantitative measures of the perfusion (RQ) and ventilation (RFV) impairment as percentages of the affected lung volume. Morphological MRI was evaluated using a CF-specific score. N2-MBW provided information regarding global (lung clearance index, LCI) ventilation inhomogeneity.

Results

MRI detected functional impairment in all patients with CF: RFV ranged from 19% to 38% and RQ ranged from 16% to 35%. RFV and RQ were strongly correlated with LCI ($r = 0.76$, $p < 0.001$; $r = 0.85$, $p < 0.001$, respectively), as well as total morphology scores and sub-scores.

Conclusions

Non-invasive functional MRI is a promising method to detect and visualize perfusion and ventilation impairment in CF without the need of contrast agents or breath holding maneuvers. Ventilation and perfusion impairment of the lung correlated strongly with the LCI. We assume that functional MRI has the potential to detect ventilation and perfusion inhomogeneities, which may be the earliest changes of the airways and potentially still reversible.

#J27 – Tidal Breathing during High Flow Nasal Cannula (HFNC) and Nasal Continuous positive Airway Pressure (CPAP) at Equal End-Expiratory Pressures (EEP).

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Rationale

CPAP and HFNC are used in preterm infants to treat respiratory distress syndrome. Whilst the mechanisms of action of CPAP have been extensively investigated, this is not the case with HFNC. Infants often receive flow rates of 8-10L/min with limited understanding of its effects on breathing mechanics. Traditionally, tidal breathing measurements in infants receiving CPAP are difficult to perform and most studies have been performed using uncalibrated respiratory inductive plethysmography with uncertain accuracy. Electromagnetic inductance plethysmography (EIP, Volusense™) has recently been validated in preterm and term infants to measure tidal breathing parameters (TBP).

Objective

To compare the effects of CPAP and HFNC on TBP at equal EEP and to investigate the effects of reducing HFNC flow from 8 to 2L/min on TBP in preterm infants receiving non-invasive ventilation.

Method

A prospective observational randomized crossover study, measuring TBP at varying flow rates (2-8L/min) of HFNC and CPAP 6 cm H₂O in 20 preterm infants (mean birth gestation 27 weeks, mean current weight 1.5 kg). EEP was estimated from pharyngeal pressure. TBP including weight corrected tidal volume (Vt/kg), minute volume (MV/kg), respiratory rate (RR), flow-volume gravity mid-point (FVg) and phase angle were measured using EIP. A minimum of 10 consecutive stable breaths were selected for analysis. Oxygen saturation (SaO₂) was recorded.

Results

Mean EEP at HFNC 8L/min and CPAP 6 cm H₂O were similar (6.17 and 6.46 cm H₂O, $p = 0.51$). Vt/kg was similar between HFNC 8L/min and CPAP (3.67 and 3.88, $p = 0.315$). MV/kg (0.22 vs. 0.27) and RR (60.1 vs. 66.7) were significantly higher on CPAP ($p < 0.05$). FVg was similar between the two modes of respiratory support. There was a trend (Figure 1) towards better reduction of phase angle during CPAP versus HFNC 8L/min but this did not achieve statistical significance (mean 69 vs. 102, $p = 0.12$). Changing HFNC flow rate from 8 to 2L/min resulted in significant reductions in EEP to 2.29 cm H₂O ($p < 0.001$) and SaO₂ ($\Delta 4\%$, $p < 0.001$) while RR (67.9, $p < 0.05$) rose significantly. Vt/kg (3.48, $p = 0.5$) was slightly reduced whilst MV/kg (0.24, $p = 0.39$) and phase angle (114, $p = 0.39$) were increased.

Conclusion

At equivalent EEP, HFNC 8L/min when compared to CPAP 6 cm H₂O resulted in lower MV/kg and RR whilst maintaining Vt/kg, possibly explained by less discomfort on HFNC. However, CPAP produced

better phase angle reduction than HFNC 8L/min. Reduction in HFNC from 8 to 2L/min resulted in a significant reduction of EEP and SaO₂ while RR was significantly raised. MV/kg and phase angle were increased whilst Vt/kg was maintained although these were not statistically significant. In summary, EIP provides a non-invasive method which can be used to measure and detect changes in TBP in infants on HFNC and CPAP without the need for sedation. This technique can potentially be a useful clinical adjunct tool in respiratory management.

#J39 – Bronchial Hyperresponsiveness and Airway Inflammation Markers in Primary Ciliary Dyskinesia.

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Background

Primary ciliary dyskinesia (PCD) is a clinical and genetic heterogeneous disease with reduced mucociliary clearance that leads to bronchiectasis in more than 80% of patients. Although bronchial hyperresponsiveness (BHR) has been postulated as a risk factor that could accelerate the appearance of bronchiectasis, it has been poorly studied in PCD. There are few studies with direct agonists (methacholine) whereas there is no data with indirect agonists (adenosine 5-monophosphate, AMP). The relationship between BHR and airway inflammation markers, namely exhaled nitric oxide (FENO) and exhaled breath condensate (EBC), could provide new data regarding PCD.

Objectives

1. To study the prevalence and parameters of BHR using direct and indirect agonists (methacholine vs. AMP) in PCD patients and controls.
2. To determine the differences in airway inflammation markers; FENO and its two compartments: bronchial (JawNO) and alveolar (CalvNO), and pH of EBC.
3. To identify the relationship between BHR parameters and airway inflammation markers.

Subjects and Methods

Observational, prospective and randomized study (PCD and healthy volunteers). Prick-test, baseline spirometry and bronchial provocation test with methacholine/AMP were performed. The response was expressed by PC20 (agonist concentration decreasing FEV₁ $\geq 20\%$) and reactivity index (RI). FENO determination was made by electrochemical analyzer (NO Vario®), using a bicompartmental model with multiple flows to assess JawNO and CalvNO. EBC samples were collected using a condenser and pH was measured with a specific electrode.

Results

64 individuals (32 PCD, 32 controls) were studied (54.6% pediatrics). Response to methacholine was clearly increased in PCD, both

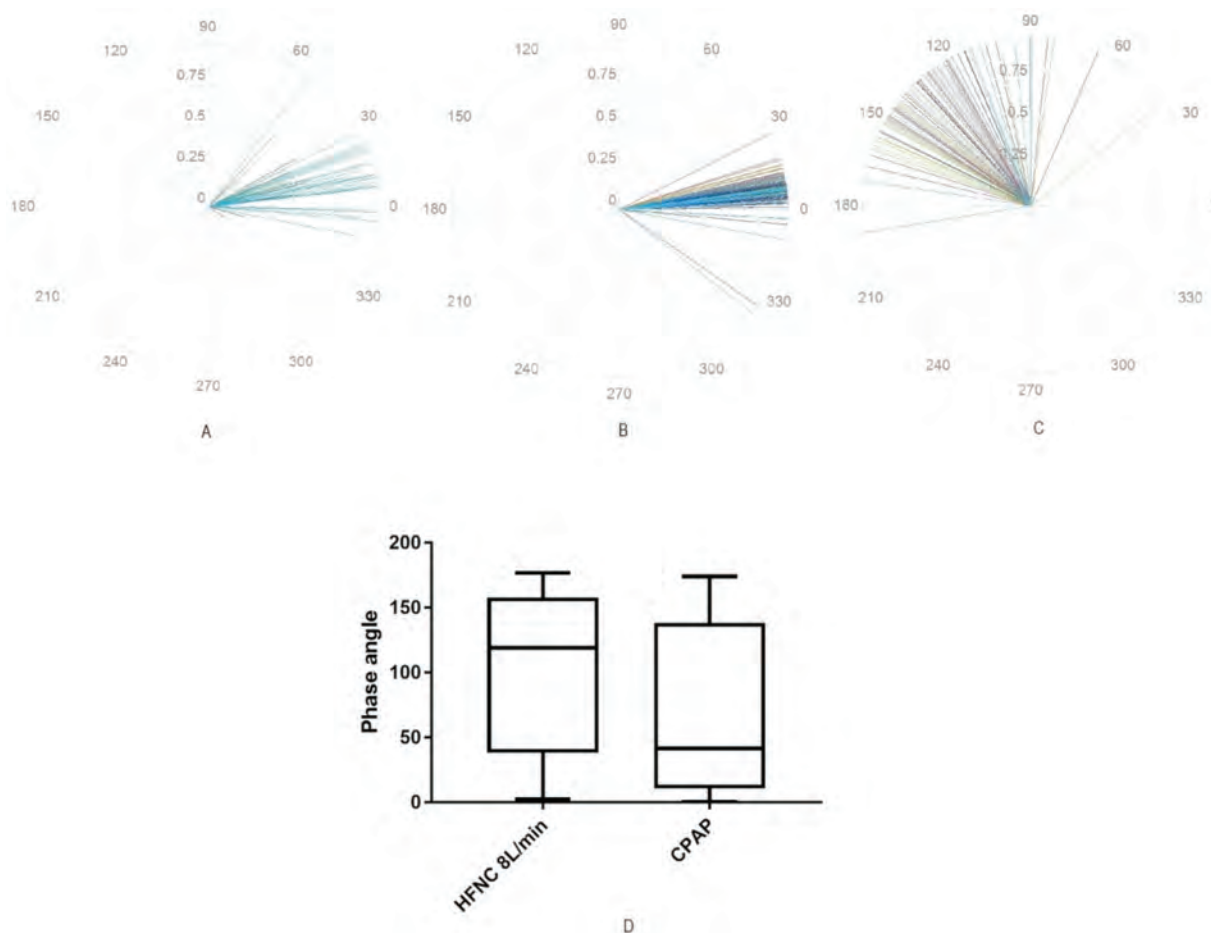


FIGURE 1 Phase angle comparison of HFNC versus CPAP. A represents phase angle of an infant on CPAP of 6 cm H₂O. B represents phase angle of same infant on HFNC 8L/min and C represents same infant on HFNC 2L/min. D represents boxplot comparison of HFNC 8L/min versus CPAP 6 cm H₂O in 20 infants at equivalent EEP.

categorically (31.2% vs. 9.3%) and quantitatively ($p = 0.04$). No significant differences were found using AMP ($p = 0.36$). FENO was significantly lower in PCD ($p = 0.0003$) at the expense of the bronchial compartment ($p = 0.007$), with no differences in the alveolar compartment ($p = 0.4$). These results were maintained after excluding atopsics (positive prick-test). The pH of EBC was significantly more acidic in PCD ($p = 0.001$). Only a weak correlation between CalvNO and reactivity to AMP was found ($r = 0.38$, $p = 0.03$). No other significant correlations were found between BRH and inflammation markers.

Conclusions

BRH in PCD is dependent on persistent alterations of the airway structure and not on acute inflammatory changes, as shown by the fact that no correlation was found between BRH and active bronchial inflammation markers (FENO and $\dot{V}awNO$). FENO is significantly lower in PCD at the expense of the bronchial component, but not alveolar. These results support that the cause of the low NO values in PCD is mainly due to ciliated epithelium dysfunction, present in the bronchial region but not in the alveoli. Our study originally documents a significant acidification of EBC in PCD, hence the study of oxidative stress could open new paths of investigation in this disease.

#N43 – Pulmonary Hemorrhage: Etiology, Clinical Profile and Outcome in Children.

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Objective

To describe etiology, clinical profile, treatment options and outcome in children with pulmonary hemorrhage.

Method

A chart review of children who were diagnosed to have pulmonary hemorrhage at AIIMS, New Delhi, India. All children from 1 month to 16 years of age with confirmed pulmonary hemorrhage during the period from January 2006 to July 2016 were included. Hemorrhages secondary to coagulopathies were excluded.

Results

A total of 38 children (mean age 77.4, SD45.2 months, 23 boys) with pulmonary hemorrhages were analyzed. They were symptomatic since mean age of 54.8(SD42.5) months, with a mean 10.1(SD10.2) month delay in establishing the final diagnosis. This gap was higher in the

absence of hemoptysis. The etiologies for pulmonary hemorrhage were immune mediated disorders 8(21%), infection-related sequelae 8(21%), cardiac/vascular anomalies 5(16%) and airway pathologies 2(5%). Exact etiology could not be found in 14(37%) cases despite a battery of investigations and hence labeled as idiopathic pulmonary hemosiderosis (IPH). Cough was the main symptom followed by hemoptysis and breathlessness. Main signs in descending order of frequency were pallor, clubbing, hepatomegaly and splenomegaly. Lowest hemoglobin ranged from 3.7 to 12.4g/dl and 66% children received at least one blood transfusion. Diffuse shadows were found in chest radiographs in 52% of children. Diffuse or patchy ground glass opacity was the main chest CT finding (60%) followed by consolidations, nodules and septal thickening. Bronchoscopy was performed in 33(89%) children, with hemosiderin laden macrophages found in 93% of cases. Children received treatment as per underlying cause. Three children were managed successfully with bronchial artery embolization, while 6 required surgical interventions. Children with immune mediated disorders and IPH were managed with systemic steroids and steroid-sparing agents. All of them achieved initial remission with oral steroids. Four (28%) children with IPH and 3(39%) children in the immune group developed relapses. Inhaled corticosteroids and hydroxychloroquine

were also commenced at the beginning of treatment. Those who had relapses or renal involvement received azathioprine or cyclophosphamide. Patients with immune-mediated disorders took relatively longer time to respond and had more relapses.

Conclusion

Pulmonary hemorrhage is rare in children although an important cause of morbidity. A high degree of suspicion is essential to prevent the delay in diagnosis, especially if hemoptysis is absent. Clinical clues, chest imaging and immunological studies contribute to identifying specific etiologies in 2/3 of cases. The remaining 1/3 could be managed as IPH. Infections, immunological and cardiovascular disorders are the leading specific etiologies for pulmonary hemorrhage other than IPH. Children with immune-mediated pulmonary hemorrhage and IPH can be treated with systemic steroids and steroid-sparing agents with fairly good outcome.

How to cite this article: Abstracts from CIPP XVI Meeting.
Pediatr Pulmonol. 2017;52:S94–S99.
<https://doi.org/10.1002/ppul.23730>

ABSTRACT**Abstracts from CIPP XVI Meeting****VII. POSTERS****A. BRONCHIAL ASTHMA AND OTHER CHRONIC OBSTRUCTIVE PULMONARY DISEASES****#A14 – Accuracy of Wheezing in Infants and Preschool Children by Written Questionnaire.**

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Introduction

The prevalence of wheezing in preschool children is unknown. In school children, prevalence is between 2–38%.⁽¹⁾ Epidemiological studies are based on information provided by parents.^(2,3) However, it is often inadequate and video questionnaires may be an alternative. Two studies showed that a significant proportion of cases are inaccurate.^(4,5) This study aimed to determine the perception of wheezing by the caregivers of infants and preschoolers compared with the video. **METHODS:** a cross-sectional study with infants and preschoolers was performed at the IMIP, in Brazil, between January and June 2016, with scheduled appointments for any complaint and no exclusion criteria. A researcher first applied the written questionnaire, then exhibited a video of a baby with wheezing on a tablet and applied the second questionnaire. Data analysis was performed using SAS version 8. The Generalized Estimation Equations method was used for confounders. The project was approved by the ethics committee (number 5554). **RESULTS:** of the 196 interviews, the median age of the caregivers was 28.5 years, 182 were female and only 109 studied >8 years. In the written questionnaire, 100 (51.0%) of the children had experienced wheeze in their lifetime, 58 (59.8%) had ≤3 episodes/year, 124 (63.3%) had previous breathlessness and 69 (66.9%) had ≤3 episodes/year. Twenty-seven (13%) had diagnosed asthma, 120 presented snoring and 87 had stridor. After the video, 67 (34.2%) of the children had wheezing at least once in their lives, and 57 (85.1%) had up to three episodes/year. Seventy-six (38.8%) had had dyspnea, of which 59 (77.6%) had ≤3 episodes/year. In multivariate analysis, the written questionnaire had a slight influence on confounders. The crude OR

was 1.99 (95% CI 1.53–2.56) and the adjusted OR was 1.86 (95% CI 1.23–2.80). **DISCUSSION:** the determination of wheezing in infants and preschool children exclusively by written questionnaire is inaccurate and in agreement with Michel et al.⁽⁴⁾ and Cane and McKenzie⁽⁵⁾. Among adolescents, the written questionnaire has acceptable accuracy. This difference with our study can be justified by the greater expertise of teenagers' parents. Thus, the video questionnaire is a necessary tool in determining wheezing in preschool children and possibly in infants whose parents are even less experienced.

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#A24 – Severe Asthma and Bronchiolitis Obliterans in Children and Adolescents: How to Differentiate with regard to Tomographic, Functional and Inflammation Aspects?

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Introduction

Treatment-resistant severe asthma (TRSA) and post-infectious bronchiolitis obliterans (PIBO) are obstructive pulmonary diseases whose characteristics can overlap and, in some cases, even with clinical history data, pulmonary function and tomography, the differential diagnosis can be difficult. In addition, no exclusively pediatric study has compared both of these diseases. **Objective:** Identify which alterations in lung function, tomography and exhaled nitric oxide (ENO), induced sputum cellularity, IgE and allergic tests allow differentiating TRSA and PIBO in children and adolescents.

Methods

A transversal study was performed, involving 40 pediatric patients, 20 with PIBO and 20 with TRSA. Pulmonary function was performed with a KoKo spirometer. Bronchial provocation was performed with inhalation of carbachol until achieving a drop of 20% in FEV1. ENO was performed with Nioxmino® in a registered exhaled stream of 0,35L/s. Induced sputum cellularity was obtained using a 4.5% hypertonic saline solution or 0.9% physiological solution in stable patients and with FEV1 values after bronchodilator higher or equal to 60% of predicted or lower than 60% respectively, during four periods of five minutes each, totaling a maximum time of 20 minutes of inhalation. Alterations in tomography were analyzed through a score punctuation and by the presence of tomographic alterations. ROC curves were performed to evaluate which variable could discriminate these two diseases. Results: The patients with PIBO had lower values of FEV, FEF25-75% and FEV1/FVC and total lung capacity (TLC). The most frequent tomographic alterations in POBI were: bronchiectasis (90%), air trapping (90%) and mosaic attenuation (85%), all with statistical significance comparatively to TRSA. In ROC curves, an area under curve (AUC) higher or equal to 0,8 was observed for the following variables: *Blomia tropicalis*, ENO, tomographic score, severity of bronchiectasis, generation of bronchial division, mosaic attenuation, air trapping, FEF25-75%, FEV1/FVC, variation in FEV1 after oral corticosteroids and the association of mosaic pattern and ENO. In this study, no parameter of atopic markers reached a sensitivity and specificity higher than 80% while, for pulmonary function parameters, only FEF25-75% and FEV1/FVC reached these levels. However, only the tomographic score and mosaic attenuation showed a sensitivity and specificity higher or equal to 95. Only two studies were found in the literature comparing PIBO and TRSA both of which involved mixed samples including children, teenager and adults. In one of the studies, a statistically significant difference was only observed in mosaic attenuation, while in the other, a statistically significant difference was observed in mosaic attenuation, air trapping and bronchiectasis.

Conclusion

The presence of higher scores in tomography and the presence of mosaic attenuation were found to best differentiate TRSA and PIBO.

#A26 - Azithromycin Decreases in vitro Bronchial Smooth Muscle (BSM) Cell Proliferation in Severe Pediatric Asthma.

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Background

Severe asthma in childhood is associated with decreased lung function in adulthood. This is linked to airway remodeling

and increased BSM mass. Preschool children with increased BSM mass are at a greater risk of developing asthma at school age. Adult asthmatic BSM cells have an increased mitochondrial content leading to greater BSM cell proliferation.

Hypothesis

Mitochondria may represent a new target for treating BSM proliferation in severe childhood asthma.

Objectives

To investigate in vitro BSM cell proliferation in severe asthmatic children. Moreover, we sought to determine the effect of conventional and non-conventional anti-asthma treatments on BSM proliferation and verify whether the underlying mechanisms involve mitochondria.

Methods

BSM cells were cultured from bronchial biopsies obtained from severe asthmatic preschool children (1 to 4 years old). BSM cell proliferation was assessed by manual counting and flow cytometry (CFSE, CellTrace proliferation kit) after 5 days in culture medium containing 10% fetal calf serum (10% FCS). Cells were then treated with Dexamethasone, Montelukast, Tiotropium Bromide, Omalizumab, Methoxy-Verapamil or Azithromycin (10⁻⁹ to 10⁻⁶M for all agents) in the presence of 10% FCS. Cell viability was assessed using Trypan blue staining solution and flow cytometry after diamidino-phenylindol (DAPI) staining. Cellular cycle and apoptosis were assessed after DAPI and Annexin-PI staining, respectively. Mitochondrial mass, biogenesis and autophagia were assessed by Western blot and Flow Cytometry, using anti-Porin, anti-mitochondrial transcription factor A and anti-LC3A/B antibody, respectively.

Results

Cells were attributed to 2 groups according to muscle mass on histochemical analysis: big and small BSM ((BM and SM respectively) based on the Z-score determined from normal samples. The mean+SEM number of cells in the BM group significantly increased after 5 days of culture vs. the SM group 186 700 + 35 800 vs. 61 560 + 11 900 BSM cells, respectively, $p < 0.001$). Only Azithromycin (10⁻⁷M) significantly decreased BSM cell proliferation by 1/3 without increasing the number of dead or apoptotic cells or blocking the cell cycle. Azithromycin decreased mitochondrial mass by 1/4 in particular in BM cells, by increasing autophagia but had no influence on mitochondrial biogenesis.

Conclusion

BSM cells from severe asthmatic children show varying degrees of proliferation. Increased BSM mass is an indicator of increased mitochondrial content in BSM cells. Azithromycin decreased mitochondrial mass by increasing autophagia, and decreasing BSM cell proliferation, particularly in the BM group.

#A53 – Once-daily Tiotropium Respiat Add-on Therapy Improves Lung Function in Patients Aged 6–17 Years with Severe Symptomatic Asthma.

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Introduction

Tiotropium Respiat (tioR) add-on therapy to inhaled corticosteroids (ICS) with or without additional controllers has been shown to improve lung function in Phase II and III studies of adults, adolescents and children with symptomatic asthma. We present a pooled analysis of lung function data in adolescents and children with severe symptomatic asthma.

Method

Two Phase III, randomized, double-blind, placebo-controlled, parallel-group, 12-week trials in patients aged 6–11 years (VivaTinA-asthma; NCT01634152) and 12–17 years (PensieTinA-asthma; NCT01277523) with severe symptomatic asthma. Patients received once-daily tioR 5 µg (two doses of 2.5 µg), tioR 2.5 µg (two doses of 1.25 µg) or placebo Respiat (pboR) as add-on to high-dose ICS plus another controller or as add-on to medium-dose ICS plus two other controllers. ICS dose was as defined in the Global Initiative for Asthma 2009 (PensieTinA) and 2010 (VivaTinA) guidelines. Patients were required to have a ≥3-month (PensieTinA) or ≥6-month (VivaTinA) history of asthma and be symptomatic at screening and before randomization by Asthma Control Questionnaire (interviewer-administered; VivaTinA) mean score of ≥1.5. The primary end point of both studies was change from baseline (response) in peak forced expiratory volume in 1 second within 3 hours post-dose (FEV1[0–3h]); the key secondary end point was trough FEV1 response (measured 10 minutes before the next dose of study medication); a further end point was forced expiratory flow between 25% and 75% of the forced vital capacity (FVC; FEF[25–75%]) response; the post hoc end point was trough FEV1/FVC ratio. All end points were measured at Week 12.

Results

793 participants (VivaTinA n = 401; PensieTinA n = 392) were randomized across both trials; 792 were included in this pooled full analysis set. Baseline demographics and disease characteristics were balanced between treatment groups. TioR add-on therapy improved lung function in the pooled population at Week 12, with tioR 5 µg showing superior and significant improvements in peak FEV1(0–3h) response, trough FEV1 response, FEF(25–75%) response and FEV1/FVC ratio versus pboR, and tioR 2.5 µg showing superior improvements in peak FEV1(0–3h) response, FEF(25–75%) response and FEV1/FVC ratio versus pboR, with numerical improvements in trough

FEV1 response versus pboR (Table). The safety and tolerability of tioR in both trials were comparable with those of placebo.

Conclusion

Tiotropium Respiat add-on therapy is an effective bronchodilator, producing clinically meaningful improvements versus placebo in lung function in patients aged 6–17 years with severe symptomatic asthma, mirroring findings in adult patients with symptomatic asthma.

#A55 – HMGB1 as a Biomarker of Inhaled Corticosteroid Treatment Response in Moderate-Severe Asthmatic Children: A Single Center Pilot Study.

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Introduction

High mobility group box 1 (HMGB1) is a new molecule involved in pro-inflammatory responses, abnormally expressed in serum and sputum of allergic asthmatic patients [1, 2]. The aim of this study was to investigate the role of HMGB1 as guidance for treatment management of asthmatic children.

Materials and Methods

30 asthmatic patients and 44 healthy children were enrolled. The patients were classified according to GINA disease severity criteria (mild, moderate and severe). Sputum HMGB1 Levels and lung function indices (FEV1%; FEF 25–75%) were recorded in the cohort study at baseline (T0) and after 3 (T3) and 6 (T6) months of inhaled corticosteroids (ICS) treatment (Table 1).

Results

Sputum HMGB1 Levels were significantly higher in all patients with asthma ($p < 0.0001$). An inverse correlation between sputum HMGB1 Levels and pulmonary function parameters was observed only in moderate (T0: FEV1% $r: -0.9891$, $p < 0.001$; T3: FEV1% $r: -0.6763$, $p < 0.001$; T6: FEV1% $r: -0.5419$, $p < 0.05$) and in severe asthmatic children (T0: FEV1% $r: -0.8696$, $p < 0.001$; T3: FEV1% $r: -0.6477$, $p < 0.05$; T6: FEV1% $r: -0.8627$, $p < 0.001$) (Fig. 1). After ICS treatment, a significant decrease of sputum HMGB1 Levels was noted in moderate (T0: 93.44 ± 20.65 ng/ml vs. T3: 77.96 ± 1.81 ng/ml vs. T6: 67.75 ± 3.01 ng/ml; $p < 0.0001$) and in severe asthmatic children (T0: 130.3 ± 7.48 ng/ml vs. T3: 156.9 ± 1.09 ng/ml vs. T6: 116.08 ± 4.77 ng/ml; $p < 0.0001$). The area under the ROC curve, performed in order to define the diagnostic profile of sputum HMGB1 Levels in identifying asthmatic children, was 0.713.

Conclusions

In addition to the findings that HMGB1 is a sensitive biomarker of allergic asthma in children, our data firstly demonstrate a significant correlation between the decrease in HMGB1 Levels and a successful treatment response.

Figure 1. Correlations between sputum HMGB1 Levels and FEV1% in moderate (T0, T3, T6) and severe asthmatic children (T0, T3, T6).

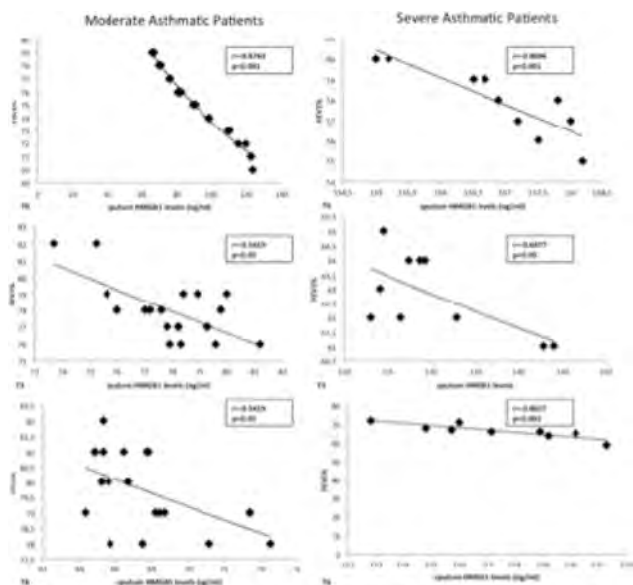


Table 1. Clinical findings of asthmatic children and healthy controls

	Asthmatic children	Healthy controls	P value
N	30	44	
Age (years)	10.56 ± 0.32	11.07 ± 2.12	0.21
Gender Male/Female	18/12	22/22	0.12
BMI (Kg/m ²)	17.38 ± 0.23	17.49	0.11
Family history of asthma/atopy	11	18	0.80
Serum Total IgE (IU/ml)	162.67 ± 20.85	16.79 ± 7.31	< 0.0001
Sputum HMGB1 levels (ng/ml)	125.02 ± 21.53	9.23 ± 3.71	< 0.0001
FEV1% predicted	66.35 ± 4.24	91.95 ± 3.27	< 0.0001

#A70 – The Impact of Severe Respiratory Syncytial Virus (RSV) Infection during the First 2 Years of Life on Development of Asthma.

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Introduction

Respiratory syncytial virus (RSV) is the leading cause of lower-respiratory tract infection (LRTI) in infants, with severe cases requiring hospitalization.(1) In addition to this acute burden, there is increasing evidence to suggest a relationship between severe RSV infection during infancy and recurrent wheeze or asthma.(2) This study aimed to identify and quantify any relationships between RSV

infection during the first 2 years of life and confirmed asthma in later life.

Methods

Datasets collated by the Information Services Division (ISD) of the NHS National Services Scotland were utilized. All live born infants for the period 2000–2011 were identified and divided into two cohorts based on whether or not they had a RSV-related hospitalization during the first 2 years of life. Available data on events, admissions, and hospital attendances during childhood (up to 16 years) were extracted.

Results and Discussion

A RSV cohort of 32,981 infants (4.45% of total) and a non-RSV cohort of 707,437 infants were identified. In the RSV cohort, 9.41% (3,102/32,981) of children had at least one hospitalization for asthma during childhood compared to 2.24% (15,833/707,437) of the non-RSV cohort ($p < 0.001$). 19.72% of all admissions for a confirmed diagnosis of asthma came from the RSV cohort (7,167 vs. 29,182 in non-RSV cohort). The relative risk of asthma admission for infants in the RSV cohort was 3.68 (95% CI 3.56–3.80, $p < 0.001$). The admission rate for asthma was over 5 times higher in the RSV cohort compared to non-RSV cohort (217.31 per 1,000 infants vs. 41.25 per 1,000 infants, respectively). Use of any asthma medication was also higher in the RSV cohort (26.8% vs. 14.4% in non-RSV cohort).

Conclusions

Severe RSV infection during infancy was significantly associated with the development of asthma during childhood, with the risk of a hospital admission for asthma being nearly 4 times higher in these children than in those with no history of RSV hospitalization. This study provides further evidence of the long-term consequences of severe RSV infection in infancy.

#A71 – Influence of Anti-inflammatory Treatment on Exhaled Breath Temperature in Atopic and Nonatopic Asthmatic Children.

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Asthma is an inflammatory disease characterized by the heterogeneity of its endotypes. Elevated temperature caused by increased blood flow is considered a typical feature of inflammation. Measurements of exhaled breath temperature are being investigated as a potential marker of disease exacerbation.

The aim of this study was to investigate the influence of inhaled glucocorticosteroids on exhaled breath temperature in atopic and nonatopic asthmatic children.

Patients and Methods

37 asthmatic children (5 – 17 years; median: 11 years) were evaluated. Children were recruited during scheduled follow-up visits or exacerbations. Exhaled breath temperature (EBT), atopic status including food allergy and medication used in the previous four weeks were assessed in each child.

EBT was measured using the hand-held X-Halo® device (Delmedica, Singapore). Children were inhaling through the nose and exhaling into the thermal chamber of the device through the mouthpiece while tidal breathing. The average of two maneuvers taken 15 minutes apart was recorded. Prior to the maneuver, axillary body temperature was recorded and the measurements were performed at a room temperature of 22–28 °C.

Statistical Analysis

SPSS 20 (IBM Corporation, USA) and STATISTICA 12 (StatSoft, Poland) were used for statistical analysis. The results are expressed as mean \pm SD for numerical data with normal distribution or as medians with interquartile range (IQR). Differences between groups were analyzed using Student's t-test for normally-distributed data. Within-group differences were evaluated with the paired t-test or Wilcoxon rank sum test where appropriate. Statistical significance was accepted at a level of 0.05.

The study was approved by the Ethics Committee of Poznan University of Medical Sciences. Parental written informed consent was obtained in each case.

Results

We performed 95 measurements in 37 children (19 males): 67 measurements were performed in stable condition and 28 measurements during exacerbation. 27 children (72.9%) were sensitized to aeroallergens. 31 children (83.8%) were treated with inhaled glucocorticosteroids (ICS) and 2 (5.4%) received systemic steroids (SCS). The median [IQR] EBT in the whole group was 32.7 [1.7] °C; in stable patients 32.3 [1.1] °C and in exacerbations 33.3 [1.7] °C ($p < 0.001$). There was no difference in mean EBT in atopic and non-atopic children (33.6 ± 1.2 vs. 33.8 ± 1.1 °C; $p = 0.78$ in exacerbation and 32.6 ± 0.8 vs. 32.6 ± 1.2 °C; $p = 0.9$ while stable). There was also no difference in mean EBT in children treated with either ICS or SCS and corticosteroids naïve (32.7 ± 1.5 vs. 32.5 ± 2.2 °C; $p = 0.83$ and 33.0 ± 1.4 vs. 32.6 ± 1.8 °C; $p = 0.45$ respectively).

Conclusions

Neither atopy nor anti-inflammatory treatment influenced EBT in asthmatic children, rendering it a valuable marker of asthma exacerbation regardless of atopic status or current treatment.

#A85 – Is there an Association of Asthma Control with Vitamin D Levels and Spirometry in Children and Adolescents?

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Objective: To assess asthma control and its association with vitamin D levels and spirometry in children and adolescents.

Methods

We selected all children and adolescents with asthma from 7 to 17 years old, who were attended in the Pediatric Pulmonology Outpatient Clinic of the University of Campinas, Brazil, between March and October/2016. In order to evaluate the asthma control level, the Asthma Control Test was applied and the patients were classified into 3 Groups, Controlled Asthma(CA) when the questionnaire score was 25 points, Partially Controlled Asthma(PCA) with 20–24 points and Uncontrolled Asthma (UNA) with scores less than 20 points. A blood sample was taken to measure 25-hydroxvitamin D(vitD) levels and the patients were classified in Sufficient Group (greater than 30 ng/ml), Insufficient Group (20–29.9 ng/ml) and Deficient Group (less than 20 ng/ml). Questions regarding frequency and time of sun exposure, use of sunscreen and vitD supplementation were administered. Sun exposure above 2 hours per week was considered sufficient for suitable metabolism of vitD. Patients also underwent lung function measurement by spirometry. Data analysis was performed using Chi-square, Fisher-Freeman-Halton and Kruskal-Wallis tests ($p = 5\%$).

Results

We included 85 children and adolescents with asthma, of whom 48 (56.5%) were male and the mean age was 10.99 ± 2.82 years, with a median age of 11.00 (7–17) years. According to asthma control level, 14 (16.5%) patients were classified in the CA Group, 35 (41.3%) in the PCA Group and 36 (42.4%) in the UNA Group. Regarding vitD level, 20 (23.5%) asthmatics were classified in the Sufficient Group, 55 (74.7%) in the Insufficient Group and 10 (11.8%) in the Deficient Group. There were no differences between age, height and body mass index between groups. We did not find an association between vitD levels and asthma control groups ($p = 0.294$). Our patients presented a mean frequency of 3.16 ± 2.35 days per week and 59.76 ± 86.69 minutes per day of sun exposure in activities such as playing football, playing on the street, walking to and from school. However, only 15 (17.6%) patients presented sufficient sun exposure. We also did not find association between frequency and time of sun exposure and groups of vitD level ($p = 0.546$). In our study, 78 (91.8%) children and adolescents did not use sunscreen daily and 5 (5.8%) asthmatics took vitD supplementation. Regarding lung function measurement, there were no significant differences between groups in vitD levels and spirometric values, such as FEV1 ($p = 0.501$), FEV1/FVC ($p = 0.984$) and FEF25–75% ($p = 0.866$).

Conclusions

In this study, we did not find an association between asthma control, vitD levels and spirometry in children and adolescents.

Reflections and Proposals

This is the first announcement of our study. There is a lack of studies regarding the relationship between asthma control and vitD levels in children and adolescents, hence we expect to contribute to the improvement on the knowledge with regard to this theme.

#A103 – Coaching via House Visits in Asthmatic Children and Their Effect on Respiratory Morbidity and Health Care Utilization.

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Background

Patients' adherence to medical treatment is a major problem in the management of chronic diseases such as asthma. Non-adherence to asthma medications is associated with frequent emergency room visits, hospitalizations and use of oral corticosteroids. The aim of the study is to assess whether coaching asthmatic children via house visits will improve adherence to medical regimens and therefore will reduce respiratory morbidity and health care utilization.

Methods

A prospective interventional pilot study enrolling children aged 3–18 years, admitted to the Soroka Medical Center between October 2015 and May 2016 due to asthma exacerbation (intervention group). During one year of follow up, the children were coached by a Pediatric Pulmonologist in the clinic and by a highly trained nurse in house visits. The control group included asthmatic children who were admitted during the same time period, but did not go through any intervention. Medication purchase and health care utilization were extracted from the 'Clalit' HMO databases. Asthma control was assessed through self – questionnaires (Asthma Control Test™ (age 12–18) and Childhood Asthma Control Test* (age 3–12) in the intervention group.

Results

The intervention group included 42 children (mean age 7 years ± 3 months) and the control group included 212 children (mean age 7 years ± 4 months). The intervention group consumed significantly more asthma medications, controllers and relievers (median 6.5, IQR 3–13), when compared to the control group (median 4, IQR 2–9, p-value 0.023). There was no significant difference in the amount of clinic visits, ER visits and hospitalizations, attributed to respiratory symptoms, between the two groups. There was a significant improvement in the subjective feeling of asthma control, as reflected from the questionnaires, filled before and after the intervention (p-value < 0.001).

Conclusion

Coaching asthmatic children via house visits was found to be associated with higher asthma medication consumption, similar ER visits & hospitalizations and an improved subjective feeling, as reflected from ACT questionnaires.

A141 – Asthma Phenotypes in the First Three Years of Life and Correlation with Active Asthma at 6 Years of Age: A National Population-based Study in Taiwan.

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Background

Wheezing phenotypes in young children and their associations with subsequent wheezing in later life have been reported; however, longitudinal data based on physician-diagnosed asthma in early life are scant.

Objective

To identify asthma phenotypes in the first 3 years of life, and to investigate their associations with active asthma at 6 years of age.

Methods

Children with physician-diagnosed asthma in the first 36 months and at 6 years were studied in a national population-based cohort. We used latent class analysis to identify asthma phenotypes, and multivariate logistic regression to analyze risk factors for outcomes at 6 years of age.

Results

From 2000 to 2011, 5013 children had physician-diagnosed asthma in the first 36 months, 1055 of whom had active asthma at 6 years of age. Three asthma phenotypes were identified: transient early (34.9%), late-onset (45.4%), and persistent (19.8%). Among these phenotypes, gender, age at first episode, number of asthma episodes in the 1st, 2nd, and 3rd years, total number of asthma episodes, coincidental allergic rhinitis, and atopic dermatitis were all significantly different. The prevalence of active asthma at 6 years of age was 13.6% in the transient early, 24.3% in the late-onset (OR = 2.038, p < 0.05), and 26.6% in the persistent (OR = 2.299, p < 0.05) group.

Conclusion

Three asthma phenotypes in the first 3 years of life contributed to the natural course of pediatric asthma. Based on high risk of subsequent asthma at 6 years of age, the children in late-onset and persistent asthma phenotypes may need aggressive treatment to prevent persistent airway illnesses.

#A154 – Sputum Eosinophil Peroxidase (EPX) Differentiates Pediatric Severe Therapy Resistant Asthma (STRA) from Difficult Asthma (DA).

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Background

Children with STRA have poor control despite maximal therapy and having ensured modifiable factors, such as poor adherence,

have been addressed. Those with difficult asthma (DA) are on high dose treatment, but in whom modifiable factors are identified as contributing to poor control. Analysis of biomarkers in induced sputum provides an attractive tool for indirect assessment of lower airway inflammation in such children. However, using sputum eosinophils to guide therapy is not beneficial in children with STRA (Thorax. 2012 Mar;67 (3): 193-8). Eosinophil peroxidase (EPX) can be measured in sputum supernatants, thus avoiding the need for labor-intensive manual processing, and is a surrogate marker for eosinophil activation status. While it has been validated in adult asthmatics (Allergy.2013 Sep;68(9):1177-84), its utility in children is unknown. We hypothesized that sputum EPX in STRA would be higher than DA, and there would be no correlation between sputum eosinophil numbers and EPX.

Methods

EPX was quantified by ELISA in sputum supernatants from 21 STRA (median age 12.9 [8.9,16.1] years) and 14 DA (N = 14, median age 14 [8.1,16.5] years) children. Results were expressed as ng/ml/gram of sputum. Paired sputum samples were also analyzed in 6 STRA patients before and four weeks after intramuscular Triamcinolone.

Results

Children with STRA had significantly higher sputum EPX levels (median 6.7 ng/ml/gm) compared to DA (median 2.6 ng/kg/ml), $p = 0.01$ (Fig 1A). In 6 paired sputum supernatants, there was a reduction in EPX post administration of systemic steroids (6.7 ng/ml/gm vs. 4.8 ng/ml/gm) in 4/6 children (Fig 1B). There was no correlation between sputum EPX or Eosinophil count levels and sputum eosinophils, forced expiratory volume at 1 second (FEV1), fractional exhaled nitric oxide (FeNO) or asthma control test (ACT).

Conclusion

These data suggest sputum EPX may be a potential biomarker in children with asthma. Sputum EPX can differentiate children with STRA from those with DA and may be a potential surrogate to assess response to intervention in children with STRA as 4/6 STRA patients had reduced sputum EPX following Triamcinolone. No correlation was noted between EPX and eosinophil counts as EPX is said to be a specific marker for eosinophil activation.

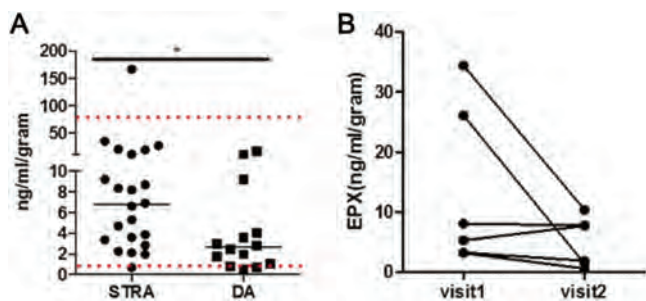


Fig 1A: Significantly higher sputum EPX levels in STRA patients

compared to DA, $P = 0.01$, Mann Whitney test. Fig 1B: Trend towards reduction in EPX levels 4 weeks post Triamcinolone injection ($n = 6$). $P = 0.15$, Wilcoxon signed rank test

#A161 – Risk factors for Wheezing after an Acute Respiratory Infection: Results from a Birth Cohort Study.

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Objectives

To evaluate risk factors for wheezing after an acute respiratory infection in young children from India.

Methods

The infants enrolled in this prospective birth cohort study were followed up regularly every 6 months and whenever they developed acute respiratory infections (ARI). ARI episodes were evaluated for presence of wheezing and their etiology (testing of nasopharyngeal aspirate for viruses). Wheezing was assessed clinically by a pediatrician. Demographic and laboratory parameters were compared between ARI episodes with wheezing and without wheezing. Total IgE levels and cytokines (IFN γ , TNF α , IL-12, IL-4, IL-5, IL-10 and IL-13) were measured at baseline and at one year and two years of age. The infant pulmonary function tests [PFT: Tidal Breathing Flow Volume Loop (TBFVL), Rapid Thoracic Compression (RTC), Raised Volume Rapid Thoracic Compression (RVRTC)] were performed at baseline and thereafter every six months and after an episode of acute respiratory infection.

Results

We enrolled 310 newborns (167 boys). During the follow up until three years of age, 234 children had 906 episodes of acute respiratory infections. Of these, 101 children had 137 episodes of wheezing. Demographic parameters including asthma/allergy in family member, gender, smoking at home, pet at home, cooking source, and type of residence did not differ between children with and without wheezing. Levels of cytokines and total IgE levels at baseline, at one year, and at two years of follow up were similar between the children with and without wheezing except for a proportion of children with abnormal IgE (levels >15.3 kU/L) that were higher in children with wheezing compared to children without wheezing (30/71 vs. 34/175; $p = 0.006$). All of the infant PFTs were also similar in children with and without wheezing. All children having wheezing with ARI had cough. Fever was also more common in ARI episodes with wheezing compared to without wheezing (104/137 vs. 393/769; $p < 0.001$). Lower respiratory tract infection was also increased among ARI with wheezing (30/137 vs. 27/769; $p < 0.001$). Among 906 episodes of ARI, nasopharyngeal aspirates were processed in 798 samples and viruses (single or mixed) were detected in 449 episodes (56.3%). The wheezing occurred significantly more in ARI episodes when virus/es were detected (77/449 vs. 41/349; $p = 0.033$). The type of virus

detected differed among ARI episodes with or without wheezing. Among viruses, detection of RSV (27 out of 51 had wheezing), Rhinovirus (18 out of 122 had wheezing) and Human Metapneumovirus (12 out of 25 had wheezing) during an ARI episode were more commonly associated with wheezing.

Conclusion

Detection of virus/es and type of virus determined the wheezing after an ARI episode. Fever and cough during an ARI episode were associated with wheezing. Demographic profile, cytokine levels, and infant PFT were not different among young children with wheezing after an ARI episode.

#A184 – Increased BMI and Risk for Asthma and Treatment Outcomes in Children- Is It a Specific Asthma Phenotype?

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Background

Asthma and obesity have a considerable impact on public health. Obesity is a risk factor for asthma and can reduce pulmonary compliance and lung volumes. The increase in the normal functioning of adipose tissue in obese subjects leads to a systemic proinflammatory state.

Objectives

To assess the effect of increased BMI on the risk for asthma, levels of inflammation and treatment outcomes in children with asthma.

Methods

A cohort of 475 children with asthma was recruited. They underwent physical examination, basic anthropometric measurements, blood sampling and lung function tests. We clinically assessed their health status and treatment outcomes at the time of diagnosis and after 6 and 12 months. Genetic material was extracted from peripheral whole blood samples and subsequently genotyped for the rs242941 locus in the CRHR1 gene, previously associated with treatment success with inhaled corticosteroids.

Results

Participants were categorized into 4 groups according to BMI percentile: underweight (0–3 centile), normal (5–85 centile), overweight (85–95 centile) and obese (>95 centile). Increased BMI was more frequent in male than in female participants. Baseline levels of both hsCRP and FeNO were elevated in both overweight and obese participants, compared to children with normal BMI. When treatment success was assessed by changes in airway inflammation after 6 months, FeNO levels were higher in obese children compared to those with normal BMI. Additionally, obese children exhibited a higher level of small airway obstruction (according to changes in MEF50 lung function parameters after 6 months of ICS use) as well as poorer disease control (according to GINA guidelines), compared to those with normal bodyweight.

When treatment outcomes were assessed by changes in FeNO, the frequency of CC genotype was significantly higher in good responders compared to the AA genotype and poor response to treatment, but only in children with increased bodyweight, not those with normal BMI. Moreover, the frequency of the C allele was significantly higher in good versus poor responders compared to the A allele, but again only in overweight and obese children (BMI percentile >85). Finally, the overall risk for asthma was higher in overweight participants compared to children with normal BMI, but not in the obese.

Conclusions

Being overweight increases the risk for asthma while obesity rather increases the level of airway and systemic inflammation and potentially affects the level of disease control and response to asthma treatment. Additionally, a specific genotype-related response is evident only in children with increased BMI (compared to those with normal bodyweight), which suggests that overweightness and obesity might also contribute to a specific (more severe) asthma phenotype.

#A188 – Risk Factors of Exercise-Induced Bronchoconstriction in Asthmatic Schoolchildren.

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Background

The role of physical activity in the improvement of lung function has been emphasized. On the other hand, exercise-induced bronchoconstriction (EIB) limits participation of asthmatic children in sports or physical education classes.

The aim of this study was to identify alterable and unalterable risk factors of EIB in asthmatics.

Methods

This was a cross-sectional study. The children with asthma (aged 6–18 years) on therapy (1–4 step according GINA guidelines) were recruited from the Pulmonology and Allergy Outpatient Clinic of the University Children Hospital in Krakow. Asthma severity (based on GINA criteria), control (Asthma Control Test, ACT), peripheral eosinophilia, total IgE level, fractional exhaled nitric-oxide (FeNO) level, type of allergic sensitization and BMI were evaluated. The study comprised baseline spirometry and spirometric exercise challenge test (ECT). Exercise-induced bronchoconstriction (EIB) was positive when FEV1 dropped at least 10%. All of these data, as well as asthma treatment were analyzed. The association between EIB and other evaluated parameters were assessed by logistic regression analysis.

Results

A total of 49 asthmatic children were enrolled in the study (mean age 11.9; 30 boys, 22 well-controlled). Nine children were on GINA treatment step 1 (18%), 14 on step 2 (29%), 23 on step 3 (47%) and 3

on step 4 (6%). The ECT was positive in 12 (24%) patients. There was a strong correlation between EIB and FeNO level ($p = 0.002$) and between EIB and total IgE level ($p = 0.036$). FeNO level in the EIB (+) group was 42 vs. 15 ppb in the EIB (-) group. The high FeNO level (>25 ppb) was a good predictive value for EIB (75% sensitivity and 83% specificity). The FeNO level also correlated positively with asthma severity ($r = 0.32$, $p = 0.026$).

Asthmatic patients with allergic rhinitis (AR) were more predisposed to positive EIB than children without AR ($p = 0.035$). Other analyzed parameters did not correspond with EIB.

Conclusion

Elevated FeNO level is a good predictor of EIB, despite good clinical asthma control. The correlation between EIB and other asthma severity markers or asthma treatment was poor.

#A197 – Exhaled Breath Temperature as a Noninvasive Lung Inflammation Marker in Pediatric Patients with Asthma.

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Introduction and aim

Asthma is a chronic inflammatory disease of the airways and therefore requires regular control and reevaluation. In the last few years, there has been an increasing interest in noninvasive measurement possibilities of the level of airway inflammation in asthmatic patients such as exhaled breath temperature.

The aim of this study was to examine the importance of exhaled breath temperature as a new and noninvasive method which could potentially prove to be a useful tool in the assessment of children with asthma.

Methods

This study included 51 patients, children with previously diagnosed asthma, aged 5–15 from Croatia treated at the Children's Hospital Srebrnjak. An X-Halo thermometer device was used to determine the peak breath temperature values. Patients were divided into 2 main groups – patients without asthma or airway inflammation (control group) and patients with asthma. The second group was divided into two subgroups – asthma with and without exacerbation. Additionally, FeNO and routine blood tests of patients were analyzed to determine other possible underlying factors.

Results

Results showed a statistically significant difference between the exhaled breath temperatures of patients with asthma and those with asthma exacerbations ($p = 0.022$). The mean values of exhaled breath temperatures were: Asthma = 33.07047619, Asthma with exacerbation = 33.81619048, Control group = 33.24666667. No statistical significance was found within the two subgroups of asthmatic patients and patients from the control group ($p > 0.05$). Additionally, no correlation between other factors (blood eosinophil count, basophil count, CRP, FeNO) was detected in our study ($p > 0.05$).

Conclusion

As we hypothesized, there exists a significant difference between measured exhalation breath temperatures (as a means to determine airway inflammation) of asthmatic patients with well controlled asthma and those with acute asthma exacerbations. Therefore, this method could prove to be a useful tool for evaluation and follow-up of children with asthma.

The reason for the lack of correlation between these two groups and the control group may be due to the therapy used in asthmatic patients, although this should be further evaluated. An even broader analysis of the underlying factors and clinical manifestations of different asthma phenotypes should also be considered.

#A205 – Post Infectious Bronchiolitis Obliterans: Importance of High Resolution Computed Tomography in the Diagnosis.

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Introduction

Post infectious bronchiolitis obliterans (PIBO) is an increasingly recognized form of a chronic obstructive lung disease, secondary to lower respiratory tract infection during childhood. We aim to describe the etiology, clinical and radiological characteristics, treatment and course of patients diagnosed with PIBO.

Methods

In this retrospective cross-sectional study, we reviewed the clinical records of children with PIBO followed in Pediatric Pulmonology consultation from November 2006 to November 2016. Recorded information included demographic data, clinical information, etiology, results of complementary diagnostic tools, treatment and clinical course. Data collection and statistical analysis were performed with IBM SPSS Statistics v.24®.

Results

During the study period, 26 children were diagnosed with PIBO. The median age at diagnosis of PIBO was 30 (IQR 24–38) months. All children had prior history of severe bronchiolitis or pneumonia, the majority within the first three years of life ($n = 23$, 88.5%). In 80.8% ($n = 21$) of cases, a pathogen was identified: Adenovirus was the most isolated pathogen ($n = 15$, 57.7%), followed by Respiratory Syncytial Virus ($n = 3$, 11.5%). Hospitalization was required in 24 children (92.3%), 3 of whom in intensive care units for mechanical or noninvasive ventilation. All patients developed permanent auscultatory alterations on physical examination, leading to further investigation. High-resolution computed tomography (HRCT) was performed after a median of 21 months (IQR 13.0–39.8) from the triggering infectious episode ($n = 26$) and was fundamental for diagnosis in all patients. The main findings were mosaic pattern and/or air trapping (100%), bronchial wall thickening (69.2%), atelectasis (61.5%) and bronchiectasis (53.8%). Twelve patients (46.2%) repeated HRCT after a mean of 4.3 (± 2.5), presenting pulmonary imaging deterioration

with bronchiectasis and fibrosis. Fifteen patients underwent pulmonary function tests (PFT): the last tests performed showed a mean value of FEV1 61.7% (± 19.3) and FEF 25–75 33.1% (± 24.1) of the age predicted. Several other chronic lung diseases were investigated; 3 cases of alpha-1-antitrypsin deficiency were also diagnosed. All patients started treatment with inhaled corticosteroids, with 69.2% associated with long-acting β -agonists. Azithromycin was introduced in 11 children (42.3%) with an apparent reduction in the number of exacerbations. All initiated respiratory rehabilitation program especially in exacerbations. The mean follow-up time is currently 4.8 (± 3.1) years. Despite all treatments, only 4 patients had significant clinical improvement.

Conclusions

In our cases, diagnostic acuity of HRCT confirmed the clinical suspicion and avoided invasive procedures, such as lung biopsy. New therapeutic options, such as macrolides, appear to have some benefit, although their use is still controversial.

B. ALLERGIC BRONCHOPULMONARY DISORDERS (EXCLUDING BRONCHIAL ASTHMA)

#B177 – Chronic Eosinophilic Pneumonia: A Case Report.

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A 14-year-old female was assisted in consultation after hospitalization for acute asthma exacerbation. Her medical history included symptoms since age 4 of recurrent wheezing and dyspnea on exertion, nasal congestion and perception of hearing loss. She attended a horse training school where she lived during the week, cleaning the stables and grooming. Pulmonary function tests (PFT) showed an obstructive pattern and bronchodilator reversibility. The chest radiograph revealed images suggestive of bronchiectasis, confirmed on high resolution computed tomography (HRCT) as well as millimeter pulmonary nodules. Bronchofibroscope (BF) revealed bronchial casts, with no evidence of infection in bronchoalveolar lavage (BAL). A sensorineural hearing loss was confirmed and paranasal sinuses CT revealed pansinusitis. The investigation only showed elevation of ANA titles (1/160).

One year later she was admitted with productive cough, chest pain and nasal congestion, without other symptoms. She associated the beginning of the symptoms with the cleaning of a stable that had been closed for many years. She was afebrile, with normal vital signs and oximetry. Breath sounds were diminished at the right lower lung. Chest radiograph showed peripheral nodular diffuse opacities (Fig 1). Antibiotics, short course of systemic steroids and inhaled bronchodilator were initiated with slight improvement of symptoms.

Ground glass areas, atelectasis of the lingular segment and areas of obstructive bronchiolitis were evident on HRCT. BF revealed stenosis of the mid lobe and lingula, with negative microbiologic exams.

Symptoms worsened with shortness of breath, reduced exercise tolerance and dizziness. There was also a concurrent radiographic deterioration, with nodular opacities of variable location.

Further investigation revealed increased peripheral blood eosinophils (2430/uL) and inflammatory markers, raising the suspicion of eosinophilic lung disease. BAL demonstrated an intense eosinophilic alveolitis (43.6% eosinophils) and PFT exhibited a decreased CO diffusing capacity. Serum precipitins, Aspergillus-specific IgE and parasitological stool exam were negative; ANCA were negative but ANA continued to be positive. She was started on prednisolone 1 mg/kg/day with a remarkable clinical improvement in 48 hours and radiological resolution in 2 weeks, confirming the diagnosis of chronic eosinophilic pneumonia (CEP). Steroids were gradually reduced over a period of 4 months. Ten months later she was readmitted with a relapse and the HRCT showed bilateral subpleural consolidations, with peripheral ground glass opacities. She improved again on systemic steroids treatment and is now asymptomatic, slowly tapering the dose.

Discussion

CEP is a rare disease in children, posing some diagnostic challenges. This case illustrates the diagnostic complexity, with progressive clinical features and no identified predisposing factor, enhancing the need to integrate clinical, laboratory and radiological findings.

#B202 – Non-systemic Allergic Bronchopulmonary Aspergillosis (ABPA) in Cystic Fibrosis.

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This is the case of a seven-year-old boy with lifetime diagnosis of cystic fibrosis (CF), pancreatic insufficiency, chronic sinusitis and hypogammaglobulinemia.

The patient presented with sinus tenderness, increasing cough, and complaint of right chest tenderness to chest physical therapy (CPT). After failing 2 weeks of oral antibiotic therapy at home, the patient was admitted for treatment of an acute CF exacerbation and acute sinusitis. He was started on intravenous (IV) antibiotic therapy targeting his known infecting bacteria; *Pseudomonas aeruginosa* (PA) and Methicillin-sensitive *Staphylococcus aureus* (MSSA).

Lung exam revealed few crackles and minimally decreased aeration over the right middle lobe (RML). Decreased aeration of the RML was obvious by day 3 of admission and CXR revealed right lower and middle lobe atelectasis. He was discharged home to continue triple IV antibiotic therapy, prednisone, dornase alfa, hypertonic saline, as well as Vibr Lung treatments and aggressive CPT by his home respiratory therapist. After a week's treatment, lung exam worsened. Repeated CXR showed progressive atelectasis and mediastinal shift to the right.

Flexible bronchoscopy showed thick mucus obstructing all segments of the right lung sparing the right upper lobe, all of which were painstakingly suctioned. Smear of the tenacious mucus from the right sided bronchoscopy revealed fungal elements with eosinophils. BAL cytology revealed 22% eosinophils. The patient responded to

corticosteroid therapy. A repeat bronchoscopy 2 months later revealed no visual airway changes, eosinophils on bronchoalveolar lavage (BAL), or fungal growth.

This CF patient presents with acute severe lung involvement with tenacious mucoid impaction of most large bronchi of the right lung, with dramatic radiological changes in the absence of overt clinical lung disease. The bronchoscopy revealed tenacious airway impaction that failed all medical intervention and mandated physical bronchoscopic removal. All cultures of the removed material and BAL were negative, but direct smear revealed fungal elements and eosinophils, confirmed by 22% eosinophils on BAL.

This entity is reminiscent of cast bronchitis. The severe topical findings point to an allergic response to fungi as would be expected in Allergic Bronchopulmonary Aspergillosis (ABPA). However, this child who had intermittent blood eosinophilia, did not present with the conventional parameters for diagnosis of ABPA; having normal serum IgE, negative IgE/IgG to *Aspergillus fumigatus*, and negative skin test to *Aspergillus*. He failed intravenous antibacterial antibiotic therapy and aggressive chest physiotherapy, but responded to physical removal of the airway secretions followed by systemic corticosteroid at the conventional regimen for ABPA.

We are hypothesizing that an allergic response to fungi (likely *Aspergillus*) can present with a limited severe entity reminiscent of ABPA that also responds to treatment of ABPA but lacks its systemic markers.

C. BRONCHOPULMONARY AND PLEURAL INFECTIONS (INCLUDING TUBERCULOSIS)

#C9 – Different Clinical and Laboratory Characteristics in Children with Necrotizing Pneumonia by *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*.

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Objectives

To evaluate the clinical features of necrotizing pneumonia (NP), and compare the different characteristics of *Streptococcus pneumoniae*-necrotizing pneumonia (SPNP) and *Mycoplasma pneumoniae*-necrotizing pneumonia (MPNP).

Methods

A retrospective, observational study of NP cases hospitalized in our hospital from January 2008 to December 2014 was conducted, and clinical manifestations, laboratory data, imaging performance, hospital course and outcomes analyzed.

Results

A total of 33 cases diagnosed as NP were identified. Of these, 22 were MPNP, with a mean age of 5.6 ± 2.2 years, and 11 patients were SPNP, with a mean age of 3.1 ± 2.1 years. They had markedly increased CRP levels. 28 (84.8%) patients had pleural effusion and 19 cases required pleural interventions. However, patients with MPNP had significantly

lower levels of blood WBC count and CRP values, compared to those with SPNP ($P < 0.01$). In addition, the values of pleural fluid cell count were $760 (68 \sim 1860) \times 106/L$ and $16820 (944 \sim 50000) \times 106/L$, the median values of LDH were 2671 (673 ~ 3993) IU/L and 7320 (3192 ~ 29382) IU/L, and the median values of glucose were 5.93 (4.38 ~ 7.87) mmol/L and 0.11 (0.00 ~ 2.47) mmol/L, respectively in the MPNP and SPNP group, all with a significant difference ($P < 0.01$). Meanwhile, higher rate of pleural effusion septation was observed in the SPNP group when compared with the MPNP group (100% versus 0%, $P < 0.01$), and 90.9% of the patients in the SPNP group underwent chest drainage versus 17.6% in the MPNP group ($P < 0.01$). Although the clinical course was prolonged, all patients with NP recovered without death.

Conclusions

NP caused by SP and MP are found to be severe, yet, reversible. Clinical and laboratory data can help to differentiate MPNP from SPNP.

#C28 – Is the Clinical Course of Community-Acquired Lobar Pneumonia Related to Conjugated Pneumococcal Vaccinations in Children

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Introduction

The aim of this study was to evaluate whether the clinical course of lobar pneumonia in children is related to vaccination status against *Streptococcus pneumoniae*. Some studies implicated the possibility of more complicated disease in children who were vaccinated. The Polish government only partially reimburses in the vaccination program against this pathogen, because of economic reasons. Such epidemiological situation allows to identify two groups of children (vaccinated and non-vaccinated) and to perform a comparison between them.

Methods

The study was conducted at the University Children's Hospital in Krakow, Poland between Sept.2015 and Aug.2016. The inclusion criteria in this study were as follows: diagnosis of community-acquired pneumonia requiring hospitalization, chest radiograph with consolidation covering at least one lobe.

Children were divided into two groups: vaccinated against *S. pneumoniae* (PCV[+] group) and non-vaccinated (PCV[-] group). The following data were analyzed: (A) occurrence of complicated pneumonia (i.e.: significant pleural effusion or empyema requiring surgical interventions or abscess formations), (B) length of hospital stay, (C) level of acute-phase reactants on admission day.

Results

During the 12 months of the study, there were 58 children (36 boys) who met the inclusion criteria. Their median age was 4.1 years (range from 5.7 months to 17.5 years). There were 36 (62%) children under the age of 5 years. The median length of hospitalization was 14 days (range from 5 to 29). Complicated pneumonias were identified in 25 cases: 19 empyema treated with thoracoscopy (decortication and drainage insertion), 3

significant pleural effusions requiring drainage, 1 empyema with bronchopleural fistula treated with thoracoscopy, 1 large abscess requiring drainage and 1 abscess treated conservatively. Causative organisms were only identified in 3 cases: 2 *Streptococcus pneumoniae* (1 in fluid culture, 1 in PCR analysis of fluid), 1 *Streptococcus pyogenes* (in fluid culture).

The comparison between PCV[+] group (n = 18) and PCV[-] group (n = 40) revealed no significant differences in: children's age (median years: 4.2 IR (interquartile range)[3.3–6.4] vs. 4.2 IR[3.2–10]; U Mann-Whitney test, p = 0.7), gender (males: 55% vs. 65%; Chi2 test, p = 0.5), number of preschool-children (aged under 5 years: 67% vs. 60%; Chi2 test, p = 0.6), number of complicated pneumonia cases (55% vs. 37%; Chi2 test, p = 0.2) and days of hospital stay (17 IR[10–24] vs. 12.5 IR [8–19.5]; U Mann-Whitney test, p = 0.2). Moreover, C-reactive protein levels, white blood cells and platelet counts were not significantly different between the study groups.

Conclusion

In this study, clinical course of community-acquired lobar pneumonia in hospitalized children is not related to vaccination status against *Streptococcus pneumoniae*. Proportions of complicated pneumonia are similar in vaccinated and non-vaccinated children.

#C34 – National Survey on Management of *Pseudomonas aeruginosa* Infection in Children with Neurodisability or Long-Term Respiratory Support.

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Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) is associated with increased intensive care admissions, worsening morbidity and mortality. However, there are currently no guidelines for management of *P. aeruginosa* in children with neurodisability and/or long-term respiratory support.

Aim

To investigate UK management practices of *P. aeruginosa* infection in children with neurodisability and/or long-term respiratory support.

Methods

A national questionnaire was distributed to all tertiary respiratory centers in the UK using Typeform.

Questions included demographics (institution, role, populations), structural (clinics and referral criteria) and clinical management (*P. aeruginosa* screening, treatment, definition of eradication and management of recurrence).

Results

There were 16 responses (50% of UK tertiary respiratory centers). Acknowledging probable underestimates from respondents, there was a mean of at least 74 children in each center with neurodisability, 22 with tracheostomy, 61 with long-term non-invasive ventilation and 40 with long-term oxygen.

Although 80% of centers did not have referral criteria for respiratory assessment of patients with neurodisability, 63% offered elective respiratory care for children with neurodisability in a respiratory clinic and 38% in a joint respiratory and neurology clinic.

81% did not have a protocol for management of *P. aeruginosa* in these patients. Half the centers screen for *P. aeruginosa*, mostly at clinic appointments. The most common samples routinely taken were cough swabs (79%), tracheostomy secretions (64%) and endotracheal secretions (50%). 47% of centers would treat *P. aeruginosa* only if symptomatic, 40% would treat *P. aeruginosa* regardless of symptoms and 13% would not treat *P. aeruginosa* in these patients. The most common first line antibiotics were oral ciprofloxacin for 2–3 weeks and nebulized colomycin for 3 months.

Following isolation of *P. aeruginosa*, there was no consensus on how often we should routinely sample patients. 57% of centers defined eradication as 3 successive clear swabs greater than 1 month apart over a 3 month period. Following eradication, if a child had a subsequent recurrence of *P. aeruginosa* infection, 94% would treat this recurrence with antibiotics, 81% only if symptomatic. In addition to antibiotics, 75% would also treat patients with chest physiotherapy, 50% with airway hydration and 38% with mucolytics.

Conclusions

There are large numbers of children with neurodisability and/or long-term respiratory support. The majority of tertiary centers do not have a protocol for management of *P. aeruginosa* and there is huge variation in frequency of sampling and treatment practices. However, there appears to be consensus that these high risk children should be treated especially if symptomatic and that first-line antibiotics should be ciprofloxacin and/or nebulized colomycin. There is need for guideline development and further research for management of these patients.

#C35 – Community Acquired Pneumonia in the Pediatric Emergency Department.

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Introduction

The British Thoracic Society (BTS) guidelines on Community Acquired Pneumonia (CAP) aim to identify cases of CAP from amongst the many cases of viral upper respiratory tract infections and other differentials, to rationalize antibiotic prescriptions. The BTS guidelines advise to consider antibiotics if the child has fever >38.5°C and clinical signs of respiratory distress. If the diagnosis of CAP is clear, chest X-ray is not indicated. However, due to time pressure, parental demands and diagnostic uncertainty, antibiotics are likely being overprescribed.

Aims

To audit antibiotic prescribing in the pediatric emergency department (ED) for suspected community acquired pneumonia against the BTS guidelines.

To investigate our decision making process in antibiotic prescribing.

Methods

All antibiotics prescribed to patients discharged from ED were retrieved for 01/03/2016 – 31/03/2016 for children <16 years. The pediatric ED Symphony system was used to identify all cases of CAP (coded 'LRTI') on discharge letters and this was cross-referenced to the antibiotics list. Using Symphony, each discharge letter and ED episode (scanned clerking and observations chart) was examined for patient demographics and whether they followed the BTS guidelines. Comments in relation to rationale for antibiotic prescribing were noted. A survey of ED doctors was conducted to investigate the decision making process involved in antibiotic prescribing.

Results

There were a total of 2437 pediatric ED attendances in March 2016; 77 (3%) received a diagnosis of CAP coded as 'LRTI'. Only 44 (57%) of these were given antibiotics; 39% were given amoxicillin, 32% were given co-amoxiclav and 25% were given clarithromycin. 23 children (30%) had a chest X-ray and 14 (61%) had CAP confirmed on imaging. Only 17% of antibiotic prescriptions met the BTS guidelines; 39% had documented fever >38.5°C (78% just 'fever') and 17% had documented respiratory distress. Non-BTS reasons for prescribing antibiotics were persistent symptoms and parental pressure (17% had symptoms for longer than one week), focal features on examination (56%), productive or persistent wet cough and high risk comorbidities such as trisomy and congenital heart disease. Six junior doctors responded to the survey; they all agreed that antibiotics should be given for all children with suspected CAP, but none were aware of the BTS criteria for considering antibiotics.

Conclusions

Data showed that many children receiving a diagnosis of 'LRTI' did not receive antibiotics and of those receiving antibiotics, most did not have a fever >38.5°C and documented signs of respiratory signs since doctors were not aware of these BTS criteria for considering antibiotics. There is scope for improvement in antibiotic prescribing for these patients. We have adopted a multifaceted approach with interactive education sessions, local guidelines and patient information leaflets on why antibiotics are unnecessary for viral infections.

#C78 – Prevalence and Clinico-Demographic Profile of Pediatric Drug Resistant Tuberculosis in Satellite Tuberculosis Centers in Manila: A Retrospective Study.

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Background

Drug resistance hampers the eradication of tuberculosis, the leading infectious cause of morbidity and mortality globally²⁹. No studies on prevalence or profiles of drug-resistant tuberculosis in pediatric patients within Manila are published. This baseline data can contribute to faster detection, control of spread, and efficacy of treatment of the disease.

Objective

To determine the prevalence and clinico-demographic profile of drug-resistant tuberculosis among patients 0–18 years old enrolled in Satellite Tuberculosis Centers within Manila from January 2010 to August 2016.

Methodology

This is a retrospective, descriptive study on pediatric patients previously and currently enrolled in the drug-resistant TB registry of Manila Satellite Tuberculosis Centers (STCs) from January 2010 to August 2016. Permission was obtained from the Manila Health Department to review records of drug-resistant tuberculosis patients from Manila STCs who fulfill the criteria. The prevalence rate of drug-resistant tuberculosis was computed. Information on the demographic profile, clinical and laboratory findings, treatment regimen, adverse effects and outcome was obtained. Data were arranged in tables and expressed as proportions and percentages.

Results

Twenty-six patients were included in the study. The prevalence rate was 3.71%. Most were 16–18 years old (69.3%), from Manila (92.3%), and denied risk taking behaviors (61.5%). Parents were mostly unemployed (76.9%) and most were high school graduates (57.6%). Most had a history of previous tuberculosis treatment (88.5%), presented with cough (65.3%), with normal nutritional status (42.4%), no visible BCG scar (61.6%) unremarkable physical examination (92.4%), and CBC (96.2%). Most were Rifampicin-resistant (88.5%), HIV negative (65.3%) with findings on sputum examination (92.4%) and X-ray (88.5%). Commonly used medications were Pyrazinamide (96.1%) and Levofloxacin (96.1%). Most had joint pains as an adverse effect (19.1%). Most patients are still receiving ongoing treatment (50%).

Conclusion

The prevalence rate was within range compared to related literature. Patients were mostly adolescents from Manila with previous tuberculosis treatment and positive sputum and CXR findings. Baseline data can be used to improve case detection rates and assist in the control of infection by identifying high risk groups, raise awareness on drug-resistant tuberculosis and provide insight to ongoing treatment regimens for this disease.

#C110 – What Is the Ideal Duration of Antibiotic Treatment for Community-Acquired Pneumonia in Hospitalized Children – A Pilot Randomized Controlled Study.

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Introduction

The optimal duration of antibiotic treatment in community-acquired pneumonia is unclear. The World Health Organization recommends 3–5 days of antibiotics for uncomplicated childhood pneumonia. Nevertheless, some studies have reported shorter course of antibiotics with higher treatment failure rates while longer courses may reduce the risk of persistent inflammation that may impair lung function later in life.

Objectives

To determine if 10 days of amoxicillin-clavulanic acid is superior over 3 days, at discharge from hospital.

Methodology

This was a single-center, double-blind, randomized placebo-controlled study on children, aged 3 months to 5 years, hospitalized for uncomplicated pneumonia. Pneumonia was defined as an acute illness of ≤ 7 days with the presence of cough, increased respiratory rate, chest retractions, fever $\geq 38.0^\circ\text{C}$ within 24 hours of admission and alveolar infiltrates on a chest radiograph. Children with asthma or other significant chronic diseases were excluded. All children received 1–3 days of intravenous antibiotics as prescribed by their clinician before they were stepped down to oral antibiotic, upon discharge. Children were randomized into two groups: 3 days versus 10 days of oral amoxicillin-clavulanic acid at 60 mg/kg/day in 2 divided doses. Patients were then followed up at 1 month, 6 months and 1 year post-discharge to monitor for respiratory sequelae. Measured outcomes were rehospitalization and persistence or recurrence of respiratory symptoms within 1 month.

Results

Nineteen children were enrolled. The median age was 14 months for both groups (ranged 6–33 months for the 3-day group and 8–55 months for the 10-day group). Median duration of intravenous antibiotics received by both groups was 3 days. About 80% and 89% from the respective groups were infants < 24 months old. *Haemophilus influenzae* was the commonest bacteria isolated, in about 32% of children. None of the children from the 3-day group had respiratory sequelae at 1 month, whereas 2 out of 9 (22%) of the 10-day group had either persistent or recurrent respiratory symptoms. None of the children required rehospitalization for respiratory complications. All children who completed follow up until 1 year (6 from the 3-day group and 5 from the 10-day group) were well except one from the 3-day group who had episodic viral wheeze. Four children (1 from the 3-day group and 3 from the 10-day group) defaulted follow-up but they all reported no respiratory sequelae by parents via phone interview. The remaining 4 children who have not completed their 1-year follow-up are well.

Conclusion

A longer duration of antibiotics in uncomplicated childhood pneumonia is not superior to the shorter course.

#C119 – Follow-up 6 Months after Life-Threatening Respiratory Syncytial Virus Infection.

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Introduction

Infants hospitalized for respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) are at increased risk for recurrent wheezing and reduced pulmonary function, particularly during the first decade of life. To date, there is no pediatric data on infant respiratory morbidity in patients mechanically ventilated for life-threatening RSV LRTI. This study was part

of a structured RS follow-up program that provides regular assessments of (respiratory) symptoms, growth, and developmental parameters and lung function of infants ventilated for life-threatening RSV disease.

Methods

Infants mechanically ventilated for life-threatening RSV disease between January 2012 and August 2016 were seen for follow-up 6 months after discharge from the pediatric intensive care unit. All patients had been mechanically ventilated in a time-cycled pressure-limited lung-protective mode of ventilation or high-frequency oscillatory ventilation (HFOV) when indicated (Vyaire, Lake Forest, IL, USA). Parents were asked to fill out a standardized questionnaire for a retrospective assessment of respiratory symptoms during the past 6 months after discharge for the presence of cough, dyspnea and recurrent wheeze and need for (inhalation) therapy. Lung function measurements including functional residual capacity (FRCp) and forced expiratory flow at FRC (V'_{maxFRC}) were performed using whole body plethysmography (Jaeger, Würzburg, Germany). A z-score of these measurements below -2 standard deviation was identified as abnormal. Data are expressed as median (25–75 interquartile (IQR) or as percentage (%) of total.

Results

Sixty-six patients were evaluated (56.1% male). Median age was 9.8 months (8.2–12.5), with median weight 8.9 kg (8.5–9.5). Fifteen (22.7%) were born prematurely (i.e. gestational age < 37 weeks). Median duration of mechanical ventilation was 7 days (5–10). Twenty-one (31.8) were placed on HFOV. Parent-reported symptoms included wheezing (53.0%), cough (66.7%), dyspnea (53.0%) and medication use (40.9%). Median FRCp was 214 mL (181–244), median FRCp z - score 0.74 (-0.20–1.47), median V'_{maxFRC} was 131.5 mL/sec (95.0–181.0), median V'_{maxFRC} z - score was -1.58 (-2.00 – -0.80). Twenty (30.3%) patients had a V'_{maxFRC} z - score < -2 ; for FRCp this was in 4 (6.1%) patients. Family history of asthma and/or allergy as well as parental smoking did not differ between patients with and without impaired pulmonary function.

Conclusions

This is the first study to report that respiratory morbidity and reduced pulmonary function is very common 6 months after invasive mechanical ventilation for life-threatening RSV disease and warrants further study into underlying mechanisms and possible preventive measures.

#C131 – In Children with Tracheal Compression by Vascular Anomalies is Chronic Cough Associated with Persistent Lower Respiratory Tract Infection?

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Background

In children with secondary tracheomalacia due to mediastinal vascular anomalies, the most prevalent symptoms are a chronic cough and recurrent lower respiratory tract (LRT) infections, thought to be related at least in part to defective mucociliary clearance. Whether this impairment may result in persistent LRT inflammation and subclinical infection is not known.

Patients and Methods

Children with tracheomalacia due to mediastinal vascular anomalies and recurrent (>3/y) LRT infections treated with antibiotics were studied while in stable condition, at least two months after the last LRT infection. Chest CT scan was undertaken, flexible bronchoscopy with BAL and basic immune function tests performed and ciliary beat pattern evaluated.

Results

31 children, 5.6 (3.6) yrs old, were included in the study: 22 with an aberrant innominate artery, 8 with right aortic and 1 with double aortic arch. Four children (12.9%), 5.9 (2.2) yrs old, were diagnosed with bronchiectasis. BAL cellularity showed neutrophilic alveolitis with 8.0 (4.1–13.4) % lymphocytes, 21.5 (10.5–66.1) % neutrophils and 0.3 (0.0–0.6) % eosinophils. Microbiological analysis of BAL fluid demonstrated a bacterial load of >10³ colony-forming units (CFU)/mL in 11 (40.7%) of the children. The majority of isolates were nontypeable *Haemophilus influenzae* (90.9%), followed by *Streptococcus pneumoniae* (36.4%), *Moraxella catarrhalis* (9.1%). A substantial proportion (45.5%) of children with a BAL neutrophilia >10% showed a *Haemophilus influenzae* bacterial load >10⁴ CFU/mL. Only 1 of the 4 children with bronchiectasis had a positive BAL culture >10⁴ CFU/mL for *Haemophilus influenzae*. Basic immune function tests and ciliary beat patterns were normal in all children.

Conclusions

Tracheomalacia due to mediastinal vascular anomalies is characterized by a persistent neutrophilic alveolitis, associated with a significant bacterial load only in a subgroup of children, but with pathogens that have the ability to produce biofilms. Caution should be used in inappropriate antibiotic prescription in these patients who may benefit from chest physiotherapy, chiefly in the presence of bronchiectasis.

#C147 – Foreign Body Induced Empyema in an Adolescent: Challenges of Management in a Resource-poor Setting.

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Background

Foreign body aspiration usually presents with cough which is of sudden onset, respiratory distress and wheeze. Complications such as recurrent pneumonia, bronchiectasis, and rarely empyema and atelectasis occur when the foreign body has been retained in the lungs for a long period of time. This case highlights the complications of the delayed diagnosis of retained foreign body in the bronchus.

Methods

The case record file of the index case was retrieved from the hospital records. Information extracted from the records included: age, sex, date of presentation, symptoms and signs at presentation and on subsequent review, final diagnosis, investigations and treatment, and outcome of treatment.

Case Report

AC is a 15-year-old adolescent female who developed right atelectasis and loculated empyema secondary to a foreign body aspirated 3yrs earlier. The foreign body (an office pin) was lodged in the right main bronchus. She presented to a nearby clinic but referral to a tertiary center for appropriate treatment was delayed. She had repeated chest infections. Symptoms were recurrent episodes of cough, fast breathing and hemoptysis over a period of 3 years for which she took over-the-counter (OTC) medications. She presented to our facility when the symptoms progressively worsened. Findings on examination were tachypnea, splinting of the chest to the right, deviation of the trachea to the left, dull percussion note, reduced breath sounds, and crepitations on the right hemithorax. Oxygen saturation in room air (SPO₂) was 93%. Apex beat was displaced. Chest X-ray (CXR) and chest ultrasonography showed features in keeping with right lung collapse with right sided pleural effusion. Computerized tomography scan was not performed owing to financial constraints. Pleural fluid microscopy yielded pus cells while culture yielded no bacterial growth. Complete blood count showed leucocytosis with predominant granulocytosis, anemia, and reactive thrombocytosis (platelet count >1000000/mm³). The Erythrocyte Sedimentation Rate (ESR) was 130 mm/hr. Screening for tuberculosis and retroviral disease was negative. She received intravenous Ceftriazone and Vancomycin. Following some degree of resolution of the opacities in the CXR, the pin was located in the right main bronchus. The patient was referred to the cardiothoracic surgeons for further management. A chest tube was inserted which drained minimally. She underwent a decortication for the loculated empyema. An attempt to search for and retrieve the foreign body through a right main bronchotomy was unsuccessful. She is scheduled for bronchoscopy in order to remove the foreign body.

Conclusions

This case highlights the need for early diagnosis and prompt removal of aspirated foreign body in order to avert the long term complications such as empyema, atelectasis and bronchiectasis which invariably reduces the individual's quality of life.

Keywords: Atelectasis, Loculated empyema, Foreign body, Thrombocytosis, Decortication

#C156 – Pulmonary Tuberculoma or a Malignant Neoplasm – Diagnostic and Treatment Challenges in an Infant.

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Introduction

Tuberculosis (TB) still remains a significant public health problem in Portugal, currently with an incidence of 18.2 cases/100,000 inhabitants. Pulmonary tuberculoma comprises the development of well-circumscribed nodules or masses in the lung due to

Mycobacterium tuberculosis (Mt) infection. They are thought to be the result of a protective mechanism by the host's immune system, which is why they are infrequently seen in children and infants. This allows differential diagnosis with other solitary pulmonary nodules. The diagnosis relies on imaging and anatomic-pathological findings, pending confirmation with the identification of Mt.

Case Report

A 10 month-old Caucasian male infant, with a close contact with a bacilliferous patient, was admitted with a 9-day history of cough and fever. The investigation revealed a consolidation on the upper left lobe on chest x-ray; a positive interferon-gamma release assay; acid-fast bacilli smear and nucleic acid amplification test (NAAT) were both negative on gastric lavage; awaiting cultures. Treatment was started with isoniazid, rifampicin and pyrazinamide (HRZ) with clinical improvement. By the 7th week of treatment, the chest x-ray revealed a large mass occupying two thirds of the left lung with mediastinal shift to the right side. Thorax CT scan presented a heterogeneous neof ormation with central hypodense areas, with mediastinal invasion, difficult to individualize from the atelectasic lung parenchyma, of roughly 35 mm. This mass caused collapse of almost the entire upper left lobe and respective bronchus. On bronchoscopy, there was a total occlusion of the upper left lobar bronchus due to exophytic lesion. Investigation for neoplastic etiology (tumor markers, peripheral blood immunophenotyping and abdominal ultrasound) was negative. The histology revealed no malignant cells and the presence of granulomatous inflammatory infiltrate. NAAT on bronchial lavage was positive for Mt, biopsy NAAT and cultures of the exophytic lesion were negative. The patient was discharged maintaining treatment with HRZ, however the tuberculoma continued to grow comprising ventilation, thus corticosteroids were added to the treatment for 2 months, with good clinical and radiological response. The infant completed 9 months of treatment with HR.

Conclusion

Tuberculomas are a rare form of lung tuberculosis in children and, therefore, cause diagnostic uncertainties. An occasionally increase in size can be observed at the initial phase of treatment, and surgical resection may be needed in such cases. Literature is sparse on this topic. In this particular case, corticosteroids were an effective adjuvant therapy.

#C181 – Pilot Study of Predictors of Response and Usability of High-flow Nasal Cannula Oxygen for Bronchiolitis across Different Levels of Care.

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Purpose

Evidence on the efficacy and safety of high-flow heated humidified nasal cannula oxygen therapy (HFNC) for acute bronchiolitis (AB) is accumulating, but uncertainty remains on its role when escalating care across inpatient settings. Our primary objective was to identify predictors of response to HFNC in moderate/severe AB; we also aimed to assess its usability across different centers and levels of care.

Methods

Interim analysis of an ongoing pilot prospective prognostic study conducted in 5 pediatric centers in different settings (short stay unit-SSU, pulmonology ward-PW, intensive care-ICU) (Dec 2015-Oct 2016). We included children with AB (<24 months, 1–3 episodes) and either age-adjusted tachypnea, SpO₂ <94% or moderate/severe retractions, after low-flow O₂ therapy. Exclusion criteria were: immediate respiratory support, pneumonia or upper airways disease, chronic cardiopulmonary disease, neonates, GA <34 weeks, previous air leak. We used a standard protocol for stepping up (target 2l/min/kg, max 15l/min) and weaning; 3 types of devices were available. Using a standard case report form, we assessed: early/late response based on respiratory parameters (including the PASS score) and a global rating scale (GRS) by healthcare professionals and parents; and usability (validated questionnaire, 1–7). We evaluated symptoms, use of healthcare resources and treatment at 3–4 weeks. The predefined primary outcome was need for respiratory support during the episode; a posthoc secondary outcome was length of O₂ therapy. We evaluated the univariable association of predefined clinical risk factors at baseline with primary and secondary outcomes.

Results

We included 15 participants from 3 centers (9 started in SSU, 6 in PW). Median age was 1.8 months [IQR 1.4–4.7] and mean weight was 5.1 kg (SD 2.1). 13 had a first episode of AB (11 RSV +). On starting HFNC, all had moderate/severe retractions, mean respiratory rate (RR) 63.9 cpm (SD 14.3), mean heart rate (HR) 161.8 bpm (SD 14.0), median PASS 2 [IQR 2–3], 3 had SpO₂<95%, and 3 had pCO₂>55 mmHg. There were 3 ICU admissions (2 ventilated). HFNC was given for median 2.2 days [IQR 0.9–3.7], O₂ therapy for median 5.4 days [IQR 3.4–9.0]. At 120 minutes, change scores for PASS were –1.4 (SD 1.4), RR –13.2 (SD 13.5), HR –18.25 (SD 20.9); 9/15 improved to none/mild retractions and 1/3 to pCO₂<55 mmHg; physicians, nurses and parents noted moderate to significant improvement in 5, 8, and 5 cases, respectively. Three adverse events were reported (including 1 case of apnea after initiation). Usability scores from physicians and nurses were 1.5 (SD 1.2) and 1.9 (SD 1.0), respectively. There were no readmissions. Exploratory univariable analysis did not identify outcome predictors.

Conclusion

HFNC was well tolerated with good usability across settings and health professionals. In this exploratory interim analysis, we found low recruitment rates and did not identify any predictors of HFNC response.

#C189 – Clinical Characteristics of Empyema Thoracis and Effect of Intrapleural Fibrinolytic Therapy in Children in a Developing Country: A Retrospective Study.

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Empyema thoracis is a significant cause of morbidity and mortality in children. Intrapleural Streptokinase has been used in empyema thoracis with good success rate although the exact protocol for doses is still not established. We retrospectively reviewed the records of children with empyema admitted to our institute from July 2013 to December 2016. During the study period, initially from July 2013 to February 2016, we were giving 6 consecutive doses of streptokinase to our patients who had internal echos or septations on ultrasound chest but later we restricted this to 3 doses of streptokinase and early surgery for non responders. We analyzed the effect of liberal (6 doses) use of streptokinase over morbidity and length of hospital stay as compared to early surgery.

We analyzed 200 patients aged 1 month to 144 months admitted over 42 months; 44 (22%) were infants. Mean age at admission was 48 + 39 months. Among all 200 enrolled children, 123 (61.5%) were males. Most common presenting complaint was fever observed in 199 (99.5%) patients. Mean duration of symptoms prior to presentation was 16 + 15 days. History of prior hospital admission was observed in 171 (85.5%) patients; 141 (70.5%) received antibiotics while an intercostal drain was inserted in 31 (15.5%) patients. On investigations, 127 (63.5%) patients had serum albumin less than 2.5 g/dL. Positive blood culture was observed in 15 (7.5%) patients; methicillin-sensitive *Staphylococcus aureus* was found in 6 (3%) children, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter*, *Candida*, *Staphylococcus hemolyticus*, *Staphylococcus epidermididis*, *Pseudomonas aeruginosa*, *Staphylococcus hominis*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae* in 1 (0.5%) each. Pleural fluid culture was positive in 66 (33%) children; methicillin-sensitive *Staphylococcus aureus* was found in 33 (16.5%), methicillin-resistant *Staphylococcus aureus* in 11 (5.5%), *Acinetobacter* in 6 (3%), *Pseudomonas aeruginosa* in 5 (2.5%), *Klebsiella pneumoniae* and *Burkholderia* in 3 (1.5%) each, *E. coli* and *Streptococcus pneumoniae* in 2 (1%) each and *Staphylococcus hemolyticus* in 1 (0.5%) child. Intercostal tube drainage was performed in 179 (89.5%) patients. Intrapleural Streptokinase was administered in 116 (58%) children. Surgery in the form of decortication was performed in 22 (11%) patients. During the time of use of 6 doses of intrapleural streptokinase over a period of 32 months, 10 (5%) patients required surgery while after restricting the doses to 3, over a period of 10 months, 12 (6%) patients required surgery. Total duration of hospital stay was 17 + 10 days. When we compared the patients who received intrapleural streptokinase only with the patients who underwent surgery, the duration of hospital stay in the patients who received streptokinase was significantly shorter [(15.6 + 7.78 days) vs. (31.4 + 12.84) p 0.002]. We concluded that there can be significant reduction in duration of hospital stay with the liberal use of intrapleural fibrinolytics.

#C211 – Retrospective Study of 121 Cases of Mycoplasma Pneumonia Infection in Children.

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Background

Mycoplasma pneumonia (MP) is a major cause of community-acquired pneumonia (CAP) among school-age children. According to the guiding principles for treatment of Mycoplasma pneumonia in Japan, it is preferable to use the loop-mediated isothermal amplification (LAMP) assay to detect mycoplasmal DNA or immunochromatography tests to detect mycoplasmal antigens in order to confirm the acute phase diagnosis of MP. The LAMP assay is increasingly used to detect MP in our hospital and throughout Japan. Generally, school-age children over 6 years old are affected with MP, however we diagnosed many children with MP under 6 years of age in a 2015 outbreak in Kagoshima city.

Objectives

The aim of this study was to evaluate age-related differences in clinical presentation and laboratory data among children with MP.

Materials and methods

A retrospective chart review was conducted on ambulatory and hospitalized children who were diagnosed with MP between May 2015 and October 2015 (6 months). All chief complaints, clinical manifestations, laboratory results (WBC, CRP, LDH) and the interval between the onset of symptoms and testing in the LAMP assay were recorded. The t-test and Fisher's exact test were used for analyzing qualitative differences. A p-value less than 0.05 was considered statistically significant.

Results

Patient age range was from 1 year old to 14 years old (mean ± SD 6.2 ± 2.9 years old). There were 61 children in the preschool-age group (≤5 years old, 3.9 ± 1.2 years old) and 60 children in the school-age group (6 ≤ years old, 8.5 ± 2.3 years old). The ratio between male and female was 1.1: 1. Clinical observation found that 46 children (84%) in the preschool-age group had wet cough compared to 27 (47%) children in the school-age group (p < 0.001). This was similarly the case with the number of children with wheezes – 11 (18%) in the preschool-age group and 6 (10%) in the school-age group (p = 0.29). The laboratory results obtained for the preschool-age and school-age groups were as follows: WBC 8,149 µl and 6,798 µl (p = 0.01), CRP 1.6 mg/dl and 1.7 mg/dl (p = 0.63), LDH 298 IU/l and 257 IU/l (p = 0.002) respectively. The mean interval between the onset of symptoms and testing in the LAMP assay was 6.5 days in the preschool group and 6.1 days in the school-age group (p = 0.38).

Conclusions

We found that MP was common in the preschool-age group as well as in the school-age group which suggests that the LAMP assay could be used for diagnosis of MP in younger children (three or four years of age) in future outbreaks. Our findings suggested that wet cough was more likely to occur than dry cough in preschool age. Although there were significant differences between WBC and LDH levels in these two age groups, it should be noted that these were normal age-related differences.

D. NONINFECTIOUS RESPIRATORY DISORDERS

#D7 – The Long-term Outcome of a Vascular Ring: Single-Center Experience.

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Objective

The aim of this study is to report our approach to vascular rings and in particular to document the long-term outcome of patients treated in our center.

Methods

A retrospective review was conducted of all patients born between 1980–2013 and diagnosed with a complete vascular ring in our center. By excluding patients with absence of 2 years of follow-up, a total of 54 patients was obtained. Patients were divided in 3 major subgroups based on the anatomy of their vascular ring and in 2 groups based on therapeutic intervention. Age and methods of diagnosis, type of surgery, postoperative complications and long-term outcome were reviewed. The χ^2 test was used for statistical analysis.

Results

37/53 (70%) of the vascular rings were diagnosed before the age of 2, most often by using a combination of echocardiography, x-ray and CT. Afterwards, 44 of the 54 patients were surgically treated with no procedural related deaths. The median follow-up was 8 years. After 2 years, complete improvement of symptoms was obtained in 10/51 (20%), partial improvement in 23/51 (45%), and no improvement in 18/51 (28%). After 10 years, 40 patients of the study population were free of complaints.

Conclusion

Surgical treatment of a congenital vascular ring is safe and mostly indicated in patients with a double aortic arch. Conservative treatment is a good option for patients with little symptoms. At long-time scale, the outcome of a considerable number of patients is still complicated with residual symptoms.

#D19 – Respiratory Problems and Bronchoscopic Findings in Children with Repaired Esophageal Atresia and Tracheoesophageal Fistula: A Large Case Series Study.

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Introduction

Children with congenital esophageal atresia (EA) and tracheoesophageal fistula (TEF) have chronic respiratory symptoms including recurrent pneumonia, wheezing and persistent cough.

Aim

The aim of this study is to describe the clinical and instrumental findings of a large group of children with EA and TEF surgically corrected in order to better understand the patients' needs and improve their long term management.

Methods

A retrospective data collection was performed on 105 children with EA and TEF followed at the Department of Pediatric Medicine of Bambino Gesù Children's Hospital (Rome, Italy) between 2010 and 2015. The review of the instrumental tests was conducted to detect residual anatomic or functional anomalies of the airways and gastrointestinal tract that could explain the respiratory clinical pictures.

Results

64/105 (61%) children were treated in the first week of life at Bambino Gesù Children's Hospital for surgical repair of EA with TEF. Of the entire sample, 82/105 (78%) children reported respiratory symptoms. 69/82 (84%) of these reported lower respiratory symptoms with a mean age onset of 2.2 ± 2.5 years and only 63/69 (91%) underwent specialist assessment at the Respiratory Unit. The first pneumological evaluation was performed at mean age of 3.9 ± 4.2 years. Respiratory symptoms occurred earlier in patients with associated heart disease (1.3 ± 1.25 years). Recurrent pneumonia (33%) and wheezing (31%) were the most reported symptoms followed by stridor (3%) and apnea (2%). According to the clinical history of recurrent lower chest infections, 29 and 53 children underwent a chest CT with contrast enhancement and a flexible bronchoscopy in order to study airways and their relationships with the vascular structures. CT scan was pathological in 28 patients, with the most detected findings being: localized atelectasis (41%), tracheal diverticulum (34%), bronchiectasis (31%), tracheal vascular compression (21%), tracheomalacia (17%), esophageal diverticulum and bronchial stenosis (14%), and recurrent tracheoesophageal fistula (7%). Flexible bronchoscopy performed under light sedation was pathological in 47 cases: tracheomalacia (66%), tracheal diverticulum (26%), recurrent tracheoesophageal fistula (19%) and vocal cord paralysis (11%) were mostly shown. 13/82 (16%) children reported only upper respiratory tract infections, none of whom underwent pneumological assessment.

Conclusion

Our study underlines that respiratory symptoms often complicate EA and TEF; their persistence despite surgical treatment of gastroesophageal reflux means that other etiological hypotheses must be examined. Associated heart disease may contribute to the early onset of symptoms. On the basis of the above considerations, due to patients' complexity and comorbidity, a delayed pneumological assessment is unjustified.

#D32 – A Comparison Between Severe Pediatric Influenza with ARDS and without ARDS.

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Background

Influenza virus infection can cause serious respiratory complications, the most serious of which is acute respiratory distress syndrome (ARDS). The objectives of this study were to compare the clinical features and outcome between severe pediatric influenza with ARDS and those without ARDS.

Methods

We conducted a retrospective cohort study of inpatients admitted to the China Medical University Children's Hospital with a positive respiratory specimen for influenza from Jan., 2012 to Feb., 2016. We compared the demographics and clinical characteristics of patients with ARDS and those without ARDS.

Results

A total of 18 pediatric patients with severe influenza infection (10 had type A, 8 had type B) admitted to our pediatric intensive care unit (ICU) during the study period. Six patients had ARDS (ARDS group) and 12 patients (non-ARDS group) had other complicated conditions. In the non-ARDS group, 6 had encephalitis, 5 had pneumonia and one had myocarditis. All of the ARDS patients were intubated, while 4 of 12 non-ARDS patients were intubated. Three patients had an underlying disease, including 2 prematurity and 1 cerebral palsy. Patients with ARDS had a lower median age (2-years-old vs. 6 years-old, $p = 0.036$), and their hospital stays were longer than the non-ARDS group (29.17 ± 45.97 vs. 9.67 ± 1.19 , $P = 0.006$). Two patients with encephalitis died in the non-ARDS group whereas there were no mortalities in ARDS group (16.67% vs. 0% , $P = 0.287$).

Conclusions

Patients with underlying disease appear to have a tendency of developing ARDS while infected with severe influenza virus. Severe influenza children with ARDS have longer hospital stays but lower mortality rates than those without ARDS.

#D54 – Three Consecutive Cases of Double Aortic Arch with Various Clinical Onset.

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Introduction

The term vascular ring (VR) refers to congenital vascular anomalies of the aortic arch (AA) system that compress the esophagus and trachea, causing symptoms related to these two structures. The most common VRs are the double aortic arch (DAA) and right AA with left ligamentum. The classic clinical presentation of a child with a VR is noisy breathing and a barking cough. Other frequent symptoms are recurrent upper respiratory tract infections, wheezing, dyspnea on exertion and dysphagia.

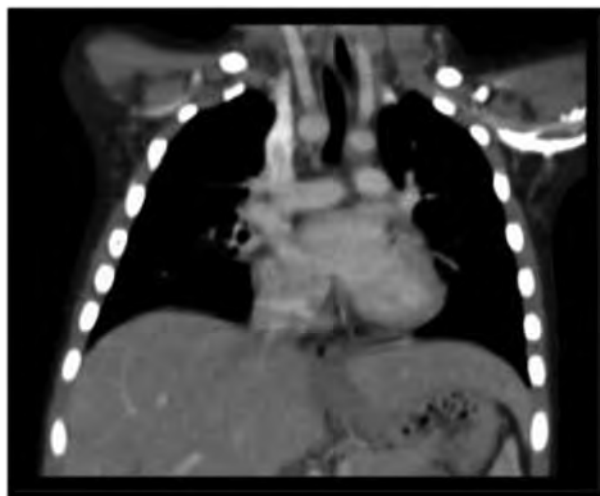
Case Reports

A 1-month-old infant presented with repeated episodes of asphyxia and coughing only during feeding with physical examination apparently normal. A contrast-enhanced esophagogram showed an anterior tracheal deviation and an esophageal notch. The tracheoscopy showed a narrowing due to extrinsic compression at about 1 cm from the carina and the hypothesis of double arch VR was subsequently confirmed at computed tomography. She underwent surgery with immediate clear improvement and complete resolution of symptoms. An 8-month-old infant born at 35 weeks gestation came to our attention due to persistent cough and inspiratory larynx stridor since the first days of life. The echocardiography highlighted a dominant right aortic arch with anterior trachea. The esophagogram showed a minor anomaly of the esophageal profile in the middle tract. VR was confirmed by CT-angiography. The infant underwent repair surgery, followed by slow partial improvement of the symptoms. A 3-year-old female infant presented with persistent barking cough and recurrent pneumonia since the first year of life. She was grunting with severe jugular and epigastric retractions, and the chest auscultation revealed rhonchi and rales throughout the lungs. Chest x-ray examination showed a right lower and middle lobe consolidation with a wedge-shaped area of increased density with apex at the hilum and the base towards the pleura. CT-angiography confirmed an area of increased density on the middle lobe due to a subtotal atelectasis, middle lobe syndrome (MLS), but surprisingly highlighted right-sided double aortic arch with VR. After repair surgery, the patient underwent physiotherapy and prolonged antibiotic therapy.

Discussion

The DAA is the most common VR and comprises 1–2% of all cardiac abnormalities. It results from the failure of the fourth embryonic branchial arch to regress, leading to an ascending aorta that divides into a left and right arch that fuse together to completely encircle the esophagus and trachea. The 3 types of DAA are dominant right arch (80%), dominant left arch (10%) and balanced arches (10%). These cases of DAA are expressed with three different dominant clinical manifestations. In general, patients with DAA tend to have symptoms at an earlier age than patients with other types of VR. Surgery to correct DAA is the only treatment in symptomatic patients and must not be delayed.

Figures 1: Coronal CT view showing the double aortic arch.



#D89 – Incidence of Airway Diseases in a Japanese NICU – A Single Center Study from 2011 to 2016.

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Purpose

To identify the incidence and characteristics of airway diseases in a Japanese NICU.

Patients and Methods

Medical records of 143 inborn infants born between April 2011 and March 2016 admitted to our NICU who underwent bronchoscopy were reviewed retrospectively. During the study period, a total of 3052 infants were born in our hospital. The most common reason for bronchoscopy was obstructive apnea or hypoxic episodes in 104 patients, followed by inspiratory stridor in 47 patients. A thin flexible bronchoscope of FI-7RBS by Pentax with an insertion tube diameter of 2.4 mm was used in unintubated patients, and both upper and lower airways were observed. The median (IQR) gestational age was 38.0 (35.8–39.4) weeks, the median (IQR) birth weight 2690 (2218–3175) grams. Sixty-four were male, 79 were female. Bronchoscopies were performed at a median (IQR) of 25 (19–35) days after birth, 41.6 (40.4–43.1) weeks in corrected gestational age.

Results

Airway diseases were found in 85 patients, 2.79% of all births and 59.4% of patients that underwent bronchoscopy. Multiple airway diseases were found in 24 patients. Common airway diseases were laryngomalacia, vocal cord dysfunction, pharyngomalacia, pharyngeal stenosis and tracheobronchomalacia. Patient characteristics are as shown in the table. Gestational age, birth weight, duration of hospital stay, corrected gestational age at time of discharge are shown as median (range), and history of endotracheal intubation, supplemental oxygen, mechanical ventilation and tracheostomy are shown as number of patients (%).

Conclusion

The incidence of airway diseases in a Japanese population in a single NICU was 2.79%, with laryngomalacia and vocal cord dysfunction being

the most common (incidence of 0.66%), followed by pharyngomalacia (0.46%), pharyngeal stenosis (0.43%) and tracheobronchomalacia (0.39%). Patients with tracheobronchomalacia tended to be born prematurely, and older at the time of discharge. Patients with laryngomalacia and vocal cord dysfunction tended to be born at term, and had shorter hospital stays.

#D92 – Granular Cell Tumor of the Trachea: A Rare Cause of Dyspnea in Pediatric Age.

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Introduction

Granular Cell Tumor (GCT) is an infrequent tumor, extremely rare in the pediatric population, of which 98% of the cases are benign. They can have any location, although over 50% are found in the head and neck region, with the trachea being the least common place. Most tracheal GCT are asymptomatic, but can present with hemoptysis, wheezing, cough, or post obstructive pneumonitis. GCT have a neurogenic origin, derived from Schwann cells, which is supported by positive immunostaining for S-100 protein. Treatment is still controversial, although bronchoscopic excision is adequate for tumors less than 1 cm in diameter, if a proper follow-up is assured, to detect possible recurrence.

Case

A 15-year-old girl was evacuated from Cape Verde with dyspnea of exertion with two years of evolution, persistent cough and progressively worsening stridor. In the last six months, she experienced dyspnea on small efforts and a loss of 10 Kg (17% of body weight). She denied having hemoptysis and fever. She was observed in her country, where she was diagnosed with asthma and medicated with inhaled beta-agonist and corticoid without improvement. She underwent a chest radiography that showed a reduction in the air column of the superior trachea, and a thoracic computed tomography scan that identified a solid image in the 1/3 proximal trachea, with 80% lumen obstruction. She was evacuated to Portugal for further investigation. In our hospital, symptoms which stood out were stridor, decreased vesicular murmur, limitation of daily

	Laryngomalacia	Vocal cord dysfunction	Pharyngomalacia	Pharyngeal stenosis	Tracheobronchomalacia
No. (%)	20 (0.66)	20 (0.66)	14 (0.46)	13 (0.43)	12 (0.39)
Gestational age (weeks)	38.3 (28.9–41.9)	38.8 (34.6–41.9)	36.1 (23.4–41.0)	37.9 (24.3–41.0)	29.9 (23.4–31.8)
Birth weight (g)	2608 (1148–3392)	3096 (1900–4088)	2308 (540–4506)	2530 (720–4506)	1183 (540–3298)
Endotracheal intubation n(%)	3 (15)	0 (0)	4 (29)	4 (31)	8 (67)
Supplemental oxygen n(%)	18 (90)	15 (75)	14 (100)	12 (92)	11 (92)
Mechanical ventilation n(%)	8 (40)	4 (20)	12 (86)	10 (77)	11 (92)
Tracheostomy n(%)	0 (0)	0 (0)	0 (0)	1 (8)	2 (17)
Hospital stay (days)	67 (24–226)	43.5 (8–154)	134.5 (30–446)	134 (23–688)	250 (58–688)
Corrected gestational age at time of discharge (weeks)	46.8 (42.1–65.4)	45.1 (41.0–56.4)	56.5 (43.3–88.9)	54.2 (40.6–138)	66.1 (46.3–138)

activities, and an episode of syncope on effort, with necessity of oxygen therapy. She underwent a bronchofibroscope (BF), which revealed a mass emerging from the left post lateral wall of the trachea, with irregular surface, pink color and vascularized, in the 1st/2nd tracheal rings, with 80% lumen obstruction. A rigid bronchoscopy (RB) was performed and the mass was removed partially, with complete resolution of the symptoms. The biopsy revealed a granular cell tumor, with pavement epithelium metaplasia, positive for S-100 protein. Given the diagnosis and the high risk of recurrence, a second BF was performed, which demonstrated the presence of residual mass with a lumen obstruction of 25–30%. The RB was repeated for removal of the residual mass with tweezers and argon plasma ablation, which was confirmed in a FB, 3 days after the treatment, along with biopsy of the lesion margins, that were free of neoplastic tissue.

Conclusion

GCT are extremely rare, and a high level of suspicion is needed for the diagnosis. They exhibit a slow growth, and when localized in the trachea, can be asymptomatic until lumen obstruction is about 50 to 80%, as observed in our case which evolved over two years. Although most are benign, they have a high rate of recurrence, whereby the removal must be total, and the follow up should be individualized and maintained at least for 5 years. Our patient follow-up will include a new BF in 4 months, to detect a possible recurrence of the tumor, and in such case, a surgical approach will be considered.

#D139 – Home Mechanical Ventilation of Pediatric Patients in Lithuania.

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Introduction

Long-term mechanical ventilation is increasingly used as a therapeutic method for chronic respiratory failure (CRF). The accumulation of experience in pediatric CRF, improvement in home ventilator system technologies and infrastructure support have led to a growing demand for prolonged home mechanical ventilation (HMV) among children worldwide. However, data regarding the current situation of HMV in Lithuania are lacking.

Aims

To summarize and analyze data of all Lithuanian pediatric patients receiving HMV during the 2005–2015 period.

Methods

We performed a retrospective data analysis of pediatric HMV recipients during 2005–2015. We inquired regarding their age, gender and analyzed their clinical causes for HMV, as well as HMV starting date, course and organizational peculiarities of home ventilation service.

Results

The first Lithuanian HMV service was initiated in 2005 at the Intensive Care Unit of the Pediatric Clinic of Hospital Kaunas Clinic at the Lithuanian

University of Health Sciences. According to our data, the Center of Chronic Respiratory Diseases in Children of the same Pediatric Clinic remains the only provider of HMV for children in Lithuania to date.

Eleven (11) patients, 27.3% of whom were female, required prolonged HMV during the analysis period. The estimated prevalence was approximately 2.4 per 100,000 children. HMV was initiated at a mean age of 78 ± 57 mo. The average age of HMV patients at the end of 2015 was 124 ± 57 mo.

A multidisciplinary team consulted patients for home ventilation application. Neuromuscular diseases (7 cases) were the principal indication for the HMV. Other reasons were as follows: autoimmune encephalitis, CNS hypoventilation syndrome, brain tumor and muscular weakness associated with severe combined inherited immunodeficiency.

The average total duration of HMV was 42.2 ± 33.6 mo. At the beginning, seven patients received invasive home ventilation and non-invasive ventilation (NIV) was applied in 4 children, although at the end of our analysis period, the ratio of INV and NIV was 4:6. One patient died due to a different cause not associated with HMV.

Hospitalization events before HMV application were mostly related to respiratory infections and CRF exacerbations. Meanwhile, the improvement in respiratory status after HMV implementation and additional adaptation of cough assistant devices led to a mean drop in hospitalization rate from 6 to 3 hospitalizations per year. These hospitalizations were mainly associated with prophylactic check-up visits.

Conclusion

We present the first summarized data regarding HMV children in Lithuania.

Such data are important for planning and improving respiratory care of these often critically ill children in the country. The national ventilation program is still under development.

#D158 – Clinical Evaluation and Bronchoscopy Findings of Patients with Peripheral Eosinophilia.

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Background

Pulmonary eosinophilic syndromes (PES) consist of heterogeneous groups of diseases characterized by prominent infiltration of the pulmonary interstitium and the alveolar spaces with eosinophils. They are divided into primary or secondary forms. Secondary forms are due to infections, toxins, drugs, connective tissue diseases and malignancy. Primary forms are rare entities in children and consist of idiopathic acute eosinophilic pneumonia (IAEP), idiopathic chronic eosinophilic pneumonia (ICEP), hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA).

Methods

We retrospectively reviewed the clinical, radiological and bronchoscopy findings and etiology of 23 children investigated for peripheral eosinophilia between 2006 and 2016 at the Hacettepe University Department of Pediatric Pulmonology.

Results

The mean age of patients was 8.6 years (9 months–21 years). The median (min–max) age at diagnosis was 69.7 (3–204) months. Female/male ratio was 16 (69.6%) / 7 (30.4%). Consanguinity was positive in 47.5%, and 78.2% patients had at least one respiratory symptom. Cough was the most common symptom (69.6%) at initial assessment of patients. CMV was the most common pathogen in bronchoalveolar lavage (BAL) (n = 3). BAL eosinophilia was detected in 7 (30.4%) patients evaluated for peripheral eosinophilia and 17.4% of these patients had BAL eosinophil counts greater than 25%. There was no correlation between initial peripheral eosinophil count and BAL eosinophil detection. Mean initial peripheral eosinophil count was 8345/mm³ (900–31700). After systemic steroid treatment, a decline in eosinophil count was detected in all patients who received steroids (n:19) (p < 0.001). After treatment, the mean peripheral eosinophil count was 830/mm³ (0–4200). Elevated IgE levels were detected in 8 (34.7%) patients. There was no correlation between peripheral eosinophil count and IgE levels. Peripheral eosinophil counts in patients who had ground glass appearance on computerized tomography were significantly higher than others (p = 0.043). The underlying cause was identified in 17 (73.9%) patients, namely ICEP (n:4), HES (n:3), hyper IgE syndrome (n:3, one with concomitant B cell lymphoma), parasitic infections (n:1), CMV pneumonia (n:1), Severe Combined Immune Deficiency (n:1), interstitial lung disease (n:1), atopic dermatitis (n:1) and pulmonary hemosiderosis (n:1).

Conclusion

- Different etiological results can be found in underlying causes of peripheral eosinophilia.
- Diseases can present with variable degrees of organ involvement and bronchoscopy is a helpful diagnostic tool for identifying lung involvement.
- BAL eosinophilia was detected in 30.4% of patients. Previous CS treatments may affect detection of eosinophils in BAL samples.
- Independently of the diagnosis, patients usually respond dramatically to systemic corticosteroids (CS)

#D196 – Neuroendocrine Hyperplasia of Infancy Syndrome (NEHI): A Challenge for the Pediatrician.

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Our patient, full term male, with normal growth and development, hyperactive, presented at the age of 3 years and 6 months with a history of intermittent tachypnea and hypoxemia correlated with RTIs, inconstantly accompanied by wheezing. The episodes started at about

1 year of age, usually triggered by an RTI, when symptoms were more severe, and persisted, even when being well, mostly during sleep.

At the age of 2 years, suspicion of intrabronchial foreign body led to bronchoscopy, which was negative. Cardiologic evaluation was normal. Viral-induced wheezing was suspected and Flixotide 125 mcg bid and Singulair was recommended.

At the age of 3 years and 6 months, after a careful clinical and history examination, with negative results for GERD and respiratory allergen sensitization, earlier recommended medication was stopped. Parents were suggested to record respiration patterns for a future evaluation.

A following presentation, during a mild LRTI, consisted in tachypnea with 83 – 91% desaturation mostly during sleep, infrequent dry cough and crackles, which improved with supplemental oxygen therapy.

Chest X ray showed perihilar interstitial markings and hyperinflation in the lower lung fields.

No immune deficit and normal laboratory values were noted. There was no response to systemic corticosteroids or antibiotics.

Normal sweat test excluded cystic fibrosis.

Polysomnography showed nocturnal desaturation and alternation of short cycles of hypoventilation/hyperventilation. Cerebral MRI was normal.

Persistent tachypnea with desaturation with onset during infancy, triggered by RTIs, led to high suspicion for interstitial lung disease (ILD). This was followed by recommendation for a lung CT.

Air trapping in the lower lobes, inhomogeneity and ground glass opacities in the right middle lobe and lingula were observed.

According to the specific HRCT findings and clinical symptoms, interpreted by two external specialists, diagnosis of NEHI syndrome was established.

After spontaneous improvement, the patient was discharged with indication for supplemental home oxygen therapy.

As the patient grew older, acute respiratory infections led to shorter periods of tachypnea and oxygen therapy. No complications have been noted up to the present time.

Diagnosis of NEHI, a rare form of ILD, is based on clinical evaluation, imaging and lung biopsy. Clinical suspicion is often difficult for the inexperienced pediatrician. Interpretation of HRCT of the chest is a valuable and most reliable tool that can suggest NEHI and differentiate the latter from other types of ILD. This could potentially obviate the need for lung biopsy.

In the presented case, the patient is probably “outgrowing” tachypnea episodes, which may be a proof of improvement over time in uncomplicated cases, as shown in other reports.

#D198 – Neuroendocrine Cell Hyperplasia of Infancy: Report of Two Cases.

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Background

Neuroendocrine cell hyperplasia of infancy (NEHI) is a disorder of unknown etiology that typically manifests in the first year of life with

chronic tachypnea, retractions, hypoxemia and crackles as well as occasionally wheezing on chest auscultation. Chest radiograph almost invariably shows hyperinflation, whereas high-resolution computed tomography (HRCT) imaging typically shows air trapping, geographic ground glass opacities (GGO) attenuation pattern affecting at least 4 lobes; most conspicuous in the right middle lobe and lingula. Most patients with NEHI are born at term after uncomplicated pregnancies, but cases occurring in late preterm infants have been reported. Many patients come to our attention with persistent symptoms after a presumed viral infection, although further history usually reveals respiratory symptoms that predate the acute illness. Patients with NEHI frequently have failure to thrive and gastroesophageal reflux is common. Our purpose is to present 2 cases of NEHI, with different degrees of severity.

Case Descriptions

The first case is a previously well 10-month-old male infant followed at the Pediatric Pulmonology Unit. Reported clinical onset of progressive dyspnea mostly at sleep time was at the age of four months. There were no respiratory problems in the neonatal period, or any relevant familial antecedents and absence of consanguinity. Physical examination revealed normal weight and length, tachypnea, retractions, hypoxemia and crackles on both lungs. The patient started a continuous home oxygen supplementation. An extensive diagnostic workup was performed including complete blood count and measurement of serum immunoglobulin levels, sweat test, blood gas analysis and echocardiography. The HRCT imaging revealed diffuse ground-glass opacities mostly in the right middle lobe, lingula and zones of air trapping. Because of the typical findings of clinical improvement, we decided not to perform open lung biopsy. During the followed period, there was significant clinical and radiological improvement and no more oxygen requirement at 2 years of age.

The second case is a previously healthy child of 5-months, diagnosed with NEHI from chest CT with typical findings of the disease, made during investigation of dyspnea and triggered by an acute viral bronchiolitis of atypical evolution. The child was late preterm, without complications or any respiratory problems in the newborn period. He had a prolonged hospitalization due to wheezing, crackle, retractions, hypoxia and feeding problems. Despite of normal swallowing fluoroscopy, the patient experienced gagging and wheezing was difficult to treat due to probable gastroesophageal reflux.

Conclusion

NEHI is a rare childhood disorder presenting in the first 2 years of life with common but challenging key clinical features, in particular hypoxemia, respiratory distress and failure to thrive, and distinct imaging and histological findings. Close follow up is necessary since patients can have different outcomes.

#D206 – The Story of a Challenging Diagnosis – A Chronic Pulmonary Condition in a Child.

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Introduction

Chronic pulmonary disease is a rare entity in Pediatrics, with manifestations ranging from mild to severe and a usually early onset. To improve the treatment and overall prognosis of the patient, an early diagnosis is paramount.

Case Description

MPFG, male, 4 years old was sent to our clinic for the investigation of bronchiectasis. From his past history, we highlighted a hospital admission at 7 months old for hypoxemic bronchiolitis – during this episode, digital clubbing was first described. Since that age, MPFG developed a persistent cough, without wheezing or respiratory distress. The investigation subsequently revealed bilateral reticulo-nodular effusion on chest radiography and bilateral alveolar effusion and para-septal emphysema in the chest CT scan. The investigation followed with the performing of a sweat test and a Pancreatic elastase measurement, both within normal range, a Cystic Fibrosis genetic study, which was normal, HIV serology, negative, an immunological study, normal and normal bronchofibroscopy with unremarkable bronchoalveolar lavage.

At present, the child is 6 years old, and has a daily productive cough, with mucopurulent sputum, respiratory distress elicited by moderate exercise and weight in the 5th centile.

A new CT scan revealed diffuse, bilateral, confluent cystic lesions with cylindrical bronchiectasis amidst the latter. The genetic studies for primary ciliary dyskinesia and surfactant deficit were both negative. Nevertheless, in electronic microscopy, an absence of the inner arm of Dynein in 80% of the peripheral microtubules was observed, which is compatible with the diagnosis of primary ciliary dyskinesia.

Discussion and Final Comments

Primary ciliary dyskinesia is an uncommon disease with variable clinical manifestations; hence it can easily be misdiagnosed.

Only 50% of the cases manifest with the presence of situs inversus, and its absence renders the diagnosis highly difficult. Despite the fact that this disease does not have a specific diagnosis, the authors would like to emphasize the importance of an early diagnosis to optimize the clinical care and provide a reliable prognosis.

#D203 – Pulmonary Capillary Hemangiomatosis: A Case Report in a Newborn.

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Introduction

Pulmonary capillary hemangiomatosis (PCH) is a rare progressive lung disease in which an uncontrolled proliferation of pulmonary

capillaries occurs that infiltrate the interstitium, airways and vascular pulmonary structures. It is a cause of severe and progressive pulmonary arterial hypertension (PAH) that is often fatal. The most common manifestation is dyspnea. Lung biopsy is required to confirm the diagnosis. Veno-occlusive disease is the most important histopathological differential diagnosis. Supportive and symptomatic treatment may include anticoagulants, diuretics, ACE inhibitors, and oxygen. The use of α -interferon may be beneficial. Prostaglandins, which are the treatment of choice in primary pulmonary hypertension of other causes, are contraindicated as they worsen this condition. The definitive treatment is lung transplantation.

Objective

To report the case of a newborn with PAH and histopathological diagnosis of PCH that evolved with a rapidly progressive and fatal disease.

Case Report

Newborn, female patient, born at full-term, with appropriate weight and length for gestational age, with history of respiratory distress from birth. On the 5th day of life, the newborn's condition evolved with cyanosis and worsening respiratory distress. On the 19th day of life, she was transferred to a tertiary hospital with acute respiratory failure. In less than 24 hours, she was submitted to tracheal intubation. Physical examination showed oxygen saturation close to 77% with 100% FIO₂, serious general condition, cyanosis, pallor, tachydyspnea, with normal cardiac and pulmonary auscultation. Transthoracic echocardiography revealed severe pulmonary hypertension with pulmonary artery pressure of 120 mmHg, small atrial septal defect (2.8 mm), and significant dilation of the right chambers. Chest radiography showed pulmonary hyperinflation with perihilar central opacities (Image A). Chest HRCT scans showed diffuse thickening of the septal interstitium (Image B). Open lung biopsy was performed. Vasodilator was prescribed (sildenafil). The newborn evolved with severe low saturation and died on the 6th day of hospitalization. Microscopy revealed exuberant capillary proliferation in the lung interstitium (Image C). Immunohistological examination of lung tissue was compatible with PCH: focal involvement of the pulmonary vascular axis by proliferation of small capillaries (CD31 and CD34 positive) with dilatation, tortuosity and engorgement of capillaries in the microcirculation; focal and discrete dilatation of lymphatic vessels (D2-40 positive); fibrocellular thickening of the wall of arterioles and venules of the alveolar septa.

Discussion

This case report aims to emphasize the need for a high degree of clinical suspicion for PCH in patients with severe and progressive PAH, not responsive to therapy, for early recognition and correct management; the diagnosis with accurate pathological study is essential for allowing appropriate treatment.



Image A

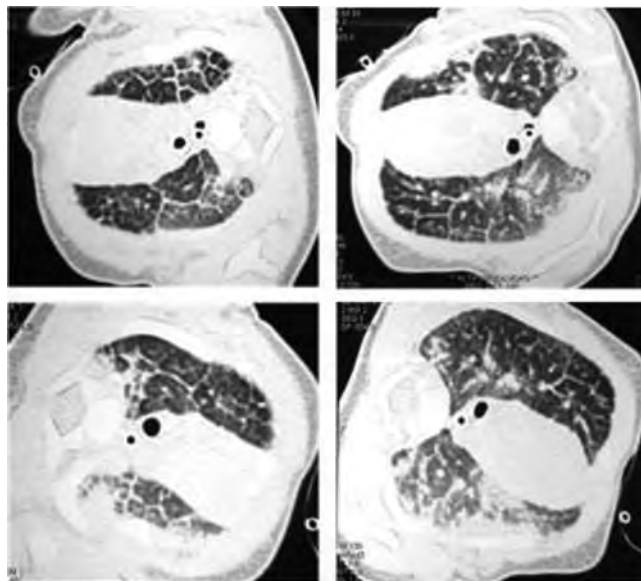


Image B

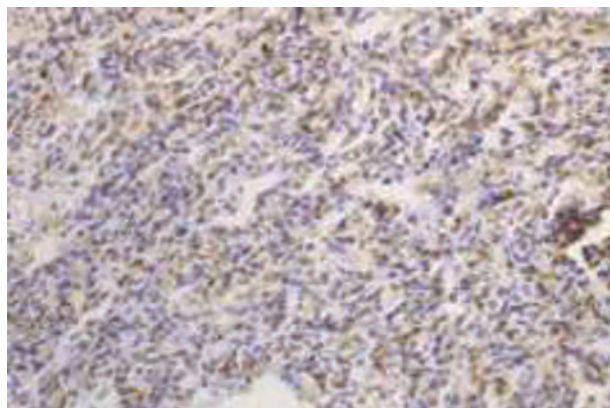


Image C

#D216 – Stridor: About Two Clinical Cases.

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Introduction

Stridor is caused by the oscillation of a narrowed airway, and its presence suggests significant obstruction of the large airways. Commonly encountered as a presenting symptom in the pediatric population, stridor is an important physical finding that requires prompt evaluation and occasionally requires emergency intervention. Two clinical cases of stridor are presented.

Case 1

17-month-old child, male, with prior late prematurity, gemelarity and delayed psychomotor development. At 11 months of age, as a cause of a first epileptic seizure, he was intubated. After elective extubation, a noisy respiration was noted with progressive breathing difficulties. On physical examination, he had tachycardia, hypoxemia (SpO₂ – FiO₂ 21%: 89–90%), superficial breathing, tachypnea, nasal flaring, use of accessory respiratory muscles and a biphasic stridor. Furthermore, respiratory sounds were symmetric with good air entrance bilaterally and expiration time was prolonged. After institution of systemic corticotherapy, the respiratory difficulties improved with persistence of the biphasic stridor, aggravated with manipulation and associated with cyanosis during his cry. An overnight pulse oximetry was performed which did not reveal any episode of desaturation or tachycardia. Bronchofibroscopy revealed a moderate subglottic stenosis resistant to probe progression, with a fibrotic aspect and approximately 3.5 mm in diameter – stage III Cotton-Meyer.

Case 2

7 year-old child, female, with irrelevant past medical history, was admitted in the intensive care unit for a seizure with acute respiratory failure and need of mechanical ventilation. Extubation was attempted after five days but immediately thereafter she developed worsening respiratory distress and had to be reintubated with a 5,5 mm cuffed tube. She was ventilated for a total of 9 days and after extubation, dysphonia and biphasic stridor began. On physical examination, she had adequate oxygen saturations in room air, a respiratory rate of 20 bpm, mild subcostal retractions, without nasal flaring or cyanosis, rare bilateral wheezing and a biphasic stridor. Treatment with nebulized epinephrine, budesonide and prednisolone was administered, with some signs of improvement but persistence of stridor. An overnight pulse oximetry was performed, showing no repercussion on sleep quality or oxygen saturation. A bronchofibroscopy and a computed tomography were performed, showing, respectively, a subglottic stenosis and paralysis of the left vocal cord and a narrowed caliber of the subglottic trachea.

Discussion

Although they can be congenital, 90% of the subglottic stenosis cases are acquired, with intubation and mechanical respiratory assistance

being the main cause. The incidence of post-intubation stenosis ranges from 0.9%-3%. Treatment should be individualized and various endoscopic or surgical techniques are

E. FETAL AND NEONATAL RESPIRATORY DISORDERS

#E13 – Severe Bronchopulmonary Dysplasia with Pneumatoceles in an Extreme Preterm Newborn.

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Introduction

Bronchopulmonary dysplasia (BPD) is a major complication of extreme prematurity. The lungs are characterized by areas of emphysema, and fibrosis. Large pneumatoceles due to acquired localized emphysema overinflation are recognized but relatively rare in advanced BPD.

Clinical Case

A male newborn of 580g birth weight was born at 26 weeks of gestation by C-section to a 33-year-old 4G, 3P, gipsy mother, after a full cycle of corticosteroids. The pregnancy was regularly followed, and complicated with gestational diabetes, preeclampsia and intrauterine growth restriction. The 1st/5th/10th minute Apgar scores were 3/5/7.

The newborn was intubated after birth and received synchronized conventional mechanical ventilation from the 2nd minute of life. He needed surfactant three times due to a severe respiratory distress syndrome (RDS). On day (D) two of life, he presented pulmonary hemorrhage. On D17 he was moved to high frequency oscillatory ventilation and a course of systemic dexamethasone was started. Large cystic pneumatoceles appeared in the right and left lower lobe on D19. The attitude was expectant and the pneumatoceles spontaneously regressed on D32.

Overall, during neonatal intensive care unit stay, the baby was under mechanical ventilation for 90 days, suffered from two episodes of hypertensive pneumothorax (D14 and D25), two episodes of nosocomial sepsis (D48 and D80), underwent one surgery for retinopathy of prematurity (D68) and presented one episode of necrotizing enterocolitis (D48). He died on D96.

Discussion

Large cystic pneumatoceles are rare in advanced BPD. They are a manifestation of intrathoracic air-leaks of prematurity and are markers for ventilator-induced lung injury and are associated with significant mortality similar to other intrathoracic air-leaks. They may need percutaneous evacuation under fluoroscopic guidance and/or lobectomy in worsening disease. If the clinical condition allows, an expectant attitude is advised, since many cases may resolve spontaneously. Our patient's course was complicated with

significant neonatal comorbidities, and the pneumatoceles appeared despite high frequency oscillatory ventilation and a systemic course of dexamethasone. Since the disease did not worsen, close expectant observation was sufficient since the pneumatoceles spontaneously regressed.

#E122 – Predictors of Hospitalization for Acute Lower Respiratory Infections in the First Two Years of Life in Preterm Infants with Bronchopulmonary Dysplasia

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Background

Although predictors of hospitalization for acute lower respiratory infections (ALRIs) in infants with bronchopulmonary dysplasia have been reported, there is a recognized need for studies performed in low- and middle-income countries (LMIC), where the morbidity and mortality attributable to these infections is the greatest. This study set out to examine predictors of hospitalization for ALRIs in a population of infants with a history of bronchopulmonary dysplasia.

Methods

In a prospective cohort study, we determined independent predictors of the number of hospitalizations for ALRIs during the first two years of life in a population of infants with a history of bronchopulmonary dysplasia. In multivariate analyses, we included both clinico-demographic variables and underlying disease characteristics as predictor variables of hospitalization for ALRIs.

Results

Of a total of 138 patients included in the study, 83 (60.1%) had at least one hospitalization for ALRI during the follow-up period. After controlling for potential confounders, we found that independent predictors of the number of hospitalization for ALRIs in our population included ambulatory oxygen therapy between 90 and 119 days (IRR 1.98; CI 95% 1.11–3.53; $p = 0.021$), ambulatory oxygen therapy greater than or equal to 120 days (IRR 2.44; CI 95% 1.50–3.98; $p < 0.001$), and mean days of duration on mechanical ventilation (IRR 1.01; CI 95% 1.00–1.02; $p = 0.029$). Likewise, a significant interaction between breastfeeding and female gender was associated with a significant decreased risk of hospitalization for ALRIs (IRR 0.31; CI 95% 0.13–0.71; $p = 0.006$).

Conclusions

Duration of mechanical ventilation and duration of subsequent ambulatory oxygen therapy are significant predictors of the number of hospitalizations for ALRIs. Likewise, breastfeeding females had a protective effect against hospitalizations for ALRIs in our population of infants with a history of bronchopulmonary dysplasia.

#E143 – Lobar Emphysema in a 7-year-old girl: Acquired Form or Late Onset Congenital Form?

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Introduction

Lobar Emphysema is a rare disease, characterized by lobar over-distension, leading to compression and displacement of adjacent normal lung tissue. Congenital form is rare. Most cases are sporadic, with a few having autosomal dominant inheritance. Frequent respiratory symptoms appear during the neonatal age. Acquired Lobar Emphysema is a complication of foreign body inhalation or airway inflammatory processes.

Case Report

We report a case of a 7-year-old female child, admitted to our center for respiratory distress and fever. Anamnestic records showed: at age of 2 years, bronchoscopy for foreign body extraction, followed by bacterial pneumonia; at age of 4 years, thoracotomy surgery for atrial septal defect (ASD) (Ostium II type). She was admitted in our ward with a severe asthma crisis and presented fever, tachypnea, pectus excavatum, accessory respiratory muscle use and hypoxia. Treatment with intravenous antibiotics, bronchodilators, oxygen and steroids was successful. Chest angio-CT showed a large air cyst (62 mm x 48 mm) in the upper right lobe with thin and regular wall, compatible with Lobar Emphysema. Echocardiography revealed tricuspid regurgitation with PG > 40 mmHg and right ventricle overload due to pulmonary hypertension. The young girl is waiting for surgery.

Discussion

Congenital Lobar Emphysema (CLE) probably has multifactorial etiology, involving bronchial cartilage abnormalities, vascular anomalies and alveolar disease. Congenital heart disease may be found in 12–20% of cases. Clinically, children present respiratory distress which may be abrupt or insidious; others may remain asymptomatic for years. Physical examination shows tachypnea, accessory respiratory muscle use, wheezing, cough, fever due recurrent infections.

Diagnosis is based on chest X-ray. Chest CT scan and MRI usually confirm diagnosis in order to choose the correct surgical strategy. Differential diagnosis is with pneumothorax, bronchopulmonary sequestration, bronchogenic cyst, congenital diaphragmatic hernia or congenital cystic adenomatoid malformation (CCAM). Also CCAM is discovered both in newborns and in older children with respiratory distress and recurrent infections but radiological patterns are irregular air cystic lesions with septa; whereas Lobar Emphysema radiology aspects are usually characterized by lobar radiolucency, contralateral shift of the mediastinum, adjacent lung compression and homolateral hemidiaphragm flattening. The management of CLE in symptomatic children is surgical resection either by thoracotomy or thoracoscopic approach. Patients with minimal or without symptoms can be managed conservatively.

Conclusion

Congenital Lobar Emphysema is a rare disease which affects mainly children within first 6 months of life. Acquired Lobar Emphysema could explain the late onset of symptoms in our case that had a foreign body extraction with an associated pneumonia and a thoracotomy for ASD.



#E151 – Predictors of Abnormal Lung Function in a Cohort of Latino Schoolers with History of Bronchopulmonary Dysplasia.

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Background

Results obtained from international cohorts have suggested that there may be an association between bronchopulmonary dysplasia, asthma and altered lung function; however these results have been obtained from analyses involving preterm infants in health and socioeconomic conditions that differ with respect to those of Latin American communities. It is very plausible that the difference in these aforementioned conditions can nurture risk factors inherent to this community not identified in developed countries.

Methods

In a prospective cohort study we determined independent predictors of altered lung function at nine years of life in a population of schoolers with a history of bronchopulmonary dysplasia. In multivariable analysis, we included both clinico-demographic variables, underlying disease characteristics and pulmonary function test as predictor variables of lung function.

Results

Of a total of 40 patients included in the study, 20 (50%) had a diagnosis of asthma, 11 (55%) of whom were using controller medication. Regarding level of control, 9 (45%) had controlled asthma while 11 (55%) had uncontrolled or partially controlled asthma. When pulmonary function tests were performed, 11 (27.5%) presented some type of alteration in lung function, 9 (82%) were confirmed with obstructive ventilatory disorder, 1(9%) with a restrictive pattern and 1 (9%) with mixed ventilatory disease. The most frequent alterations in spirometry were decreased FEF 25–75 in 10 (25%) of the 40 children, followed by decreased FEV1 in 9 (22.5%). A reversibility response to albuterol was evidenced by an improvement in FEV1 and FEF 25–75% in 25% and 30% of the whole group, respectively. Oscillometry results were similar to those of spirometry with predominance of the obstructive pattern in 8 (20%) while 12 (30%) showed response to albuterol. To establish the existence of predictors independently associated with the presence of obstructive ventilatory disorder, we performed a multivariate analysis using logistic regression modeling, observing that after controlling for gender, gestational age, days of oxygen dependence, exposure to breastfeeding over 6 months, history of maternal or paternal asthma, a higher birth weight was identified as a protective predictor (OR 0.99 (95 % CI: 0.98–0.99, p = 0.014). Additionally, to identify predictors that indicate a better response to bronchodilator, we ran a second multivariate analysis controlling for gender, gestational age, days of oxygen dependence, exposure to breastfeeding greater than 6 months, history of maternal or paternal asthma, finding that higher birth weight was independently associated with best response to albuterol (OR 0.99 (95% CI: 0.98–0.99, p = 0.043).

Conclusions

Higher birth weight is a significant predictor of abnormal lung function in schoolers with history of bronchopulmonary dysplasia. Likewise, lung function abnormalities appear to remain altered during the school years in one third of the entire cohort.

#E162 – Use of Chest Ultrasonography in Term and Near-term Babies in the First 6 Hours of Life: Three Case Reports.

Gambi B

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Background

In term or near-term babies with respiratory distress syndrome, the therapeutic approach has traditionally been based on respiratory distress grading according to Silverman score, blood gas examination and chest radiography. Many diseases manifest themselves as a respiratory distress syndrome. Currently, chest ultrasonography performed early (between the second and sixth hour of life) appears to be the most sensitive and specific technique to predict clinical evolution and to choose appropriate treatment allowing to avoid the use of chest radiography.

Case Reports

We describe three cases of term or near-term infants with signs of respiratory distress that were hospitalized and were submitted to an early chest ultrasonography between the second and sixth hour of life. Case 1: a baby born by Cesarean section delivered out of labor, Case 2: a baby with increased infectious indices, Case 3: a near-term baby with transient tachypnea of the newborn. All showed a chest ultrasonography characterized by prevalence of A-lines (type 3) or prevalence of B-lines (type 2). No performed chest ultrasonography was classified as a type 1 (white lung). Clinical symptoms were characterized by tachypnea, grunting and low saturation values. The Silverman score was below 4. None of the newborns required surfactant administration or ventilatory support, whether non invasive ventilation or mechanical ventilation. All of the symptoms disappeared within 24–72 h.

Conclusions

Early chest ultrasonography in term or near-term babies with a mild respiratory distress syndrome appears to be highly specific and sensitive and is able to identify the need of non invasive ventilation without performing chest radiography. Early chest ultrasonography in itself allows to predict the outcome and to establish treatment, particularly in newborns by non-labor Cesarean section, with increased infection indices or with transient tachypnea of the newborn. We conclude that lung ultrasonography at bedside is an accurate method for predicting the treatment of term and near-term babies with mild RDS and is advantageous over chest radiography.

#E179 – Congenital Pulmonary Lymphangiectasia and Pulmonary Vein Stenosis: Diagnostic Challenges and Therapeutic Uncertainties.

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Congenital total pulmonary lymphangiectasia is a rare disease of unknown prevalence, usually manifested in the first days of life with acute respiratory failure. Congenital pulmonary vein stenosis is a rare congenital heart disease, which presents with pulmonary hypertension of variable onset and evolution. The authors report the case of a newborn with a fatal evolution, whose autopsy revealed the co-existence of these two rare entities.

A female singleton of 3200 grams was delivered at 39 weeks' gestation by vaginal delivery. Pregnancy and prenatal laboratory screening were unremarkable, except for a positive group B streptococcal screen, and an adequate prophylaxis with penicillin was administered to the mother. There was no notice of meconium staining of the amniotic fluid at delivery. Apgar scores were 4 at 1 minute, 5 at 5 minutes and 7 at 10 minutes. Neonatal resuscitation was performed, the baby was intubated and admitted to the neonatal intensive care unit (NICU). She evolved with sustained, refractory

hypoxemia despite 100% oxygen, not responsive to high frequency oscillatory ventilation, surfactant, inhaled nitric oxide (iNO) and vasopressor therapy. The chest X-ray revealed a severe diffuse homogeneous bilateral reticular image. Laboratory studies excluded an infectious etiology. A complete echocardiographic evaluation did not allow the exclusion of a total anomalous pulmonary venous return and cardiac catheterization was performed, which identified persistence of the fetal circulation associated with probable pulmonary vascular malformation. This procedure was, however, interrupted due to the clinical instability of the newborn, not allowing the measurement of pulmonary capillary pressures. At this time the neonate presented a PaO₂ of less than 25 mmHg, a peripheral oxygen saturation below 57% (pre and post ductal) and a severe metabolic acidosis, not responding to the established therapeutic measures. EEG brain monitoring showed a trace of very low voltage. Given the newborn's clinical condition on admission and the likelihood of a poor prognosis, ECMO was not provided. The autopsy of the newborn described findings of diffuse congenital pulmonary lymphangiectasia and pulmonary venous drainage to the left atrium through two ostia, one right and one left (variant of normal), but with common small-caliber pulmonary veins (the right only allowed the passage of a 1 mm stylet; the left offered resistance to the passage of the same stylet).

The authors intend to present and discuss the association of two rare pathologies, the clinical course of which mutually worsen, in which one of the therapeutics instituted for pulmonary hypertension (iNO) may be harmful due to the coexistence of pulmonary vein stenosis. The decision not to offer ECMO was taken by the team based on the patient's clinical condition at admission, and taking into account the likelihood of a fatal diagnosis in which ECMO would be futile.

#E190 – Congenital Pulmonary Lymphangiectasis – Case Series.

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Congenital pulmonary lymphangiectasis (CPL) is a rare congenital anomaly. We report on five clinical cases of CPL that were admitted to our level III neonatal intensive care unit over the last 20 years.

Case 1

A 37-week/ 2990g male was born by C-section and admitted for congenital chylothorax. During pregnancy, a right voluminous chylothorax was diagnosed and a pleuro-amniotic shunt was placed at 30 weeks. The Apgar score at birth was 9/10 and the drain was clamped and removed at 5 minutes of life. Later outcome was good.

Case 2

A 32-week/2010g female was born by C-section after an ultrasound diagnosis of hydrops fetalis. Bilateral thoracocentesis and bilateral drains were inserted for chylothorax and octreotide was started. She died on D11. The autopsy revealed a cardiac tamponade as a complication of a CVC, and the presence of lung lymphangiectasis complicated with chylothorax, as well as small areas of mediastinum, pancreatic and mesenteric lymphangiectasis.

Case 3

A 38-week/3800g male born by C-section, resuscitated at birth with an Apgar score 5/7/7, was started on mechanical ventilation and 100% oxygen for refractory hypoxemia with no response to iNO. He presented a cystic lymphangioma of 6 × 8 × 4.5 cm on the right hemithorax near the axilla. Echocardiographic examination, angioCT and catheterization revealed an obstructive supracardiac totally anomalous venous return. Deceased on D3. Autopsy revealed significant dilation of pulmonary lymphatic vessels and a thoracic cystic lymphangioma and confirmed the congenital heart disease.

Case 4

A 30-week/1530g male newborn, delivered by C-section, was admitted for prematurity and hydrops fetalis. Pleural drains for chylothorax were inserted and octreotide was started. He died on D2 of life. The autopsy revealed pulmonary hypoplasia, bilateral chylothorax, dilation of lymphatic vessel of the neck, mediastinum, lungs, and also in the skin, kidneys and mesentery.

Case 5

A female of 3200 grams was delivered at 39 weeks' gestation. She evolved with sustained, refractory hypoxemia, not responsive to HFOV, surfactant, iNO or vasopressor therapy. The chest X-ray revealed a severe diffuse homogeneous bilateral reticular image. She died on D2. The autopsy described findings of diffuse congenital pulmonary lymphangiectasia and pulmonary venous drainage to the left atrium through two ostia, one right and one left (variant of normal), but with common small-caliber pulmonary veins.

Conclusion

In our small series, congenital chylothorax was the commonest lymphatic anomaly, two of which were associated with hydrops fetalis while the third case was not associated with hydrops fetalis probably due to a pleuro-amniotic shunt inserted *in utero*. Two cases of CPL were associated with obstructive congenital cardiac anomaly. The mortality was high (80%).

F. CYSTIC FIBROSIS**#F29 – Prediction of Lung Function in Children Using Intelligent Nebulizers.**

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Recent advances in nebulized therapy in Cystic Fibrosis (CF) have resulted in smaller and quicker devices for drug delivery called intelligent nebulizers (I-nebs). Many factors contribute to reducing the efficiency of inhalation therapy such as patient adherence with a treatment regimen, aerosol particle size, the individual's breathing pattern as well as on airway geometry.

Aim

The aim of this study was to determine if a CF child's predicted FEV1 (%) will drop if their adherence to the I-neb system decreases.

Methodology

Twenty CF patients between ages 5 to 15 were enrolled from the pediatric CF clinic in Royal Manchester Children's Hospital, UK. Retrospective data from the one-year period was downloaded from each patient's I-neb system. This data was correlated with patient's predicted FEV1. Adherence (the percentage of the number of doses taken divided by the expected number) was calculated for each month of the given period for each patient.

Results

The correlation between adherence and predicted FEV1 for all data did not prove linear dependence. After dividing the group of patients regarding the number of drugs prescribed and the numbers of treatments per day, positive correlations were proven in groups of patients who were homozygous for delta f 508 (p value < 0.05) but not for other mutations. This study also shows that the group of pediatric patients with one prescribed drug and two treatment sessions per day presented the best relationship between adherence (I-neb) and predicted FEV1. With an increase in adherence, predicted FEV1 increased, in contrast to the group with two or three drugs with various numbers of treatments per day (3–5) where with increased adherence resulted in a decrease in predicted FEV1.

Conclusion

A decline in predicted FEV1 has no linear relationship to I-neb adherence except children with homozygous mutations of delta f 508. We need a prospective study with larger numbers to prove this relationship due to complexity of treatment in CF patients. Increasing the burden of treatment is likely to reduce the adherence of treatment.

#F30 – Rate of Sufficient Sweat Sample Collected in Very Young Infants Referred for Sweat Testing in Minas Gerais State, Brazil.

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Background

Obtaining an adequate volume of sweat to measure chloride concentration is a challenge for many cystic fibrosis (CF) centers, mainly in low-middle income countries. The Cystic Fibrosis Foundation (CFF) recommends a quantity not sufficient (QNS) rate of ≤ 10% in infants <3 months of age referred for sweat chloride analysis. However, some infants fail to produce a sufficient quantity of sweat, meaning disease confirmation is delayed.

Objective

To assess the QNS frequency among participants of a state-wide, two-tiered immune reactive trypsinogen (IRT)-based newborn screening program in a setting with a low incidence (by one per 10,500) of CF.

Methods

Infants with two subsequent tests for IRT higher than 70 ng/mL, born from uncomplicated pregnancies and deliveries were eligible and consecutively selected. We excluded subjects with a gestational age of lower than 37 weeks, with a birthweight of lower than 2500 g, who remained in the hospital after delivery regardless of their condition, who had meconium ileus or other clinically detectable abnormalities and who were older than 60 days at the date of the sweat test. Sweat collection was performed only at the newborn screening program referral lab. We used the Wescor Macroduct Sweat Collection System[®], from one collecting site in a 30 minute period. When a patient did not produce a sweat sample lower than 15 μ L in the coils, the attempt was counted as QNS. Frequency distribution and its respective 95% CI were calculated to determine the proportion/variation of QNS and non-QNS.

Results

1,076 infants, aged 34 to 60 days old (median 45 days) were enrolled; among these only 71 (6.6%, 95% CI, 5.5%-8.8%) produced less than 15 μ L.

Conclusion

Our results demonstrate the effectiveness of our program to attain QNS rates that meet the CFF criterion.

#F31 – Blurred Hyperoxia Response in CF Infants.

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Introduction

Hyperoxia alters breathing patterns especially in infants. Biphasic response to hyperoxia (initial decrease in ventilation followed by increase to or above initial values) is well recognized, however it is not known if this reaction is universal or if there are diagnosis-specific patterns of response. Aim of the study was to investigate the changes in ventilation in infants with cystic fibrosis (CF) after exposure to 100% oxygen.

Methods

Study group (CF group) consisted of 17 infants with classical form of CF, control group (nonCF group) included 17 infants with upper airway pathology or risk of developing asthma (based on modified Asthma Predictive Index). Patients with preterm birth, prolonged postnatal adaptation and/or need of supplemental oxygen were excluded from the study. The two groups did not differ in terms of age, weight and length. All infants underwent repeated

measurement of flow, O₂ and CO₂ concentration in breathed air during quiet sleep as a part of a multiple breath nitrogen washout test using Exhalyzer D, Eco Medics. Raw data were processed by non-commercially developed software enabling calculation of respiratory rate (RR), tidal volume (V_t) and minute ventilation (VE) during normoxia (NO) and first 10s, 20s and 30s of hyperoxia (hyper10s, hyper20s and hyper30s). Hyperoxia response time (HRT) for VE was estimated as the time from beginning of hyperoxia to the first breath out of 4 consecutive breaths with calculated VE being under the 5th percentile of normoxic breaths. Differences between respective groups were tested using t-test, between NO and hyperoxia by paired t-test and difference in number of detected positive hyperoxia responses were tested by one-sided test for the difference between two independent proportions.

Results

There were no significant differences between groups under normoxic and hyperoxic conditions (hyper10s, -20s, -30s) in RR, V_t and VE. A clear hyperoxia response – i.e. sustained decrease in VE under the 5th percentile of normoxic values for at least 6 breaths \approx 10s followed by increase to normoxic values – could be detected in 34 out of 54 CF traces (62.96%) and in 35 out of 44 traces (79.55%) in the nonCF group – the difference being significant ($p = 0.04$). NonCF patients showed prompt decrease in VE with HRT being 3.64 ± 1.72 s (mean \pm SD), while CF patients showed blurred decrease – HRT 5.02 ± 1.79 s, the difference being significant ($p = 0.03$).

Discussion

The function of peripheral chemoreceptors has a marked impact on ventilation and plays an important role in adaptation to hypoxia. This function can be influenced by “abnormal resetting” soon after birth as a result of impaired postnatal adaptation (preterm birth per se, insufficient blood oxygenation etc.). Based on our data, CF infants show quantitative and qualitative changes in peripheral chemoreceptor function as assessed by modified hyperoxia response test. These impairments seem to be independent of early postnatal influences. The diagnosis of CF per se may alter function of peripheral chemoreceptors.

#F48 – Pancreatic Insufficiency in Cystic Fibrosis: Influence of Inflammatory Response Genes.

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Background

Pancreatic insufficiency in patients with cystic fibrosis (CF) is a crucial clinical marker for severity and disease progression. There is association of pancreatic insufficiency with CFTR mutations, environmental factors and modifier genes. In our study, 125 modifier genes and their SNPs were associated with the presence of pancreatic insufficiency.

Methods

We prospectively evaluated 214 patients with CF admitted at one hospital over a 2-year period (2014–2015). The control group consisted of 491 healthy adults. CF patients were evaluated for presence of pancreatic insufficiency. Pancreatic insufficiency was associated with clinical variables and SNPs related with inflammatory response considering CFTR mutations. An Open Array technique was used to perform SNP identification in inflammatory response genes.

Results

For pancreatic insufficiency, after correction by multiple test, there were six SNPs with positive association in patients with CF and two CFTR mutations Class I, II and/or III. The odds ratio amplitude was 0.087 (95%IC = 0.004 to 0.544) for rs9870255*CG (CTNNB1 gene) to 11.06 (95%IC = 1.746 to 252.3) for rs729302*AA (IRF5 gene). For all patients with CF combined, nine SNPs showed a positive association. The odds ratio amplitude was 0.144 (95%IC = 0.028 to 0.602) for rs2348071*AA (PSMA3 gene) to 5.809 (95%IC = 1.536 to 37.54) for 11702779*AA (RUNX1 gene). In our data, we observed an interaction between CFTR mutations rs9870255*CTNNB1, rs9378805*IRF4 and rs7664617*KCNIP4 ($p = 0.020$) with pancreatic insufficiency.

Conclusions

Multiple SNPs in inflammatory response genes showed an association with pancreatic insufficiency in patients with CF when considering CFTR mutations screening. To the best of our knowledge, the interaction between the SNPs represents a first description of genetic interaction with pancreatic insufficiency in patients with CF.

#F57 – Plasmatic Amino Acids in Patients with Cystic Fibrosis: An Observational Study.

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Introduction

Malnutrition in patients with Cystic Fibrosis results from a mismatch between nutrient requirement and consumption. Energy deficit depends on 3 factors: lost energy, energy taken with food and energy expenditure. Genetic mutation depletes Cystic Fibrosis Trans-membrane Regulator (C.F.T.R.) function on the surface of epithelial cells in the digestive tract and in other compartments, where Cl⁻, other ions and water secretions are impaired. This modifies pH and dehydrates secretions that precipitate and obstruct the lumen, causing inflammation and damages. Associated conditions include exocrine pancreatic insufficiency, impaired bicarbonate and bile secretion and aberrant mucus formation, leading to maldigestion and malabsorption, particularly of fats and fat-soluble vitamins. Multiple factors can contribute to the reduction in energy intakes such as anorexia, gastroesophageal reflux, Distal Intestinal Obstruction Syndrome and lung inflammation. Declining pulmonary function is associated with the Resting Energy Expenditure (R.E.E.) increase from 10 to 20%. Chronic lung disease

exacerbations lead to an increased R.E.E. value, which returns to basal levels some weeks after resolution of inflammation. Attempting to balance the energy gap justifies precocious and aggressive nutritional intervention, which begins in the early years and continues throughout life. However, an increase in caloric intake is not sufficient to neutralize protein-calorie need resulting from R.E.E. value growth. Non-energy intake results in reduced respiratory muscle function and decreased exercise tolerance, causing a chronic and irreversible deterioration in patient status, until death.

Aim of The Study And Methods

The aim of our study is to observe and analyze the evolution of Plasmatic Amino Acids in a sample of 34 CF patients, 17 men and 17 women, treated with appropriate low-carb, high-fat, high-calorie, high-glucose diet, tailored to anthropometric values, age and gender, as well as recommended by the latest guidelines, and to assess a possible correlation with the patient's clinical phenotype nutritional state. RESULTS Aminoacidogram showed that: 16/34 patients (47%) had significantly reduced Plasmatic Amino Acid levels; when considering patients with severe malnutrition, 63% presented an altered Amino Acid profile, although 30% of those with good nutritional status also had lowered levels. These results suggest the presence of a metabolic disorder, which does not depend solely on nutritional status. CONCLUSION In conclusion, the amino acid profile seems to be influenced by different factors and somehow identifies a "metabolic disorder" that characterizes Cystic Fibrosis. Furthermore it does not appear to be outweighed only through high-calorie diet. Future studies and larger clinical samples will be needed.

#F58 – Evaluation of Oxidative Stress Degree in Patients Affected by Cystic Fibrosis or Non-CF Bronchiectasis through the Measurement of 8-isoprostane.

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Introduction

8-isoprostane (8-IP) is a molecule that belongs to the class of F2-isoprostanes, products resulting from lipid peroxidation. These molecules are synthesized as a consequence of the action of free radicals on esterified arachidonic acid, present in membrane phospholipids and released by the action of phospholipase A2. Once freed, isoprostanes reach the various tissues and body fluids where they can be quantified due to their persistence, due to chemical stability and relative abundance compared to other lipid peroxidation products. The purpose of the study was to evaluate the levels of 8-IP in serum (8-IP ERA) and condensed exhaled (EBC 8-IP) in patients with diagnosis of CF (cystic fibrosis) and patients diagnosed with non CF bronchiectasis (BnFC). These values were then put in correlation with certain clinical and demographic variables of patients to verify whether the concentration of the marker could be influenced by the latter.

Methods

The levels of 8-IP in serum and in breath were measured in eleven patients affected by CF and in eleven patients with non CF bronchiectasis. Age, body mass index, FEV1%, Tiffeneau index, pancreatic function, diabetes, atopy and FeNO index were verified in every patient.

Results

The measurement of 8-isoprostane showed higher values in CF patients compared to patients with non FC bronchiectasis both in serum (8-IP SER 873.0 ± 208.5 pg / mL in FC vs. 401.9 ± 207.5 pg / mL in BnFC, $p > 0.05$) and in EBC (EBC 8-IP 7.2 ± 2.5 pg / mL in FC vs. 5.4 ± 1.0 pg / mL in BnFC, $P > 0.05$). Furthermore, a weak statistically significant correlation was found between the values of 8-IP ERA and Tiffeneau index (R-Squared = 0.175 $p < 0.05$). The correlations between other variables and multivariate analysis did not reveal significant results both for the values of 8-isoprostane EBC and those of serum.

Conclusions

8-isoprostane is higher in CF patients compared with patients affected by non CF bronchiectasis. Further studies are needed to define its role in the pathogenesis of the disorder. The 8-IP serum levels appear to be related with the Tiffeneau index; in contrast, the other clinical and demographic variables do not appear related to serum and EBC 8-isoprostano levels. In this descriptive study in patients with CF, we found the highest values of 8 IP in those aged > 18 years, both in EBC and in serum; in subjects with BMI <18.50 in serum and finally in patients with FEV1% <70% both in EBC and in serum, although not significantly ($P > 0.05$). However the results may also be a consequence of the low sample and for this reason continuation of the study is needed in a larger population.

Keywords: 8-isoprostane, cystic fibrosis, bronchiectasis, oxidative stress.

#F80 – Variants in the IL-8 Gene and the Response to Inhaled Bronchodilators in Cystic Fibrosis

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Objective

The IL-8 protein (interleukin 8) promotes inflammatory responses, including in the airways. The presence of variants in the IL-8 gene causes altered inflammatory responses and possibly varied responses to inhaled bronchodilators (BD). Thus, this study analyzed the IL-8 variants (rs4073, rs2227306 and rs2227307) and their association with the response to BD.

Methods

Analysis of IL-8 variants was performed by RFLP-PCR. The association between spirometry markers and the response to BD was performed by Mann-Whitney and Kruskal-Wallis tests. The analysis included all

CF patients, and subsequently patients with two mutations in the CFTR gene belonging to Classes I to III. Alpha = 0.05.

Results

This study included 186 CF patients. There was no association of the rs2227307 variant with the response to BD. The rs2227306 variant was associated with FEF50% in the dominant group and in the group with two identified mutations in the CFTR gene. The rs4073 variant was associated with spirometry markers in four genetic models: co-dominant (FEF25-75% and FEF75%), dominant (FEV1, FEF50%, FEF75% and FEF25-75%), recessive (FEF75% and FEF25-75%) and over-dominant (FEV1/FVC).

Conclusions

This study highlights mainly the importance of the rs4073 variant of the IL-8 gene with the response to BD and assessment of mutations in the CFTR gene.

#F107 – Vitamin D and Risk Factors for Lung Disease in Infants and Young Children with Cystic Fibrosis

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Objectives

To associate vitamin D levels in infants and young children with Cystic Fibrosis (CF) and risk factors for evolution and severity of lung disease.

Methods

All patients between 0 and 4 years 11 months 29 days attending the Cystic Fibrosis Reference Center from the School of Medical Sciences of the University of Campinas were selected. Those who met the criterion of being positive on Newborn Screening and who later had two positive sweat tests were included. Serum levels of vitamin D were assessed using LIASON® 25 OH Vitamin D TOTAL Assay, considering insufficiency when 25(OH)D values were under 30 ng/ml, and sufficiency when above this value. At the moment of vitamin D assessment, information on age, sex, presence of *Pseudomonas aeruginosa* in oropharyngeal cough swabs, school or day care attendance, vitamin D supplementation, sun exposure and use of sunscreen, severity of lung disease, body mass index (BMI), pancreatic insufficiency (PI), use of inhaled antibiotic, prophylactic antibiotic and dornase alpha were collected. Sun exposure was considered sufficient when exceeding 2 hours a week, according to the Brazilian Pediatrics Society guidelines. Severity of lung disease was classified in severe and not severe, considering severe those patients who had first colonization by *Pseudomonas aeruginosa* younger than 6 months old or at least one hospital admission for acute respiratory insufficiency. Statistics were calculated using the Fisher Test, Mann-Whitney Test and Chi-Square test on SPSS 17.0 software, and $p < 0.05$ was adopted.

Results

Thirty-five children, 18 boys (51.4%), with mean age 22.8 months (± 16.10) and median 22.0 months (1–57) were included. There was no significant association when comparing vitamin D levels with age at the moment of blood collection ($p = 0.433$), sex ($p = 0.380$), lung colonization ($p = 1.000$), school/day care attendance ($p = 0.134$), vitamin D supplementation ($p = 0.246$), use of sunscreen ($p = 1.000$), sun exposure ($p = 0.367$), BMI ($p = 0.619$), PI ($p = 0.176$), use of inhaled antibiotic ($p = 0.486$), prophylactic antibiotic ($p = 0.700$) and dornase alpha ($p = 0.203$). However, there was association with vitamin D levels and severity of lung disease ($p = 0.018$). The analysis of severity of lung disease and BMI ($p = 1.000$) and pancreatic insufficiency ($p = 1.000$) also showed no association.

Conclusion

Severity of lung disease presented significant association with vitamin D levels, suggesting that low levels of 25(OH)D indicate a risk factor for occurrence of pulmonary events in early childhood. This result shows the importance of early investigation of associated risk factors for lung disease. Reflections and Proposals: Further studies should be carried out to define whether the low levels of vitamin D are associated with pulmonary inflammatory alterations that may be responsible for the severity of lung disease, or if it is a consequence of a worse mutation profile observed in CF patients. Lung structural damage was not assessed since CT was not performed in all patients.

#F111 – Cystic Fibrosis Carriership and Tuberculosis: Hints toward an Evolutionary Selective Advantage Based on Data from the Brazilian Territory.

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Background

The reason why Cystic Fibrosis (CF) is the most common fatal genetic disease among Caucasians is subject to speculation and has been incompletely studied up till now. We aimed at deepening the hypothesis that carrying a single CF mutation might have a relative protection against infections with *Mycobacterium tuberculosis* (Mtb).

Methods

Using a multidisciplinary, spatial epidemiological approach, we studied the link between CF carriership rate and tuberculosis (TB) incidence on two scales in Brazil: the state and municipality level. We corrected for six potential confounders in the relation: monthly income, sanitary

provisions, literacy rates, racial composition, population density, and AIDS incidence rates.

Results

On the state-level, a trend towards a negative relation between F508del carriership and TB incidence could be observed. Subsequent spatial patterns and statistical analysis on the municipality level showed a significant, negative correlation between CF carriership rate and TB incidence, independent of any of the six socio-economic, external determinants that could act as potential confounder.

Conclusion

Our study provides strong support for the hypothesis that carrying a single CF mutation plays a protective role against Mtb infections. This could be the evolutionary answer to the riddle of continued CF occurrence and encourages biomedical research into the human resistance genetics of infectious diseases.

#F132 – Imperfection of Sputum Examination for Chronic Lung Infections in Bulgarian CF Patients.

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Background

The percentage of chronic infections with *Pseudomonas aeruginosa* in Bulgarian patients with cystic fibrosis (CF) is one of the highest reported of all EU countries. Patients with CF in nearly 30–35% have difficulties in expectorating sputum (even after induction), which may be the reason for the late detection of colonization with *Pseudomonas aeruginosa* and thus the delay in implementing eradication regimens. In the global standards for the treatment of patients with cystic fibrosis, determination of antibodies to *Pseudomonas aeruginosa* is a major element in tracing these patients, displacing even standard microbiological testing.

Aim

To search for *P. aeruginosa* antibodies in patients with CF, even in the absence of a microorganism in respiratory tract samples (sputum, throat aspirate).

Material and methods

In 140 CF patients (76 males, 64 females; aged from 0.1 to 65 years), we examined secretions from the airways for a precise microbiology identification. We used an ELISA – ready kit for IgG antibodies to *P. aeruginosa* detection in peripheral venous blood.

Results

Chronic infection with *P. aeruginosa* from respiratory samples was found in 91 patients (65.40%). All these patients had high IgG levels of anti-*P. aeruginosa* antibodies (over 50 U/ml). In the remaining 49

patients without prior or current *P. aeruginosa* isolated in sputum, 6 (20%) were found to have elevated antibody levels.

Conclusion

Perhaps the reason for the negative statistic in Bulgaria is due to the fact that the test for antibodies is not routinely performed in our practice and we rely mostly on sputum/throat swabs and sometimes we are unable to have truly early detection of colonization with *P. aeruginosa* and our eradication regimens are delayed.

Acknowledgements

This work was supported by a grant from the Medical University of Sofia (Council of Medical Science, project no. 512/2016, grant no. 64/2016).

#F135 – Inhaled Antibiotic Therapy: Experience of a Specialized Cystic Fibrosis Center.

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Purpose

The efficacy of inhaled antibiotics (IA) in treating chronic *Pseudomonas aeruginosa* pulmonary infection in cystic fibrosis (CF) patients has been established. More recently its efficacy as a therapy for eradication in new infections is also known. Several regimens have been used with success. The aim of this study is to assess our practices, evaluate the safety and problems associated with the type and regimen of IA therapy, performed in CF children followed in a tertiary hospital between 2011–2015.

Methods

This retrospective study was conducted at the Santa Maria Hospital Cystic Fibrosis Center. We examined the files of all patients in an IA regimen and described demographic data, comorbidities, sputum microbiology, antimicrobial resistance, prescribed IA, regimen type and number of cycles.

Results

The mean age of the 50 included patients was 13(SD 5.69) years, 21 (42%) were male, 35(70%) homozygous for F508del mutation, 47 (94%) had pancreatic insufficiency and 3(6%) had diabetes. The median age at the first IA therapy was 5.8yrs [8mths; 16yrs]. IA was mainly instituted for *P. aeruginosa* but also for *B. cepacia*, *S. maltophilia* and *M. abscessus*.

The main microbiological agents identified in sputum samples were: *P. aeruginosa*(90%), *S. aureus*(84%), MRSA(22%), *A. xylosoxidans* (26%), *S. maltophilia*(22%), *B. cepacia*(16%) and *A. fumigatus*(38%).

The most common IA treatment regimen was monotherapy in 72.2% of the patients, while 27.8% used 2 alternate/simultaneous antibiotics.

In the monotherapy group, the antibiotics and regimens used were: tobramycin “on-off” 60.2%, colistin 25.3%, ceftazidime 8.4%, meropenem 2.4%, amikacin 1.2% and continuous tobramycin 1.2%

and in the double therapy group: tobramycin/colistin (every other month) 62.5%, tobramycin/aztreonam (alternate months) 21.9%, colistin/aztreonam (every other month) 12.5%, ceftazidime/aztreonam (alternate months) 3.1%, meropenem/colistin (simultaneously) 3.1%.

Tobramycin was prescribed in 98% of patients (monotherapy/alternate with another antibiotic), resistance developed in 5(10.2%) and 12(24%) were previously infected with resistant strains. Five patients were treated with ceftazidime (3 colonized with *B. cepacia* and 2 with *P. aeruginosa* and *B. cepacia*) and resistance developed for *B. cepacia* in 4 cases and for *P. aeruginosa* in 1 case.

A few patients reported bronchoconstriction with tobramycin that was resolved with salbutamol administration before tobramycin in all patients, except one. All patients were checked for nephrotoxicity which was not found. No other adverse events were noticed.

Median length of IA therapy was 12[1; 59] months and median number of hospital admissions during IA therapy was 2[1; 11].

Conclusion

In this center, during the study period, monotherapy was the preferred regimen of IA therapy, with tobramycin “on-off” being the most commonly used antibiotic. We classified this regimen as safe and easy to perform, but antibiotic resistance is a problem to be considered on the strategies employed.

#F142 – Genetic Mutations and Presentations in a Cystic Fibrosis (CF) Clinic in a Low Middle Income Country.

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Background

Cystic fibrosis (CF) is a common genetic disorder in the white population and is increasingly being identified in non-white populations. Black African children with CF commonly present with nutritional and growth abnormalities, with little known about their mutation status.

Objectives

To describe the characteristics of children followed up at the CF clinic at the Inkosi Albert Luthuli Central Hospital, South Africa.

Methods

A retrospective chart review of clinical, laboratory and lung function data of patients registered from January 2013 to November 2016. Means were calculated for age, weight, height, BMI and FEV1% with standard deviations for normally distributed data. Pearson correlation was used for comparing non categorical variables with $p < 0.005$ considered as significant. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu Natal (Ref. BCA 469/15).

Results

Data from 15 patients were reviewed. Their ages ranged from 26 months to 219 months and 46% were female. Sixty percent were white and 26.6% were black African. The mean age at diagnosis was higher in non-whites: 104 ± 46 months vs. whites 1 ± 1 month ($p < 0.00001$). Mean sweat chloride concentration for non-white children was higher in those with mutations: 127 ± 9 mmol/L vs. those without mutations 73 ± 22 mmol/L ($p < 0.01$), 89% were pancreatic insufficient. The white group had better nutritional status with body mass index (BMI) of 17.2 ± 2.4 kg/m² compared with 14.5 ± 1.6 kg/m² for non-whites. Age at diagnosis had a negative correlation with weight-for-age z-score (-0.61 , $p < 0.05$) and body mass index (BMI) (-0.54 , $p < 0.05$). The mean predicted forced expiratory volume in 1 second (FEV1%) was 70 ± 35 %. FEV1% had a positive correlation with weight z-score (0.83 , $p < 0.001$) and BMI (0.59 , $p < 0.05$). p_heIF508.del was the most commonly identified mutation in white patients; with 4 homozygotes and 4 heterozygotes. The South African 30 mutation panel test missed 2 of the cases of CF in 5 non-white children prior to complete CFTR gene sequencing. 1 patient of black African descent was found to have the mutation L218X/c.2788G>5 and the other of Indian descent, was found to have the mutation S1255P/R709X.

Conclusion

CF is diagnosed late in non-white children in SA, affecting their growth and lung function. A genetic panel that includes mutations specific to children of African descent is required.

#F164 – Fat Free Mass Deficit in Children and Adolescents with Cystic Fibrosis. What is the Implication in Pulmonary function?

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Background and Aim

Children with cystic fibrosis (CF) usually have poor nutritional status and this condition is associated with worsened lung function. The aim of this study was to evaluate body composition and relate the latter to pulmonary function.

Methods

Cross-sectional study with 34 children/adolescents followed in a specialized CF center. Demographic, clinical and functional data were collected: sex, age and genotype, pancreatic and respiratory function. We also collected weight, height, fat mass (FM), fat free mass (FFM) and triceps skinfold; the nutritional indexes were calculated. Statistics by IBM®SPSS® 22.

Results

Mean age was 10.3 ± 4.7 years, 61.8% female; most patients (67.6%) were homozygous for mutation Fdel508; 91.2% had pancreatic insufficiency. The mean FEV1% was 93.4 ± 20.4 %. Regarding

nutritional status, 85.3% of the patients were eutrophic and 8.8% had low weight. However, according to bioimpedance, 80% of patients were found to have excess FM, and 84% had high FFM deficit. Males had less FFM index (FFMI) than females (7.3 ± 2.5 vs. 9.9 ± 2.3 ; $p < 0.05$). A positive correlation was found between FEV1% and BMI z-score ($R = 0.414$; $p = 0.026$) and with the FFMI ($R = 0.413$, $p = 0.045$).

Conclusion

These results show that patients exhibit significant changes in body composition characterized by an excess in FM and a deficit in FFM even though the BMI showed they were eutrophic. In this context, further studies are necessary to identify the therapeutics needed to improve body composition and inflammatory activity, since a higher FFMI is associated with the best parameters of pulmonary function.

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

#G4 – Prevalence and Pattern of Respiratory Diseases in Children Living With HIV in Enugu, South-East Nigeria

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Rationale

The lung is a major target organ for human immunodeficiency virus (HIV) infection, rendering it susceptible to both infectious and non-infectious complications. This work assesses the prevalence and pattern of respiratory diseases among HIV-infected children attending our HIV specialist clinic.

Methods

A 10 -year retrospective review of HIV-infected children who were seen at the Pediatric HIV clinic of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu. HIV diagnosis was made by HIV DNA PCR testing, pneumonia diagnosis was made using WHO Pneumonia clinical algorithm; Pulmonary Tuberculosis (PTB) diagnosis was made using clinical and radiological criteria (fever, cough of >1 month duration, weight loss, history of contact with adult with chronic cough, night sweats, and at least one positive smear/Gene Xpert test of sputum or gastric aspirate while Chest X-ray interpretation was performed by an independent consultant radiologist). Reported changes included bronchovascular markings or reticular densities, parenchymal consolidation, nodular densities and hyperinflation. Socio-economic status was determined by methods as described by Oyedeji. Data analyses were performed with the Statistical Package for Social Sciences (SPSS) version 19 (Chicago, IL).

Results

A total of 522 HIV-infected children were included in the data analysis. There were 267 females (51.1%) and 255 males (48.9%) with 341

children (65.3%) being from the lower social class. Mother-to-child transmission of HIV accounted for 481 (92.5%) of the infections. One hundred and eighty-one (34.7%) study participants had respiratory infections. Fifty-three of the 181 (29.3%) children with respiratory infections had acute respiratory infections (ARI), 107 (59.1%) had PTB, while 21 (11.6%) had chronic suppurative otitis media (CSOM). The mean age at last birthday among children with respiratory diagnosis was 9.9 ± 3.8 years compared to 9.9 ± 4.9 years among those without respiratory infections ($p = 0.99$). One hundred and twenty-four of 181 children (72.5%) with respiratory infections compared to 18 of 287 (6.3%) without infections had abnormal chest x-ray ($p < 0.001$). Twenty-four of 165 children (14.5%) with respiratory infections compared to 37 of 322 (11.5%) without respiratory infections were on second-line HAART ($p = 0.39$). No data on spirometry were available for all study participants.

Conclusions

Respiratory infections are prevalent among children with HIV; the most common in our series being pulmonary tuberculosis. Chronic radiological changes are more common in HIV-infected children with clinical features of respiratory pathology. There is need for further pediatric pulmonology reviews such as serial lung function measurement in HIV-infected children with pulmonary diseases.

#G50 – Pulmonary Involvement in Children with Selective IgG3

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Objective

IgG immunodeficiency is the most frequent impairment of humoral immunity that results in severe infections in children. However, selective IgG3 deficiency is not well described. It is diagnosed if a low value of IgG3 is constantly detected whereas total IgG remains in the normal concentration range according to the children's age. The aim of this study was to identify the clinical presentation from the respiratory tract of children with selective IgG3 deficiency.

Methods

34 children (22 boys, mean age 5.7 ± 3.4 y) with selective IgG3 deficiency were examined in our unit during the last ten years. The reported presenting symptoms were lifetime and current asthma in 70.6% and 53% respectively while 20 cases (58.8%) were admitted to hospital due to pneumonia or respiratory distress. Results. In 26.5% and in 47% of the cases, chronic rhinosinusitis and protracted bacterial bronchitis, with positive sputum or BAL culture, were respectively detected. The imaging study (CXR, HRCT) showed in 38% and 41% cases consolidation and atelectasis of middle lobes, respectively. Sensitization to aero allergens was found in 26.5% of children.

Conclusion

Selective IgG3 deficiency in children frequently manifests with protracted bacterial bronchitis and chronic rhinosinusitis, often complicated with pneumonia or atelectasis. Clinical presentation seems to point to chronic inflammation of the respiratory tract and it should be suspected in cases with similar presentation.

#G52 – The relationship between Protracted Bacterial Bronchitis and Upper Gastrointestinal Diseases.

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Objectives

Protracted bacterial bronchitis (PBB) is a clinical condition characterized by chronic wet cough lasting for >4 weeks which resolves fully following appropriate prolonged antibiotic treatment. The main risk factors are impaired mucociliary clearance after viral respiratory infection, airway malacia, immunodeficiency and exposure to tobacco smoke or industrial pollution. The aim of this study was to describe four cases of PBB which presented with intense considerable upper gastric (GI) symptomatology.

Cases Presentation

Recurrent chronic rhinitis and wet cough were the main presenting symptomatology in all three cases whereas dyspnea or wheezing occurred quite rarely. Immunological profile was normal. Even though inhaler bronchodilators, corticosteroids (both during exacerbation as well as prophylactic treatment) and per os antibiotics were frequently used, none proved to be helpful. The detailed revision of their medical history revealed nutritional difficulties with recurrent symptoms of vomiting and anorexia. Bronchoscopy evaluation showed increased percentage of neutrophils (30%-88%) and three cases had increased numbers of eosinophils (30%). BAL cultures showed gram +ve bacillus >10⁵ mainly *Haemophilus Influenzae* and *Moraxella catarrhalis* in all cases. Gastroscopy evaluation revealed severe GER in one case and severe eosinophilic esophagitis in the other three with BAL eosinophilia. All symptoms completely resolved when appropriate therapy for GER disease and eosinophilic esophagitis was followed.

Conclusion

In persistent PBB, unresponsive to treatment, co-morbidity with GI disease must be thoroughly sought for and evaluated. Common embryonic origins as well as immunological signaling pathways of both respiratory and GI tract may represent one of the underlying mechanisms for the relationship found between these two different disease entities.

#G73 – Isolated Acute Lupus Pneumonitis as the Initial Presentation of Systemic Lupus Erythematosus in An 8-Year-old Girl.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disease and commonly present with arthritis, cutaneous manifestations, cytopenia and glomerulonephritis. Pulmonary involvement is broad in SLE of which the most frequent manifestation is pleuritis. Herein, we report an 8-year-old girl with isolated acute lupus pneumonitis.

Case Report

An 8-year-old female patient was referred to the Pediatric Pulmonology Department for dry cough and weight loss for one month. There was no consanguinity in the family. She had no history of recurrent infection, exposure to feathers/birds excrement or drug use. There were crepitant crackles in both lungs on physical examination. Diffuse fibrotic changes and parenchymal consolidation were found on chest x-ray and thorax CT revealed common fibrotic changes, interlobular septal thickening and subpleural parenchymal consolidation compatible with organizing pneumonia. Pulmonary function tests were compatible with a restrictive pattern. Acute phase reactants were negative. All microbiological investigations including tuberculosis were negative. ANA 2+, Anti dsDNA were positive, C3-C4 were normal. She had no proteinuria, hematuria, arthritis, rash or hematological abnormalities. Her eye examination was normal. Bronchoscopy was performed with neutrophilic dominance in bronchoalveolar fluid. Lung biopsy revealed NSIP-like areas with plasma cell-rich inflammatory cell infiltrate in addition to patchy consolidated areas with increased interstitial fibrosis and chronic pleuritis. She was diagnosed as SLE and systemic steroid treatment was initiated. On the fourth month of treatment, although her ANA and Anti-dsDNA were negative, she had a Cushingoid appearance, common stria on the legs and back, osteoporosis and mild glaucoma. Steroid treatment was progressively tapered and azothiopurine and mycophenolate mofetil were started respectively. After steroid treatment started to be reduced, ANA and Anti dsDNA results were again positive. Since there was no improvement in pulmonary function test and radiological findings after reducing steroid treatment, hydroxychloroquine treatment was added. Her radiological findings and pulmonary function tests were improved. She is currently followed without any complaint for two years.

Discussion

Pleuropulmonary manifestations of SLE include pleuritis, pleural effusion, pulmonary hemorrhage, acute lupus pneumonitis, chronic lupus pneumonitis, shrinking lung syndrome and pulmonary hypertension. Only interstitial lung involvement in SLE is very rare, especially in childhood.

#G82 – Prediction of Treatment Outcome in Children with Obstructive Sleep Apnea and Down Syndrome by Functional Respiratory Imaging.

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Purpose of the Study

Prevalence of obstructive sleep apnea (OSA) is between 24–79% in children with Down syndrome (DS). The complexity of the pathogenesis of OSA in these children is illustrated by a high incidence of residual OSA after adenotonsillectomy (AT) and by a frequent need for additional treatment. The aim of this study was to investigate whether functional respiratory imaging (FRI) could predict treatment outcome in children with DS and OSA.

Methods

Caucasian children with DS diagnosed with OSA by polysomnography were prospectively included. All children underwent a thorough evaluation and an ultra-low dose computed tomography scan of the upper airway (UA). The upper airway tract was extracted from the scan and combined with computational fluid dynamics for FRI. Decisions on the need and type of surgery were based upon findings during drug-induced sleep endoscopy. Results were evaluated by a control polysomnography (PSG) after surgery. Children without a second PSG were excluded.

Results

Twenty-nine children were included: 14 boys, mean age of 7.6 ± 5.2 years, mean body mass z-score of 0.7 ± 1.2 and obstructive apnea-hypopnea index (oAHI) of 17.1 events/hour (3.1–70). Two children had a history of AT, 1 had undergone tonsillectomy. Seven children were diagnosed with moderate, 16 with severe OSA. DISE-directed surgery consisted of tonsillectomy ($n = 8$), AT ($n = 13$) and adenoidectomy in 1 patient. Three children only received medical treatment with orthodontics. After treatment, 25 children underwent a second PSG, 17 children had persistent OSA (oAHI > 2/hr), however, 15 patients had a >50% decrease in oAHI. Children with >50% decrease in oAHI were significantly younger, had a lower conductance of the airway and less tongue base collapse. A >50% decrease in oAHI was predicted by a conductance of less than 3.58 1/kPa/L (OR 0.2; CI 0.052; -0.891, $p = 0.03$). This cut-off value had a sensitivity of 100% and a specificity of 93%. There was a difference between children younger ($n = 16$) and older than 8 years old ($n = 9$). Younger children: 13 of 16 children had a decrease of >50% in oAHI after treatment. Children with a good response to treatment had a significantly lower conductance of the upper airway ($p = 0.007$). Older children: 2 of 9 children had a decrease of >50%, tongue base collapse was observed in 7 children.

Conclusions

This is the first study predicting treatment outcome in DS children with OSA by FRI. Younger children have a better treatment outcome than older children. A conductance higher than 3.58 and tongue base obstruction in children (> 8 years) were associated with insufficient response to (adeno)tonsillectomy.

#G87 – An Infra-Diaphragmatic Cystic Teratoma as a Treatable Cause of Chronic Respiratory Insufficiency.

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Aim of the Study

To present a case of successful treatment of a midline infra-diaphragmatic teratoma compressing the chest cavity and leading to respiratory insufficiency and oxygen therapy in a toddler with Rubinstein-Taybi Syndrome.

Methods

A retrospective analysis of a clinical case.

Main Results

A 4-month-old girl with Rubinstein-Taybi Syndrome presented with stridor related to tracheomalacia, severe alimentary difficulties resulting from GER and progressive cardiac and respiratory insufficiency leading to permanent oxygen therapy, with increasing O₂ needs, that is interpreted as a result of PAD and Pulmonary Interstitial Disease. The DA was then surgically closed. At 20 months of age, due to the escalation of these symptoms and the appearance of an anterior chest wall deformity, the patient had a Thoracic CT Scan that showed, in addition to a bilateral ground glass opacity, an anterior large cystic mass in the thoraco-abdominal transition, that was confirmed by MRI. The patient underwent Kocher Laparotomy and a large infra-diaphragmatic mass that was shaping the anterior wall of the liver was identified. The mass was totally resected with no intra-operative complications. The thorax recovered its normal shape after the mass was resected. The pathology revealed that the mass was a Bigerminal Mature Teratoma. The post-operative period was uneventful. The patient was extubated at D1 after surgery. Afterwards she maintained O₂ saturations above 98% with no need for supplementary O₂. Two months after surgery, the patient remains well with no respiratory complaints.

Conclusion

Rubinstein-Taybi Syndrome is a rare condition, affecting 1 in 125.000 newborns. Children with this syndrome have an increased risk of developing respiratory problems and benign and malignant tumors. It is important to look for treatable causes of respiratory insufficiency in these patients and a multidisciplinary approach is crucial to achieve good results.

#G123 – Case Report: Malignant Peripheral Nerve Sheath Tumor Presenting with Pleural Effusion in a Teenager with Neurofibromatosis Type-1.

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Introduction

Neurofibromatosis Type 1 (NF-1) is a neurocutaneous syndrome with patients at high risk of concomitant malignancy. We present the investigation and management of unilateral pleural effusion and mediastinal mass in a pediatric patient. Case: A fourteen year-old Caucasian female with NF-1 presented with a 10-day history of worsening shortness of breath and lower back pain radiating to her left shoulder. The patient was known to have a left ulnar nerve plexiform neurofibroma since birth, which extended into the brachial plexus and intraspinal canal. This lesion was being monitored regularly and was stable according to serial MRI imaging, last performed 3 months previously. There was no history of fevers, hemoptysis, night sweats or weight loss, although the patient looked cachectic. A chest radiograph on admission showed diffuse left hemithorax opacification with contralateral mediastinal shift (Fig 1).

A chest ultrasound suggested a heterogenous mass inferior to the effusion. Initial biochemistry showed an elevated C-reactive protein (75 mg/L) and low albumin (26g/L). A 10-French pigtail chest drain was inserted, draining copious amounts of blood stained fluid. Fluid microscopy showed no organisms or acid fast bacilli. CT chest showed a heterogeneous soft tissue mass extending to the pericardium and posterior mediastinum, involving the left lower lobe and displacing the left hemidiaphragm inferiorly (Fig 2).

A laparoscopy biopsy of the mass was taken, with histopathology indicating a high-grade malignant peripheral nerve sheath tumor. The patient was referred for oncological and surgical assessment. Cardiac MRI showed invasion of the posterior pericardium, however no bone involvement was shown by isotope scan and bone marrow trephine. Discussion: A mediastinal mass in a patient with NF 1 has a wide differential, including spindle cell sarcomas such as malignant peripheral nerve sheath tumors (MPNST). NF-1 patients with plexiform neurofibromas have a 10–15% incidence of transformation into MPNST. MPNSTs are more likely to arise in adults with only 10–20% of diagnoses made in pediatric patients. The most common sites of occurrence are the trunk wall, extremities and head/neck region. Chest involvement is rare. These tumors can be highly invasive with multiple sites of metastases. Tumors are not typically responsive to chemotherapy and management focuses on surgical resection with a possibility of radiotherapy thereafter. Although a surgical procedure would probably not be curative, it was offered to the patient and her family as a life prolonging measure. She underwent surgical resection under an

adult cardiothoracic team. Conclusion: We describe a case of a rapidly growing MPNST in a pediatric patient with NF-1 leading to respiratory complications due to its uncommon location. The prognosis for this patient is poor and treatment will be centered around palliation of symptoms if complete resection proves impossible.



Figure 1 Chest radiograph on admission

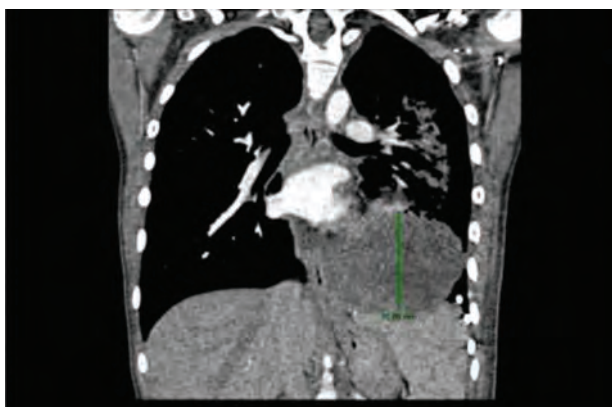


Figure 2 CT chest with contrast showing heterogenous mass in left lower hemi-thorax

#G129 – Assessment of Pulmonary Function in a Cohort of Children with Sickle-Cell Disease.

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Purpose of the Study

Pulmonary complications of sickle cell disease (SCD), such as chronic sickle cell lung disease and acute chest syndromes (ACS), are important causes of morbidity and mortality. Since the highest incidence of ACS occurs during childhood, lung alteration may start early in life. The main aim of our study was to assess the prevalence of pulmonary function alteration in children with SCD followed at our hospital. The secondary aims were to look for

association between altered pulmonary parameters and potentially deleterious variables, in order to identify potential risk factors.

Methods

We retrospectively reviewed the files of the 168 children with SCD followed in our hospital and recorded their pulmonary parameters, as well as anthropometric data, biological variables and clinical events. We then assessed their pulmonary function and looked for association with the recorded data.

Results

We found a very high proportion of patients with severe phenotype (hemoglobin SS or S β 0) and treated with daily hydroxyurea in our cohort. More than half of the patients (55%) presented a ventilatory function alteration, of which 38% were obstructive and 17% restrictive. Lower oxygen saturation, higher white blood cells, as well as a higher number of vaso-occlusive crises (VOC) were found in the group presenting an obstructive lung alteration. A significant negative correlation between the white blood cell count and FEV1/FVC as well as FEF25-75 was revealed; supporting the hypothesis that chronic inflammation could be responsible for obstruction of the small airways. A history of ACS was significantly correlated with a worse FEV1, FEV1/FVC, FVC and FEF25-75. The number of ACS and the length of stay were also significantly correlated with lower FEV1 and FEV1/FVC.

Conclusion

Pulmonary function alterations appear to start early in childhood of patients with SCD, and to be associated with clinical events such as ACS and VOC. However, further prospective studies are needed to confirm the link between ACS and obstruction of the small airways in children with SCD.

Reflections and Concrete Proposal

Young children being more likely to present ACS, and recent data showing a greater rate of decline of pulmonary function in young children, our results support the fact that screening for lung alterations should begin early in childhood, as well as asthma diagnosis and airway hyperresponsiveness detection, to prevent serious acute and chronic effects in children with SCD.

H. NEUROMUSCULAR AND CHEST WALL DISEASES (INCLUDING SIDS)

#H62 – Diaphragmatic Dysfunction in SEPNI-related Myopathy.

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Background

SEPN1-related myopathy (SEPN1-RM) is characterized by axial predominance of muscle weakness, early scoliosis, rigid spine, and severe respiratory insufficiency which is lethal without nocturnal noninvasive ventilation (NIV). The aim of the study was to characterize the mechanisms of respiratory dysfunction in SEPN1-RM patients.

Methods

Breathing pattern and respiratory muscle strength were measured by means of esophageal (Pes) and gastric (Pgas) pressures.

Findings

Seven patients aged 7–55 years (1 adult) at first respiratory muscle test, were studied. Five patients were treated by nocturnal NIV ≥ 4 months. Mean ΔP_{es} (7.8 ± 2.1 cmH₂O) was within normality during tidal breathing, whereas the $\Delta P_{gas}/\Delta P_{es}$ index indicated an increased contribution of the rib cage and expiratory muscles, as compared to the diaphragm in the pediatric patients. In the adult patient, $\Delta P_{gas}/\Delta P_{es}$ was +3, indicating bilateral diaphragmatic paralysis. Forced vital capacity (FVC) was reduced in all patients ($52 \pm 19\%$) with a mean FVC seated-supine drop of $24 \pm 7\%$. Global inspiratory muscle and diaphragmatic strengths were respectively reduced in 2 patients (sniff esophageal pressure (SniffPes), -52 ± 9 cmH₂O; sniff transdiaphragmatic pressure (SniffPdi), 40 ± 0 cmH₂O), highly reduced in 4 patients (SniffPes, -30 ± 4 cmH₂O; SniffPdi, 18 ± 7 cmH₂O), and severely reduced in the adult patient (SniffPes, -11 cmH₂O; SniffPdi, -7 cmH₂O). Expiratory muscle strength was moderately reduced in 6 patients and severely reduced in the adult patient. FVC and respiratory muscle strength remained stable in 2 patients treated by nocturnal NIV within a 3-year follow-up.

Interpretation

Diaphragmatic dysfunction is a characteristic feature of SEPN1-RM and NIV may stabilize the decline in respiratory muscle strength.

#H133 – The Impact of Scoliosis on Lung Function in Children.

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Introduction

Scoliosis is the most common abnormality of the spine with direct effects on the thoracic cage. Scoliosis has generally been associated with the development of restrictive lung disease. Pulmonary function testing (PFT) is of great importance in the evaluation of lung function. Spirometry is simple, noninvasive, and has been the most commonly-used technique in children.

Objectives

To evaluate the PFT data of children with scoliosis and compare the latter with healthy children and children with asthma.

Materials and Methods

After obtaining signed informed consent from the parents, we performed PFT in 31 children aged 5 to 17 years. The children were divided into three groups – 10 children with scoliosis, 10 healthy children (with no history of respiratory diseases) and 10 children with confirmed asthma.

Results

The three groups had similar age ($p = 0.079$), sex ($p = 0.19$) and FVC/FEV1 ($p = 0.403$) distribution. The results for FVC%pred, FEV1%pred and MMEF 25/75%pred were significantly different with $p = 0.009$, $p = 0.002$ and $p = 0.001$ respectively. The lowest FVC%pred was in the scoliosis group, while the healthy and asthmatic children had comparable higher values. The children with asthma demonstrated the lowest MMEF 25/75%, while children with scoliosis had higher values than asthmatics but lower than the healthy children. The FEV1% pred was higher in the healthy group while children with scoliosis and children with asthma had comparable lower values.

Conclusion

The children with scoliosis demonstrated diminished expiratory flow rates, while the FEV1/FVC ratio was within normal ranges. Evaluation of their PFT is essential in their management plan for early intervention should not only a restriction-type deficiency be noted.

Acknowledgements

This work was supported by a grant from the Medical University of Sofia (Council of Medical Science, project no. 513/2016, grant no. 65/2016).

#H200 – Long-term Invasive Ventilation in Children with Congenital Myopathy – Case Reports.

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Introduction

Congenital myopathies are characterized by early onset of nonprogressive symptoms such as generalized hypotonia and hyporeflexia. If left untreated, these children eventually die from respiratory failure. We describe 3 patients with congenital myopathy who required tracheostomy and home long-term invasive ventilation.

Case 1

Eleven-month-old girl with nemaline myopathy with invasive ventilation from birth and tracheostomy performed at 69 days of life. She was discharged home at 4.5 months of age and is on long-term invasive ventilation with mechanical assisted cough and chest physiotherapy as adjuvant treatment. She had one respiratory infection before discharge and no more hospital admissions thereafter. She has good

social interaction (social smile and eye contact, able to interact and play with limited limb movements) and is fed by gastrostomy.

Case 2

Sixteen-month-old girl with nemaline myopathy with mechanical invasive ventilation from birth, tracheostomy from the 62nd day of life, discharged home at 4.5 months of age. She is now ventilated and managed at home with chest physiotherapy as adjuvant treatment and had no more admissions. Main complications are occasional bleeding from the tracheostomy and chronic nasal infection with *Serratia marcescens*. She is fed by gastrostomy, has good social skills and is able to communicate through eye and head movements.

Case 3

Three-year-old boy with centronuclear myopathy, born at 30 weeks gestation, who was on invasive ventilation from birth, with tracheostomy performed on the 84th day of life. He was discharged home at 3 months of chronological age on long-term invasive ventilation, with mechanical assisted cough and chest physiotherapy as adjuvant treatment. After being discharged home, he had 6 other hospital admissions, mostly with respiratory infections. He also has cardiac dysfunction requiring diuretic medication and ophthalmoparesia as comorbidities and is fed by gastrostomy. He is severely hypotonic with inexpressive facies.

Discussion

Long term ventilation is an essential life-sustaining measure for children with congenital myopathy. Home long-term ventilation represents not only a gain in quantity of life, but mainly in quality of life for the children and their families. Nevertheless, these children's life expectancy is still very limited and the decision to perform tracheostomy should take complex ethical and economic questions into account.

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

#115 – Family History, Cord Blood Immunoglobulin E and Allergy Symptoms in the First 4 Years of Life.

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Introduction

In our prospective study, we wanted to assess the relationship between family history, cord blood Immunoglobulin E (cIgE) levels and appearance of allergy symptoms in the first 4 years of life.

Methods

A total of 139 unselected newborn babies born in the maternity department of the General County Hospital of Požega from December 2009 to September 2010 were prospectively followed

from birth up to age 4. Informed consent from their mothers was obtained and this study was approved by the local ethics committee. Umbilical cord blood was obtained by the puncture of the cord vein. Total concentration of cIgE was determined by electro-chemiluminescence immunoassay (Cobas, e411, Roche diagnostics, Tokyo, Japan). The concentration of IgA in cord blood was measured to rule out maternal contamination of the cord blood specimen. Family history was obtained using structured interview of the child's mother by the clinician. At the age of 1 and 2 years, the children were re-assessed with clinical examination and structured parental interviews by the physician. At the age of 4 (3 years and 8 months to 4 years and 1 month), interviews with parents were undertaken. The subjects' history of allergy symptoms or physician-diagnosed atopic eczema, wheezing bronchitis, food allergy and allergic rhinitis was recorded. The Kolmogorov-Smirnov test was used to assess data normality. The Chi-square test was used to analyze differences between groups with and without allergic disease regarding family history. Spearman correlation coefficients between cIgE and allergy symptoms were calculated. All P values below 0.05 were considered significant. Statistical software STATISTICA version 10.0 was used in all statistical procedures.

Results

Forty-six of the 139 children (33.0%) manifested allergy symptoms during the 4-year follow-up period. Atopic dermatitis was diagnosed in 10.1% (14/139) of the children, 16.5% (23/139) had wheezing bronchitis, 2.9% (4/139) had food allergy, and 3.6% (5/139) had allergic rhinitis. Most of the children with atopy (n = 27) had a positive family history. The values of cIgE ranged from 0.0 to 16.20 IU/ml. Twenty-seven of the 139 neonates (19.4%) presented with an elevated cIgE (≥ 0.5 IU/ml). Participants who had a positive family history for allergy were more frequently in a group with at least one allergic disease (P = 0.004). No significant correlation was found between cIgE levels and allergy symptoms in the first 4 years of life.

Conclusion

Our study did not reveal an association between cIgE levels and appearance of allergy symptoms. Children with positive family history were more likely to manifest allergy symptoms in the first 4 years of life.

We would like to emphasize the importance of research on early markers of atopic predisposition.

#1124 – Social, Demographic and Etiological Profile of Severe Pneumonia in a Pediatric Service.

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Introduction

Pneumonia (PNM) is the main infectious cause of death of children under 5 years of age and a leading cause of hospitalization in children worldwide. There are a number of factors related to the prevalence

and severity of cases, such as: nutritional condition, vaccination, breastfeeding, hygiene conditions and socioeconomic factors. It is therefore necessary to evaluate the profile of the cases in each region such that these patients can be adequately treated.

Objective

The aim of this study was to establish a social, demographic and etiological profile of pneumonias in children under 14 years of age hospitalized between the years 2010 and 2015 at a Clinical Hospital of the Federal University of Parana in Curitiba, Brazil.

Results

There were 345 cases of respiratory disease that required hospitalization in the period studied; of these, 184 cases had a clinical and/or radiological diagnosis of PNM. The profile of hospitalized children showed that they were predominantly white boys, approximately 2 years of age, residents of urban areas of Curitiba, with adequate weight for their age and complete vaccination. Sample with a report of previous hospitalizations and comorbidities, per capita income in the poverty line and parents with less than 8 years of schooling. Forty-one children were admitted to the ICU, accounting for 22.3% of the sample as severe pneumonia. In less than 20% of cases, the etiologic agent was identified. When identified, virus was the main agent followed by *Streptococcus pneumoniae*. Household agglomeration and low father's schooling was significantly more present in the severe pneumonia (ICU) group as well as time of antibiotic therapy, presence of sepsis and greater number of days of oxygen therapy.

Conclusion

Despite the limitations of a retrospective and review study, the study shows a high prevalence of pneumonia requiring hospitalization as well as the impact of social and economic conditions in this group.

#1138 – Guardian's Knowledge Regarding Foreign Body Aspiration in Young Children.

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Methods

An 8-item questionnaire was sent to the guardians of infants and toddlers whose age were 4 months old (m.o.), 1.5 years old (y.o.) and 3 y.o.. Q1 "Did you know that peanuts and other nuts can cause accidents involving FBA, Q2 "Did you know that small toys can cause accidents involving FBA?", Q3 "Did you know that sudden choking is one of the symptoms of FBA?", Q4 "Did you know that sudden coughing is one of the symptoms of FBA?", Q5 "Did you know that FBA is most frequently seen in children aged 0–2 years old?", Q6 "Did you know that you should not give peanuts to a child younger than 3 years old?", Q7 "Did you know that when a child is holding a small toy in his/her mouth, you should not make him/her cry when trying to take it

out?", Q8 "Did you know that you should not allow a child to walk or laugh while he/she is eating". Guardian's experiences regarding close to choking episodes were also inquired.

Results

From October 2015 to March 2016, in the suburb area of Tokyo, 862 answers were collected from 890 sent questionnaires, 17 were eliminated due to incomplete responses; 845 cases were analyzed. There were 284 infants in the 4 m.o. group, 273 in the 1.5 y.o. group and 272 in the 3 y.o. group. 96.5% of respondents were the mother and 46% of analyzed children were a first-born child. For Q1 to Q9, percentages of knowledge were significantly low in the first-born children of the 4 m.o. group. For Q1, 69% of mothers of 4 m.o. infants had light knowledge, while 95.1% of mothers of the same age group had light knowledge for Q2. For Q6, 42% of respondent in the 4 m.o. group had light knowledge, and moreover only 21% respondents of the first-born children of the 4 m.o. group had light knowledge. Guardians' experience of "near-miss" reached 23.8% in the 1.5 y.o. group and 8.1% in the 4 m.o. group. The same questionnaire survey was conducted in 2010 for guardians' of 1.5 y.o. group, with the results resembling the present survey.

Conclusions

A considerable number of guardians lacked the knowledge to prevent FBA. Guardians who raise younger children especially a first-born infant should be given adequate information.

#1140 – Fresh Air for Children – Results of an Enhanced Smoking Cessation Counseling Study for Smoker Parents of Pediatric Respiratory Patients.

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Introduction

Secondhand smoke (SHS) is a mixture of sidestream and mainstream smoke containing nicotine and toxic chemicals. Children can be involuntarily exposed to SHS. Exposure to SHS is associated with increased risk of respiratory infections and diseases, and is adversely associated with the onset and control of asthma in children. Fresh Air for Children (FAFC) is a collaborative study by KK Women's & Children's Hospital (KKH) and the Health Promotion Board (HPB) to assess the effectiveness of an enhanced smoking cessation counseling program compared to the existing KKH smoking cessation program.

Methods

The FAFC study was conducted among parents/caregivers of children aged 1 to 12 years old attending outpatient respiratory clinics. A questionnaire survey on demographic data and SHS exposure,

knowledge and practices was administered, after which the HPB nurse provided education and advice on SHS. Smoker parents present at the clinic who agreed to intensive smoking cessation counseling were referred to QuitLine, a HPB telephone smoking cessation helpline administered by trained smoking cessation counseling nurses. In addition, for smoker parents not present at the clinic, consent was obtained from the attending parent/caregiver for the smoker parent to be referred to and contacted by QuitLine. The KKH program provides education and advice to attending parents/caregivers of children exposed to SHS, and 1-minute smoking cessation counseling and intensive smoking cessation counseling only to smoker parents present at the clinic. The results of the questionnaire survey and the QuitLine quit rate (defined as smoke free for 6 months) for the enhanced program was analyzed. Historical data from the KKH program was used for comparison.

Results

The enhanced program screened 125 individual parents/caregivers who attended clinic reviews with their children over a 2-month period. Knowledge on SHS for smoker and non-smoker parents/caregivers attending the clinic was similar. Of these individual households, 63 (50.4%) had at least 1 household member who smoked. Lower educational level of the respondent ($p = 0.004$) and household income ($p = 0.014$) were associated with having smokers in the household. Smoker parents from lower socioeconomic group were more likely to agree to QuitLine referral. After referral, 19 smoker parents agreed to QuitLine follow up. The quit rate for QuitLine was 26% (5 out of 19). In comparison, over a 2.5 year period, the KKH program provided 1 minute counseling to 655 smoker parents/caregivers, with 30 smoker parents/caregivers receiving intensive counseling. The quit rate was 23% (7 out of 30).

Conclusion

A high proportion of KKH pediatric respiratory patients are involuntarily exposed to SHS. The quit rate for the HPB QuitLine and KKH intensive counseling were similar, but the enhanced program, over a shorter program duration, was more efficient in helping parent smokers initiate smoking cessation attempts, and to quit smoking.

#1144 – Hospitalization Rate as a Measure of Outpatient Management Quality in Children with Asthma.

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Background

Asthma is one of the most common causes of hospitalization for children in developed countries. The goal of outpatient asthma management is to minimize asthma symptoms, normalize lung function, and prevent hospital admissions for acute exacerbations.

Objective

To assess the effectiveness of the management of children with asthma at our outpatient clinic in preventing hospitalizations for acute asthma exacerbations.

Methods

We reviewed the medical records of children treated for asthma at the outpatient clinic in 2015 and the discharge data for all children hospitalized in the year 2016 for acute asthma exacerbation at the University Children's Hospital in Ljubljana.

Results

In 2016, there were 143 hospitalizations in 124 children for asthma exacerbation. The hospital covers a population of 115,000 children, thus giving a hospitalization rate of 0.12%. This is in line with the Eurostat 2012 data, estimating an average of 0.2% age-specific annual asthma hospitalization rate.

In 2015, 3678 children with asthma were seen at the outpatient clinic. In the following year, there were 100 hospital admissions for acute exacerbation among these patients, thus yielding a hospitalization rate of 2.7%. In 25% of these cases, the cause of asthma deterioration was discontinuation of anti-inflammatory therapy by the parents. None of patients was admitted to the intensive care unit. This is similar to the reported average hospitalization rate of 2.1% of children with asthma for the years 2007–2009 in USA (www.cdc.gov).

Conclusion

In our setting, hospitalization rate of children with asthma, managed at the outpatient clinic, could be used as a quality measure of outpatient care. We will follow this measure in the next years and adjust our practice accordingly.

#1175 – Respiratory Disorders in Children Admitted at the Emergency Department.

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Background

Respiratory pathology represents one of the most frequent causes of morbidity in children, particularly in the youngest. Although morbidity and mortality due to acute respiratory infections have been decreasing in the last century, they remain prevalent causes of Emergency Department (ED) visits. Chronic diseases' exacerbations, such as asthma, are also prevalent. A previous study in our center showed that one quarter of all diagnoses made at the ED are respiratory, with superior tract infections being the most frequent. The aim of this study was to characterize patients with moderate to severe respiratory diseases that were admitted for observation in the ED of our tertiary centre.

Materials and Methods

Retrospective review of clinical files of children and adolescents admitted for observation in the ER during one year (September 2015–August 2016). Statistic analysis and logistic regression were performed; p -value < 0.05 was considered significant (STATA14.1).

Results

A total of 253 patients were included in the study (13.4% of ED admissions). There was predominance of males (63.1% vs. 36.9%) and median age was 1.3 years (interquartile range 0.3–4.8). Winter admissions accounted for 45% and infectious diseases for 75% of all cases. Patients with exacerbation of chronic conditions were frequent ($n = 105$; 41.5%), mostly asthma ($n = 57$) and neuromuscular diseases with chronic respiratory failure ($n = 10$). Most frequent causes of ED admission were: acute bronchiolitis ($n = 83$; 32.8%); pneumonia ($n = 58$; 10.9%); acute respiratory failure in asthma exacerbation ($n = 15$; 5.9%) and recurrent wheezing ($n = 33$; 13%); exacerbation of chronic respiratory failure ($n = 10$; 3.9%); pneumothorax ($n = 8$; 3.2%) and superior tract infections ($n = 11$; 4.3%). Secondary diagnosis occurred in 22.9% (otitis media being the most frequent; $n = 16$; 7.2%). Most patients were subsequently hospitalized ($n = 211$; 83.7%). Oxygen supplementation and oral intolerance were the only significant predictors for hospitalization (OR 29 and 14, respectively). After hospital discharge, 18.8% were readmitted (72-hour period).

Patients with chronic diseases were older (6 vs. 2.5 years; $p < 0.01$), had more non-infectious disorders (39% vs. 15%; $p < 0.01$), and worse clinical course: more hospitalizations (89.4% vs. 79.3%; $p = 0.04$), less oral tolerance (23.8% vs. 40.8%; $p = 0.05$) and required more medical therapy except for antibiotics (oxygen and inhaled therapy $p < 0.01$; antibiotics $p = 0.28$). There was no significant difference regarding season, readmission at 72-hour, 1- or 3-months.

Conclusion

Infectious respiratory disease was the most frequent cause of admission. Chronic disease imposes great weight in admissions, probably because our ED is at a tertiary centre. Almost half of chronic patients had non-respiratory baseline conditions implying that respiratory burden is widespread. We need a high index of suspicion for prompt diagnosis and treatment of moderate to severe respiratory disorders both in healthy and chronic patients.

#1176 – Tobacco Smoke Exposure, Respiratory Infections and Health Resources in Preschoolers.

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Introduction and aim

Postnatal environmental tobacco smoke exposure (ETS) increases the risk of lower respiratory infections in the first two years of life. We aimed to evaluate the association between ETS and respiratory infections and health resources consumption in preschoolers.

Methodology

We studied 8647 children aged 4–6 years from the population-based birth cohort Generation XXI and assessed the associations between ETS and respiratory infections (pharyngitis, otitis and pneumonia) and attendance to an emergency department during the previous year, and

of ever being admitted into a hospital. Imputation analysis was used for 2922 incomplete datasets. Results are expressed as odds ratio (95% CI).

Results

46% of fathers and 35% of mothers admitted to smoking; of these, respectively 41% and 12% smoked more than 20 cigarettes/day; and 2.2% and 10.5% admitted to smoking daily in the children's presence. We found no association between TE and reported episodes of pharyngitis, otitis or pneumonia during the previous year. ETS significantly increased the risk of emergency attendance (OR 1.017 (1.003–1.031), although this association was lost after adjustment for parental education level and the family economical strata. We found a significant association between ETS and past admission into a pediatric department (OR 1.027 (1.015–1.041)).

Conclusion

Our study fails to demonstrate an association between ETS and the occurrence of recent respiratory infections in preschoolers. The increase in emergency visits seems to be related to lower levels of education and economic stratum. However, the higher hospitalization rate favors a detrimental effect of ETS in early ages.

#1178 – Tobacco Smoke Exposure, Wheezing, Rhinitis and Asthma in Preschoolers.

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Introduction and Aim

Various cohort studies have shown a modest association between environmental tobacco smoke exposure (ETS) and asthma in children aged 6 years or older. We aimed to assess the magnitude of this association in preschoolers.

Methodology

We studied 8647 children aged 4–6 years from the population-based birth cohort Generation XXI and assessed the associations between ETS and history of past or present wheezing, asthma and rhinitis. Imputation analysis was used for 2922 incomplete datasets. Results are expressed as odds ratio (95% CI).

Results

46% of fathers and 35% of mothers admitted to smoking; of these, respectively 41% and 12% smoked more than 20 cigarettes/day; and 2.2% and 10.5% admitted to smoking daily in the children's presence. After adjustment for parental education level and family income, we found a significant association between ETS from both parents and past wheezing episodes in children (OR 1.033, CI 1.018–1.047). There was no association between ETS and wheezing episodes in the previous year (OR 0.996, CI 0.987–1.015) nor with a diagnosis of asthma (OR 0.997, CI 0.966–1.048) or rhinitis (OR 0.996, CI 0.965–1.027) at 4 years.

Conclusion

ETS was significant associated with past wheezing episodes, which may reflect the increased risk of lower respiratory tract infections in the first years of life, but not with present wheeze, nor with a diagnosis of asthma or rhinitis. The longitudinal observation of the cohort may determine the evolution of these associations.

#I187 – National Trends in Hospital Admissions for Bronchiolitis, Asthma and Pneumonia among Pediatric Patients in Portugal, 2002–2012.

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Introduction

Collecting data regarding hospital admissions may impact on knowledge of disease burden and outcomes. In Portugal, scarce national-level data analysis on bronchiolitis (BR), asthma (AS) and pneumonia (PN) is available.

Aim

To analyze pediatric admissions for BR, AS and PN at the country level, to elucidate temporal trends (2002–2012) in incidence, demographics and outcomes, including health resource use.

Methods

Retrospective analysis of the Diagnosis-Related Group (DRG) database of the Portuguese Health System's Central Administration, which includes anonymized patient-level data for all hospitalizations in mainland Portuguese public hospitals. We identified patients using age-restricted International Classification of Diseases 9th Revision, Clinical Modification codes (ICD-9-CM): BR 466.1, 0–23 months; AS 493, 2–17 years and PN 480–486, 0–17 years. Variables included main/secondary diagnoses, length of hospital stay (LoS), ventilation (non-invasive-NIV or invasive-IV), age, gender and mortality. Annual incidences of hospitalizations/100,000 population were calculated from age-scaled population (National Institute of Statistics). Descriptive statistics and linear regression for trends were performed.

Results

We included main/secondary episodes for BR (52058/9595), AS (15298/10095) and PN (48143/12629). We found a variable but stable incidence of admissions across the 10-year period for BR and AS, while a decrease in incidence of PN was observed ($p=0.007$). Average LoS decreased (-0.045 days for BR and AS; -0.115 for PN) during the study period ($p<0.001$). For all conditions, a higher rate of admissions was noticed in males ($p<0.001$), while females presented longer LoS for AS admissions ($p<0.001$).

PN was the most frequent secondary diagnosis for BR and AS, accounting for a 10-year average of 3.1% and 3.6% admissions,

respectively. For PN admissions, AS was the most frequent secondary diagnosis accounting for 3.7% episodes.

NIV was reported in 0.3% AS and 2.1% PN admissions, and IV in 0.6% PN and 4.0% AS admissions (data not available for BR). Reported mortality was 11/52058 (0.02%) BR admissions and 234/48143 (0.48%) PN admissions. No deaths were registered for AS admission codes.

Conclusion

For all three conditions, the incidence of hospitalization was comparable to data reported from other high-income countries, suggesting a great burden of admissions for respiratory diseases in children. Acute bronchiolitis accounted for most DRG diagnoses; a decrease in DRG codes for PN may follow the introduction of pneumococcal conjugate vaccine. A decrease in LoS was noticed for all diseases studied. This study highlights the urgent need for auditing national guidelines and establishing benchmarks for these diseases.

#I212 – Intradermal Reaction To PPD in Children.

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PPD is a purified protein derivative from Mycobacterial TBC (MTBC); it is used intradermally and its reaction is measured in millimeters (mm). It is useful for cellular immune response, BCG vaccine response and MTBC exposure as latent infection. In Chile, almost all newborns are vaccinated in 99% of cases during the first day of life.

The purpose of this study is to characterize the pediatric population under evaluation and the PPD reaction test in the Concepcion Health Service.

Method

All data in children derived for PPD test between January 2015 and August 2016 were included. Values were consolidated in Excel and statistical tests with ANOVA were performed to verify the consistency and integrity of data and to extract relevant information.

Results

217 children were evaluated with PPD test, with ages between 5 months and 17 years (median 7 years), 68% males. The range of PPD induration was 0 to 30 mm. The median value according to age was: < 6 months: 2 mm, 6–12 months: 3 mm, from 1 to 14 years: 0 mm, > 14 years: 3 mm. There were no significant differences between 2015 and 2016 or between girls and boys. Children without latent MTBC infection were 10, chronic nephropathy, rheumatic disease and one case of (+)HIV. Their range of induration was 0 to 18 mm with median value of 0 mm.

Conclusion

PPD intradermal induration presents differences between age groups. The reaction under 1 year of age is related with the BCG vaccine

response, whereas over 14 years it is related with MTBC exposure. There are no differences according to gender.

J. INVESTIGATION AND DIAGNOSTIC TESTS

#J3 – Do Anthropometric Indices Correlate with Lung Function in Children with Sickle Cell Anemia?

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Objectives

To determine the relationship between lung function values and anthropometric variables among children with sickle cell anemia.

Methods

A prospective cross-sectional study in which children between 6 and 20 years old with sickle cell anemia were consecutively enrolled over a period of six months.

Pulmonary function measurements (peak expiratory flow rate, Forced Vital Capacity (FVC) and the Forced Expiratory Volume in 1 second (FEV1) were performed using a single mini Wright peak flow meter and an automated single breath vitalograph respectively. Anthropometric parameters (weight, height, chest circumference and body surface area) were measured and their relationships with lung function parameters were obtained.

Results

Body surface area had the highest correlation with all measured lung function values among children with sickle cell anemia. ($p < 0.01$) The strength of correlation for other anthropometric parameters were standing height, weight, age and chest circumference in decreasing order.

Conclusion

There is a strong correlation between anthropometry and lung function among children with sickle cell anemia.

#J17 – Comparison of a Mycoplasma Ag and a Mycoplasma IgM Rapid Detection Test for the Diagnosis of *Mycoplasma pneumoniae* Pneumonia in Children.

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Background

Mycoplasma infection is common in pediatric patients. Early diagnosis can help treatment early and properly. A rapid test is a convenient, immediate diagnostic tool for Mycoplasma pneumonia infection, which can be performed at bedside using throat swab mucus or

micro-hematocrit-tube whole blood, respectively. Here we compared the utility of a Mycoplasma Ag (ImunoAce Mycoplasma Test) and a Mycoplasma IgM antibody rapid detection test (BioCard Mycoplasma Test) with regard to Mycoplasma pneumonia in children.

Methods

A total of 29 pediatric patients (age: 6.7 ± 4.4 y/o, M:F = 15:14) with clinically suspected Mycoplasma infection and CXR showing bronchopneumonia or pneumonia were enrolled from September 2015 to December 2015. The diagnosis of mycoplasma infection was made by pair serology tests or PCR DNA detection from throat swabs (copy numbers > 500 dp). The clinical characters and lab data were analyzed including fever days before admission, hemogram, liver enzyme, and CRP.

Results

Among 29 pneumonia patients, 22 had definite Mycoplasma infection, in whom 15 throat swab samples were detected by rapid Ag test (sensitivity 68.2%, specificity 85.7%) while 17 whole blood samples were detected by rapid Ab test (sensitivity 77.3%, specificity 85.7%). The BioCard Mycoplasma Ab rapid test had a higher sensitivity than the ImunoAce Mycoplasma rapid Ag test ($p = 0.027$) in the diagnosis of children with mycoplasma pneumonia. The fever days before admission in positive Mycoplasma Ag and IgM groups were 5.7 ± 0.4 and 7.3 ± 1.0 , respectively.

Conclusions

Mycoplasma rapid test is a convenient diagnostic tool for children with Mycoplasma pneumonia. Both the BioCard Mycoplasma Ab rapid test and the ImunoAce Mycoplasma rapid Ag test are practicable in the diagnosis of children with Mycoplasma pneumonia for their high sensitivity and specificity. However, a negative result by rapid test cannot exclude a Mycoplasma infection in clinically highly suspected cases.

#J20 – Spirometry: A Useful and Reliable Tool for Monitoring Tracheomalacia in Patients with Esophageal Atresia.

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Introduction

Tracheomalacia is one of the major causes of respiratory problems in children with esophageal atresia (EA) and tracheoesophageal fistula (TEF). Dynamic flexible bronchoscopy is the gold standard for the diagnosis of tracheomalacia, however the need for sedation and the invasiveness makes the procedure not always feasible in settings with poor resources, limiting its use only in specialized centers. The role of spirometry in patients with tracheomalacia is rarely described. Due to

its non invasiveness and easy execution, it is particularly interesting in clinical practice.

Aim

To define the sensitivity and diagnostic predictive value of spirometry in detecting tracheal collapse in patients with endoscopically-detected tracheomalacia.

Methods

53 patients with surgically corrected EA and tracheomalacia in follow-up at the Department of Pediatric Medicine of Bambino Gesù Children's Hospital, underwent flexible bronchoscopy. Values for forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, peak expiratory flow (PEF) and FEV1/PEF ratio (mL/L/min) were recorded. The morphology of the volume-flow (F/V) loop during expiratory phase was examined in patients undergoing a spirometry test.

Results

12 patients with intrathoracic tracheomalacia and 4 patients with normal airway endoscopy underwent spirometry at a mean age of 9.3 ± 3.1 years. A restrictive ventilatory pattern was observed in 44% of the total population. A sudden and temporary drop during the expiratory phase was observed respectively in 8 and 1 patients. Mean FEV1/PEF ratio was 8.6 mL/L/min and 7.6 mL/L/min respectively in the first and second group. When compared with endoscopy, spirometry detected tracheal collapse during the expiratory phase with diagnostic sensitivity of 67%, specificity of 75% and a positive and negative predictive value respectively of 89% and 42%. FEV1/PEF ratio, which was expressive of intrathoracic obstruction, was higher in patients with tracheomalacia detected by endoscopy.

Conclusions

Spirometry is the most commonly used pulmonary function test in different EA studies while FEV1 and FVC are used to classify ventilatory defects as obstructive or restrictive. The analysis of the F/V curve provides additional information over conventional spirometry in determining the site, character and severity of airway obstruction. Even if flexible bronchoscopy remains the gold standard for the diagnosis of tracheomalacia, spirometry should be a useful and reliable tool for monitoring intrathoracic tracheomalacia in symptomatic patients and/or in patients for which sedation is not indicated.

#J21 – Comparison of Three Field Tests in Children: A Randomized Cross-over Study.

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Introduction

Even if the six minute walking test (6MWT) is the standard criterion for functional exercise performance evaluation, new field tests are

required as practical alternatives. This study aims to establish the validity of the 6-minute step test (6MST) and the 4-meter gait speed (4MGS) in children.

Method

64 healthy children from 6 to 12 years were recruited for this randomized cross-over trial. 6MWT, 6MST and 4MGS were randomly performed on three consecutive days. Pulsed oxygen saturation (SpO₂), heart rate (HR), dyspnea (VAS) and fatigue (PCERT) were used as outcomes.

Results

Distance during 6MWT was correlated to number of steps during 6MST ($r = 0.320$; $p = 0.013$) but not correlated to 4MGS ($r = -0.074$; $p = 0.575$). No correlation between number of steps during 6MST and 4MGS ($r = -0.129$; $p = 0.332$) was found. HR was lower than the theoretical maximal HR after the tests. The increase in HR was significantly higher for 6MST and significantly lower for 4MGS than for 6MWT and it was higher for 6MST than for 4MGS. Dyspnea and perceived exertion were lower after 6MWT than after 6MST and higher than after 4MGS. They were also higher during 6MST than during 4MGS.

Conclusion

6MST is a valid surrogate to 6MWT in healthy children for functional exercise performance evaluation contrarily to the 4MGS. However, cardio-respiratory response differs between the three tests.

#J49 – Assessment of Bronchodilator Response with Spirometry in Children with and without Asthma – The Relevance of the Smaller Airways.

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Background

Bronchodilator (BD) response is an important component of asthma diagnosis and management. However, most previous studies only reported forced expiratory volumes that show the function of larger airways.

Aim

To evaluate BD response in spirometry parameters, particularly forced expiratory flows, in children with and without asthma.

Methods

Data from the cross-sectional and population-based study ICAR – Control and Burden of Asthma and Rhinitis (PTDC/SAU-SAP/119192/2010) conducted in Portugal were analyzed. Children aged 3–17 years that performed acceptable and reproducible spirometry, before and after inhalation of 400µg salbutamol MDI via spacer, were

included. Forced expiratory volumes and flows pre- and post-BD were reported. Absolute mean \pm SD changes (ml) in children with and without asthma and the difference between the two groups were computed. Asthma diagnosis was physician-based and current asthma medication was also recorded. Children stopped short- and long-acting β 2-agonists at least 4h and 12h, respectively, before performing spirometry. Independent sample t-test and chi-square tests were used to compare groups.

Results

Of the 130 included children (mean \pm SD age 10.1 \pm 4.1 years; 77(59%) boys), a total of 47 (36.2% [95% CI: 27.9–44.4]) had asthma. After BD inhalation, the absolute mean \pm SD change was significantly greater in children with asthma in comparison to those without asthma in FEV1 (16.3 \pm 17.0 ml vs. 8.4 \pm 13.8 ml, p = 0.008), FEV0.5 (19.8 \pm 14.4 ml vs. 10.7 \pm 15.4 ml, p = 0.035), FEF25–75% (54.2 \pm 42.6 ml vs. 27.7 \pm 42.4 ml p = 0.001) and FEF75% (34.9 \pm 34.1 ml vs. 17.7 \pm 32.3 ml p = 0.006). The mean difference (95%CI) of the changes after BD between both groups was: 4.16 (1.45–6.87)% in FEV1; 6.18 (0.32–12.0)% in FEV0.5; 15.8 (8.4–23.2)% in FEF25–75% and 20.6 (9.8–31.4)% in FEF75%. Restricting the analysis to children with asthma, 22 (58%) had current medication. There was no difference in post-BD changes between asthma children with and without current medication.

Conclusion

The assessment of bronchodilator response using spirometry should consider parameters that reflect small and medium airways function and not be limited to FEV1. Furthermore, interpretation of significant differences in bronchodilator must be considered whether they are both statistically and clinically meaningful.

#J74 – Clinical Value of Functional Parameters in the Differential Diagnosis of Protracted and Chronic Children's Cough.

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Aim

To investigate the clinical significance of the features of functional parameters of the respiratory and cardiovascular systems in children with cough.

Patients and methods

91 children aged from 1 to 17 years with cough during more than 3 weeks were examined. All patients were divided into four groups according to diseases: 31 patients with mild persistent bronchial asthma (BA) in exacerbation and incomplete remission (group (Gr) 1); 22 patients with upper respiratory tract infection (URTI) (Gr2); 18 patients with lower respiratory tract infection (LRTI) (Gr3); 11 patients with gastroesophageal reflux disease (GERD) (Gr4). The control Gr (C) included 60 healthy children (1–17 years of age). Excluded from this

study were patients with the diagnosis of a foreign body airway (n = 1), psychogenic and neurogenic cough (n = 2), bronchopulmonary malformations (n = 6). All patients underwent history, examination, evaluation of heart rate variability (HRV); and computerized bronchophonography (CBPG) for patients under 7 years old.

Results

Children with cough due to BA were characterized by significant change in the acoustic characteristics of breath sounds: increased level of the acoustic component of the work of breathing (A) in the high-frequency zone (5.0–12.6 kHz, A3) – 69.8(4.88–600.5) mcJ (p 1-c < 0.01) and the proportion of the A in the middle-(1.2–5.0 kHz, ϕ 2) and high-frequency zone (ϕ 3) in level of the A of the general-frequency zone (respectively, 0.09 (0.0165–0.43); 0.01 (0.0016–0.03); p 1-c < 0.01). Gr1 was characterized by the prevalence of the activity of the parasympathicus (PNS) (at HRV analysis): increase in RMSSD, pNN50% and HF (respectively, 45.6 (10.9–101.3) ms, 15.3(1–76)%; 46.6(12.1–64.3) ms); reducing level of the LF (26.6(8.5–43.8) vs. Gr2, 3, 4, C (p <0.05).

The patients with cough due to URTI were characterized by minimal disruption of the functional state of the respiratory system: increase in A2(274.48(20.63–779.49) mcJ) vs. C (55.03(2.47–493.94) mcJ) (p 2-c<0.05).

The patients with cough due to LRTI were characterized by a moderate disturbance of the functional state of the respiratory system: increase in A2, A3 (respectively, 2448.26(562.67–4722.69) mcJ; 322.75(43.31–1818.78) mcJ; p 2-3 < 0.01) and ϕ 2, ϕ 3 (respectively, 0.14(0.0334–0.271); 0.021(0.005–0.096); p 3-c < 0.01). Parameters of HRV in Gr2 and Gr3 had a similar orientation as the predominance tone of the sympathicus: reduction in RMSSD, pNN50%, HF and increase in IC, LF compared with Gr1, C (p <0.05).

Changes in the functional parameters of the respiratory system were not typical for children with cough due to GERD. They had a moderate increase in activity of the PNS (RMSSD, pNN50%, HF) compared with C (p 4-c<0.05). The level of the SDNN was highest in this Gr (37.8(14.4–61.5) ms (p 4-c<0.05).

Thus, analysis of the functional state of the respiratory and cardiovascular system can be useful as additional criteria for the differential diagnosis of chronic and protracted cough in children.

#J75 – Evaluation of Nasal Patency in Children: Data of 737 Consecutive Rhinomanometry Tests before and after Vasoconstrictor Treatment.

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Background

Rhinomanometry is a simple and useful method for objective evaluation of nasal airway patency. However, there is a lack of published studies in pediatric patients. We aimed to evaluate nasal patency assessed by rhinomanometry and its variation after administration of an intranasal vasoconstrictor in children.

Methods

We included all children (age <18 years) who underwent rhinomanometry (Masterscreen Rhino[®]) pre- and post-intranasal vasoconstrictor (phenylephrine hydrochloride 2.5 mg/ml), at CUF Porto – Instituto and Hospital from July 2011 to July 2016. When more than one rhinomanometry was performed, only the first one was included in the analysis. We assessed the demographic (gender, age, race) and nasal patency variables pre- and post-vasoconstriction: inspiratory and expiratory nasal airflow in the right and left nostrils; inspiratory (RAARi) and expiratory (RAARe), right and left, airflow resistance, at a sample pressure of 150 Pa, and nasal airflow and resistance variation (Δ). The measurements of right and left nostrils were described by considering the total number of measurements regardless of laterality, and stratified in “best” and “worst” nostrils according to baseline inspiratory airflow. The Jonckheere-Terpstra test was used to identify trends across ranked groups by age.

Results

We included 737 children, 466 (63%) boys, with a mean (SD) weight of 43.5 (17.1) kg, height of 147.1 (19.4) cm and age of 10.9 (3.5) years (min-max: 4–17); 148 (20%) children were <7 years old, 142 (19%) 7–9 years, 189 (26%) 10–12 years and 258 (35%) between 13 and 17 years. Among the age groups, statistically significant differences were observed in all baseline variables ($p < 0.05$), with a trend for increasing flows and decreasing resistances with increasing age. Otherwise, the variations in flows and resistances with vasoconstriction were not significantly different across the age groups. Median (P25;P75) of the inspiratory flow in the “best nostril” was 211 (140;313) mL/s vs.

115 (72;176) mL/s in the worst nostril ($p < 0.001$). The variation in the “worst nostril” was 72% (19;146) vs. 18% (-3;58) in the best nostril ($p < 0.001$). After vasoconstrictor treatment, the pre “worst nostril” reached a flow higher than the pre “best nostril” in 32% of children.

Conclusions

The differences found between the age groups indicate that age may be an important factor that should be taken into account when evaluating nasal patency with rhinomanometry. The high proportion of children with variation after intranasal vasoconstrictor is an indication of the usefulness of assessing vasoconstrictor response at pediatric age.

#197 – Quantitative Assessment of the Effect of External Stents in Trachea-Bronchomalacia by Measuring Tracheal Collapsibility.

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Using a graft as an external stent is an effective mode of treatment in trachea-bronchomalacia, but there are cases where the airway collapses after the operation when the work of breathing increases, even though during the operation under muscle relaxant the airway seemed to be patent. We studied tracheal collapsibility aimed at quantitatively assessing the effect of external stents in tracheo-bronchomalacia.

Patients and Methods

available data of tracheal collapsibility before and after external stents were assessed in 32 patients, 44 lesions (trachea 27, left main bronchus 13, right main bronchus 5). A Gore-Tex ringed vascular

	Total (n=737)	Age groups				p-value
		<7 years (n=148)	7-9 years (n=142)	10-12 years (n=189)	13-17 years (n=258)	
Height (cm), mean (sd)	147 (19.4)	121 (6.6)	135 (6.3)	150 (8.1)	167 (11.4)	
Insp flow (ml/s), med (P25;P75)						
Pre	154.5 (90.0;248.3)	124.0 (73.0;188.0)	127.5 (76.0;200.3)	152.0 (87.0;242.0)	196.0 (121.0;306.3)	< 0.001
Δ	38.3 (3.2;105.0)	31.7 (-0.2;95.3)	54.9 (7.9;111.6)	40.4 (3.0;114.2)	32.0 (3.8;99.4)	0.603
Exp flow (ml/s), med (P25;P75)						
Pre	124.0 (69.8;211.3)	85.0 (55.8;156.5)	104.0 (56.0;162.0)	126.0 (72.0;209.0)	171.5 (100.8;265.0)	< 0.001
Δ	44.9 (4.4;116.4)	44.9 (0.0;118.9)	53.2 (5.9;130.0)	47.4 (3.9;134.0)	39.5 (5.0;100.0)	0.271
RAARi (kPa*s/L), med (P25;P75)						
Pre	0.9 (0.6;1.5)	1.1 (0.8;1.8)	1.1 (0.7;1.7)	0.9 (0.6;1.6)	0.7 (0.5;1.2)	< 0.001
Δ	-27.3 (-51.0;-3.1)	-24.4 (-48.8;0.2)	-35.1 (-52.1;-7.3)	-28.7 (-53.2;-3.0)	-23.9 (-49.6;-3.5)	0.523
RAARe (kPa*s/L), med (P25;P75)						
Pre	1.1 (0.7;2.0)	1.5 (0.9;2.3)	1.4 (0.8;2.2)	1.1 (0.7;1.9)	0.9 (0.6;1.4)	< 0.001
Δ	-30.5 (-53.0;-4.0)	-30.3 (-52.8;0.2)	-33.7 (-55.6;-5.4)	-31.8 (-57.0;-3.7)	-27.9 (-49.0;-4.7)	0.356

Table 1. Nasal airway resistances and flow and its variation after intranasal vasoconstrictor. Data of right and left nostrils were considered together. sd- standard deviation; insp- inspiratory; exp- expiratory; cm- centimeters; ml- milliliters; s- second; kPa- kilopascal; L- liters; med- median; P- percentile; Δ - variation.

graft was used as external stents in tracheomalacia. Bronchoscopy was performed intraoperatively, and airway patency was aimed for by attaching a vascular graft divided into 2 sections, one to the cartilaginous wall and the other to the membranous part. Tracheal collapsibility was assessed by the relationship between intraluminal pressure and cross sectional area of the trachea, where the intraluminal pressure and cross sectional area were measured simultaneously with bronchoscopic observation, as the intraluminal pressure changed continuously from $-10\text{cmH}_2\text{O}$ to $10\text{cmH}_2\text{O}$ under intubation and muscle relaxant. The relationship between intraluminal pressure and cross sectional area will become linear, such that the closing pressure where the cross sectional area becomes 0 is predictable, and this was defined as the airway closing pressure. If the airway remained patent under increased work of breathing after the operation, the patients were included in the effective group, and if the airway collapsed, the patients were included in the ineffective group.

Results

Out of the 44 lesions, airway patency was achieved (effective group) in 38 lesions (trachea 23, left main bronchus 11, right main bronchus 4), while airway patency was not achieved (ineffective group) in 6 lesions (trachea 4, left main bronchus 1, right main bronchus 1), with an overall success rate of 86.4%. The airway closing pressure as a whole improved significantly from $-15.4 \pm 13.4\text{ cmH}_2\text{O}$ before operation to $-168.0 \pm 199.1\text{ cmH}_2\text{O}$ after operation. In the effective group, the airway closing pressure changed from $-17.8 \pm 13.3\text{ cmH}_2\text{O}$ before operation to $-197.8 \pm 210.8\text{ cmH}_2\text{O}$ after operation, in contrast to the ineffective group where the airway closing pressure changed from $-11.3 \pm 9.4\text{ cmH}_2\text{O}$ before operation to $-32.5 \pm 15.6\text{ cmH}_2\text{O}$. Improvement in the effective group was remarkably greater compared to that of the ineffective group.

Discussion

External stents using a vascular graft is an effective mode of treatment in tracheo-bronchomalacia, but the effect may not be appreciable in all cases. A tracheal collapsibility test can quantitatively assess tracheal collapsibility even in a state without spontaneous breathing. The tracheal collapsibility test is thought to be a test that can judge the efficacy of external stents in tracheo-bronchomalacia objectively.

#J100 – The Effect of Triclofos Sodium on the Respiratory Center in Neonates and Infants.

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Purpose

In Japan, 90% of hospitals use triclofos sodium, a nonbenzodiazepine drug, for sedation during MRI in neonates and infants. Sometimes,

unstable SpO₂ can be observed due to triclofos sodium in neonates and infants, although there is no report that has quantitatively assessed the effect of triclofos sodium on the respiratory center. We report the effect of triclofos sodium on the respiratory center using the ventilatory response to CO₂ (VRCO₂: normal value $40.4 \pm 14.8\text{ ml/min/kg/mmHg}$) in which the increase in minute ventilation (MV) caused by an increase in end-tidal carbon dioxide (EtCO₂) is measured.

Methods

Neonates and infants admitted to our NICU sedated with triclofos sodium for MRI examination during October 2015 to February 2016 were included. The VRCO₂ was measured using ARFEL manufactured by Aivision Japan. The VRCO₂ was measured using Read's rebreathing method where mixed gas composed of 5% CO₂ and 95% O₂ was rebreathed in a closed circuit by means of a mask, and the increase in MV due to an increase in EtCO₂ was calculated. $VRCO_2 = \Delta MV / \Delta EtCO_2 / \text{body weight}$. Seventy to 80 mg/kg of triclofos sodium was used.

Results

Thirty patients were included in the study. The underlying diseases were low birth weight in 14 (very low birth weight in 9), neonatal asphyxia in 8, and 8 others. The average gestational age was 35.1 ± 4.1 weeks, and the average birth weight was $2112 \pm 894\text{g}$. The median (IQR) corrected gestational age was 40.3 (39.3 – 41.8) weeks, age in days 26 (15.7 – 47.7), weight 2508 (2346 – 3413) g at the time of triclofos sodium sedation. The time from triclofos sodium administration to VRCO₂ measurement was 105 (91 – 122) minutes. VRCO₂ significantly decreased ($p = 0.016$) from $42.9 \pm 11.6\text{ ml/min/kg/mmHg}$ before administration to $34.4 \pm 18.2\text{ ml/min/kg/mmHg}$ after administration. There was no significant difference between the 10 patients in whom the VRCO₂ fell below the normal values and the 20 patients in whom the VRCO₂ was above normal in terms of gestational age, birth weight, corrected gestational age at the time of triclofos sodium administration, body weight at the time of administration, history of mechanical ventilation, underlying diseases, and parental smoking history.

Conclusion

We were able to measure the effect of triclofos sodium on the respiratory center using VRCO₂. Triclofos sodium significantly decreased the reaction of the respiratory center in neonates and infants, and VRCO₂ fell below normal values in 33% of patients. There were no apparent characteristics such as underlying diseases in patients where the respiratory center was suppressed by triclofos sodium, and close monitoring is needed in all cases.

#J101 – Procalcitonin – Biomarker in Diagnosis of Community-Acquired Pneumonia in Children.

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Introduction

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin synthesized in parafollicular C-thyroid cells. Increased procalcitonin levels have been associated with localized and severe bacterial infections, non-infective systemic inflammation, etc. Studies have indicated that PCT may be a more reliable biomarker of inflammation in the diagnosis of localized mild-to-moderate bacterial infection, and in particular might be helpful when the diagnosis of bacterial infection is unclear.

Objectives

Estimate the PCT level in distinguishing bacterial from viral lung infections in children and monitor therapeutic response to antibacterial therapy and reduce antibiotic exposure. The aim of the study is to compare PCT levels with routine biomarkers of inflammation in children with community acquired pneumonia (CAP) and compare PCT level with the conducted antibiotic therapy given according to the guidelines of the American Pediatric Society.

Materials and Methods

Children (N = 77, male = 37) younger than 18 years (mean = 6.8) were treated at the Children's Hospital Srebrnjak with clinical features corresponding to CAP (the diagnosis was based on the history and physical examination results in children with fever plus respiratory signs and symptoms). Blood samples were taken for detection of inflammatory biomarkers (erythrocyte sedimentation rate-ESR, C-reactive protein-CRP, white blood cell count and PCT (> 0.5 ng/mL), along with antibiotic therapy.

Results

There was a statistically significant correlation of serum PCT levels with given antibiotic therapy ($p = 0.026$), as well as with serum CRP levels $p = 0.00$ and ESR $p = 0.035$. There was no correlation between serum PCT levels and total white blood cell count ($p = 0.138$) or segmented leukocyte count ($p = 0.736$) but there was a statistically significant negative correlation between PCT and eosinophil ($p = 0.012$) as well as lymphocyte ($p = 0.018$) count in peripheral blood.

Conclusions

Available routine inflammatory biomarkers (CRP, WBC count, ESR) have limited use in the diagnosis of bacterial pneumonia in children. PCT levels correlate well with other biomarkers of inflammation and conducted antibiotic therapy. Our results suggest that PCT levels might be a valid additional biomarker in the diagnosis of bacterial CAP in children as well as antibiotic therapy which is empirically chosen.

#J117 – Infant Multiple Breath Washout Measurements with Different Device-Setups: Results Are not Interchangeable.

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Introduction

Cystic fibrosis (CF) affects mainly the small airways, and multiple breath washout (MBW) is a sensitive test to detect and monitor CF lung disease from infancy onward. The currently available device for infant MBW, however, has the major limitation that additional corrections to the signals are required, which reduce the robustness of the system. A recently released device for infant MBW with the same tracer gas (sulfur hexafluoride, SF₆) overcomes this limitation and is expected to replace the old one.

Aim

The aim of his study was to assess the feasibility of infant MBW testing with the new device and compare the functional residual capacity (FRC) values of both devices in vivo and in vitro.

Methods

We performed 2–3 MBW measurements in four 5-week-old healthy and four 12-month-old infants with CF, as well as in a Plexiglas lung simulator using infant-corresponding lung volumes and breathing patterns, with the new (Exhalyzer D, Spiroware 3.2.0, Ecomedics) and the old device-setup (Exhalyzer D, WBreath 3.18.0, ndd Medizintechnik) in random sequence.

Results

The feasibility of MBW with the new device was 100%. We found a low intra-subject variability in FRC per device, but significant systematic differences in FRC between the devices (mean FRC difference 39.7%, range 18.9 – 65.7, Wilcoxon signed rank test, $p = 0.008$). Similar results were found in vitro. Simple user-defined corrections in both setups decreased FRC differences.

Conclusion

Overall, MBW measurements with the new device are feasible in infants. However, MBW outcomes from the old and the new device are not interchangeable and further work is needed in order to identify the source of this difference.

#J125 – Challenges in Spirometry Quality Control in Children.

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The reliability of spirometry interpretation depends on strict quality control (QC) during execution. It has been suggested that ATS/ERS QC criteria are too demanding for children.

Aims

To describe the success rate in spirometry execution by children in a pediatric lung function lab, report the compliance with QC criteria, and identify the least fulfilled criteria.

Methods

An analysis of basal spirometries conducted in children according to age groups: GA: 3–5 years, GB: 6–9 years and GC: 10–18 years was performed.

For each spirometry, the start of test criteria [back-extrapolated volume (BEV), peak expiratory flow (PEF) and loop artifacts], end of test criteria [forced expiratory time (FET), early termination, presence of plateau (GC)], number of acceptable, reproducible maneuvers and previous visits to the lab were analyzed. The Chi-Square test was used to compare independence between groups, considering a 5% significance level (SPSS® 21.0).

Results

404 spirometries were analyzed of which the main referral diagnoses were: asthma 259 (64.1%), cystic fibrosis 24 (5.9%), bronchopulmonary dysplasia 5 (1.2%), and obliterative bronchiolitis 9 (2.2%). 237 (58.7%) were male and distribution by age group was: GA: 27 (6.7%), GB: 122 (30.2%), and GC: 255 (63.1%).

All acceptability and reproducibility criteria were achieved in 300 (74.3%) spirometries [GA 21 (77.8%), GB 101 (82.8%), GC 178 (69.8%)], mainly within the school age group ($p = 0.038$). We found statistically significant differences in the number of visits to the Lab between groups ($p < 0.001$) (85.2% of GA and 37.7% of GB were in lab for the first time in 2016, compared to 62.8% of GC who were in lab more than four times), but no association was found between number of previous visits to the lab and QC ($p = 0.100$).

Start of test criteria were met in >90% of cases. End of test criteria were the least fulfilled in all groups [FET 86 (21.3%), early termination in 58 (14.4%) and in GC absence of plateau in 62/255 (24.3%) was also found].

For the 104 (25.7%) spirometries not fulfilling QC criteria, only 11/104 (10.6%) did not comply with any criteria. For the other 93 (89.4%) spirometries partially fulfilling QC criteria, 86.0% fulfilled all start of test criteria and only 4/93 fulfilled all end of test criteria.

Start of test criteria was significantly more accomplished than the end of test criteria in all groups, the hardest being FET and plateau in the GC; and FET in GB. FET was the least fulfilled QC for all groups, mainly GC ($p = 0.013$).

Conclusion

Two thirds of all children attained age-related spirometry QC criteria as defined by ATS/ERS 2005 and 2007 guidelines. School-aged children accomplished QC criteria better than the other groups. The end of test criteria were the least fulfilled, as previously described. The clinical impact of these findings must be evaluated and the need to adjust spirometry quality criteria by age further assessed.

#J127 – A Study of Hypoventilation during Wakefulness in Congenital Central Hypoventilation Syndrome (CCHS).

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Purpose

To clarify the actual condition of hypoventilation during wakefulness in CCHS.

Background

Although hypoventilation during sleep is the major symptom in CCHS, severe cases present hypoventilation even during wakefulness. Because the response against hypercapnia in CCHS is weak, there is a lack of subjective symptoms even in a hypoventilated state. Therefore, hypoventilation during wakefulness tends to be underestimated, and its actual condition is unclear. We studied hypoventilation during wakefulness since hypoventilation during wakefulness added to hypoventilation during sleep could be a risk for poor neurological prognosis.

Method

Subjects included 18 CCHS infants diagnosed by genetic testing in infancy. There were 2 cases of 25 Polyalanine repeat expansion mutation (PARM), 10 cases of 26–27 PARM, 5 cases of 30–33 PARM, and 1 case of Non PARM. The median age in months at inspection was 20.5 (range 2–69). EtCO₂ via tracheotomy or TcPco₂ and SpO₂ were monitored at rest during wakefulness without mechanical ventilation. We defined hypoventilation during wakefulness as mean EtCO₂ or TcPco₂ >45 mmHg and mean SpO₂ < 95%, and divided the patients into 2 groups, the group with hypoventilation (Group A) and the group without hypoventilation (Group B). The 2 groups were compared retrospectively through medical records.

Result

Nine cases (50%) were included in Group A, 9 (50%) cases in Group B. The median measuring time of Group A was 102.5 minutes, Group B 87 minutes. All cases with 25 PARM belonged to Group B, 5 of 10 cases with 26–27 PARM, and 4 of 5 cases with 30–33 PARM belonged to Group A. The median age in months at inspection of Group A was significantly higher than that of Group B (31, 11, respectively). In Group A, hypoventilation during wakefulness was not recognized in 7 of 9 cases at the time of CCHS diagnosis, and 8 of 9 cases were ventilated only during sleep. We examined the developmental quotient of 7 cases in Group A and 5 cases in Group B at 18 months of age. Of these cases, 5 of 7 (71%) in Group A had developmental delay, whereas only 1 of 5 (20%) had developmental delay in Group B. All cases that had developmental delay in Group A were not on mechanical ventilation during wakefulness.

Conclusion

The present study demonstrates that hypoventilation during wakefulness is observed in 50% of 26–27 PARM, which are genetically moderate in severity, and seen in a higher percentage in infants with more PARM. We should pay attention that hypoventilation during wakefulness is not rare in patients with more than 26 PARM. In addition, it is important to note that hypoventilation is often unrecognized in infancy, but becomes apparent as the infant grows older. Because the rate of developmental delay is high in those with hypoventilation during wakefulness, the respiratory status should be evaluated regularly after diagnosing CCHS for early detection of hypoventilation during wakefulness, and modify respiratory management appropriately.

#J149 – Flexible Bronchoscopy Findings in Children with Persistent Stridor.

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Abstract

Introduction

Persistent stridor is mostly associated with laryngomalacia (LM). Flexible airway endoscopy (FAE) is the procedure of choice when further investigation for a definite diagnosis is required. We aimed to review the opportunity or relevance of FAE findings in children with stridor.

Methods

Retrospective review of single-center medical records of children who underwent FAE because of referral for stridor (Jan2012-Oct2016). Demographic characteristics, symptoms, associated conditions, FAE findings, treatments, other diagnostic tests and follow-up were analyzed.

Results

Stridor accounted for 55/177 (31%) FAE performed in the period studied. From these, 50 were first time FAE. All 50 children had stridor, 35 (70%) presented feeding difficulties, 22 (44%) had symptoms suggestive of gastroesophageal reflux disease (GERD), 17 (34%) had associated conditions: previous endotracheal intubation 5 (10%), neurologic/metabolic disease 5 (10%), congenital heart disease 4 (8%) and 3 (6%) had bronchopulmonary dysplasia.

Median age for first time FAE was 3.4 (0.9–22.6) months. LM was the most frequent FAE finding, isolated in 17 (34%) and associated with other airway abnormalities in 13 (26%), 7 (14%) children showed isolated bronchomalacia and/or tracheomalacia, 5 (10%) airway stenosis, 2 (4%) extrinsic compression, 1 (2%) had incomplete vocal cord closure and 5 (10%) had normal FAE findings.

Children with comorbidities more frequently presented a diagnosis other than LM (53% vs. 18%).

Angio-CT findings of patients diagnosed for extrinsic compression were: 2 right aortic branches, and normal in one.

FAE was decisive for cardiac surgery in 2 patients, and for airway laser repair in another with subglottic stenosis. Esophageal pH monitoring performed in 11 children confirmed GERD in 4.

For the 23 children in follow-up, the median age of stridor disappearance was 15 months (9mos-4years), without differences between children with and without comorbidities.

FAE was performed at a median age of 18.6 (12.9–21.9) months, as reevaluation in 5 children with persistent stridor without improvement after 12 months age: in 3 children, persisting endoscopic signs of malacia were noticed while FAE was normal in the other 2 children.

Conclusions

As previously described, we found a high proportion of FAE performed at an early age in children presenting with stridor. Overall LM was the most common etiology found. Children with comorbidities more often

presented diagnosis other than LM. The association of airway malacia and GERD was scarce, confirming the anecdotal etiology. Although the role of FAE in stridor is controversial, we found lesions needing specific therapies in 3 children and we speculate it can alleviate parental anxiety in others.

#J153 – Accuracy of Fractional Exhaled Nitric Oxide (FeNO) in Detecting Asthma and Allergy in Children with Low Flow and High Flow Congenital Heart Disease.

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Background

Children with High Flow Congenital Heart Disease (HF-CHD) or those with left to right shunting (e.g. VSD, ASD and PDA) are observed to be prone to wheezing despite adequate management of congestion. The prevalence of allergy may be increased among these lesions. Matsuoka et al., in their study, concluded that shunt lesions enhance the manifestation of allergic diseases and asthma. Fractional exhaled nitric oxide (FeNO) has been used to screen for allergic type of asthma. Based on these findings, we hypothesize that the predictive accuracy of FeNO in detecting allergy and asthma will be enhanced when used in children with high flow CHD.

Patients and Methods

All patients with CHD ages 6–18 years old referred to pediatric pulmonology for preoperative risk stratification prior to a contemplated cardiac surgery without any active respiratory infection were included in the study. Presence of asthma, allergic rhinitis and eczema were determined through validated questionnaires. Pulmonary function test was also documented. FeNO determination was performed and patients were grouped into high flow or low flow congenital heart disease based on 2D echocardiography. Accuracy of FeNO was determined for each group.

Results

Eighty five patients completed the study. There were more children in the high flow category. Forty-nine (58.3%) had high flow lesions, mostly ventricular septal defects.

The overall accuracy of FeNO in children with low flow CHD was low at 56.1%. The sensitivity was 25.0%. The specificity was 87.1%, with a positive predictive value (PPV) of 20.0% and negative predictive value (NPV) of 90.0%. On the other hand, for high flow lesions, the overall accuracy of FeNO was high at 88.6%. The sensitivity, specificity, PPV and NPV were 92.9%, 88.6%, 76.5% and 96.8% respectively.

Conclusion

FeNO is more accurate in detecting asthma, allergic rhinitis and atopy when used in children with high flow CHD than with low flow CHD.

FeNO can be utilized to determine eosinophilic airway inflammation among this subset of CHD.

Keywords: exhaled nitric oxide, congenital heart disease, asthma

#J155 – Different Methods for Scond Calculation in Multiple Breath Washout: Any Impact on the Outcomes?

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“On behalf of the London CF Collaboration, Action Medical Research and Henry Smith Charity“

Background

Scond measured from normalized phase III slope (SnIII) during multiple breath washout (MBW) is a sensitive measure of abnormal function within conducting airways (figure 1). Different Scond calculations have been proposed (1,2). We evaluated whether the methodology for calculating Scond has an impact on results.

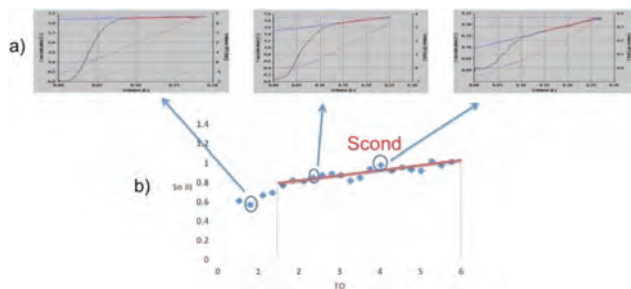


Figure 1 a) Phase III slope (slope of the red line) of 3 breaths in a MBW run. SF₆ concentration (black trace) is plotted against expired volume. b) Normalized phase III slope (SnIII) for each breath is plotted against its corresponding lung turnover (TO = cumulative expired volume/FRC). Scond measures the SnIII increase per unit TO between ~1.5–6.0 TO.

Methods

School age subjects with cystic fibrosis (CF) and healthy controls (HC), studied for the London CF Collaboration, performed SF₆MBW with a mass spectrometer (Amis 2000, Innovision, Denmark), by unconstrained tidal breathing.

SnIII analysis was performed using in-house software package (TestPoint, Capital Equipment, USA).

Quality control was performed by breath-by-breath visual inspection, eliminating breaths with no clear phase III or with artefacts due to irregular expiration or oscillation. MBW runs with >33%

excluded breaths were removed. Cystic fibrosis patients with severe ventilation inhomogeneity (Lung Clearance Index >14) were excluded.

Scond was calculated as the regression slope of SnIII values plotted against lung turnovers (TO) between TO 1.5 and 6.0, from subjects with 3 valid runs. Scond was tidal volume corrected as previously described (3).

Two methods for Scond calculation were compared:

1. For every run, SnIII values are plotted against lung TO and Scond is calculated, as in figure 1. The Scond of the MBW test is the average value between 3 runs
2. Mean SnIII values from 3 runs are plotted against mean TO for every breath, so a single Scond is calculated from averaged washout data

Results

Mean (SD) Scond was very similar by both methods in CF patients and controls (Table).

[TBL 0]

A Bland-Altman plot of the average Scond by the two methods against the differences for every subject resulted in a Bias of 0.0002 (0.011) with 95% Limits of Agreement from -0.023 to 0.022 (Figure 2).

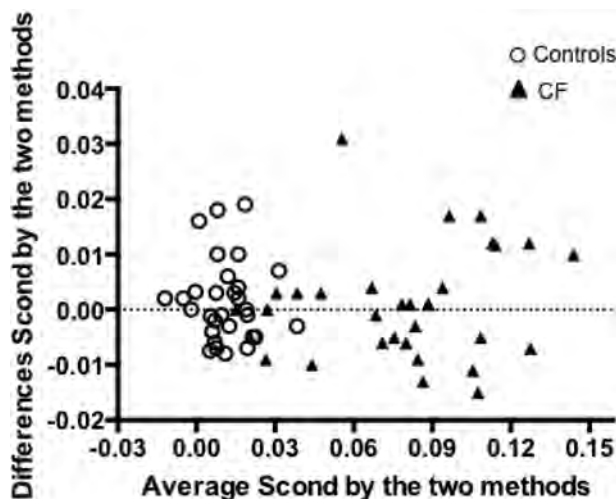


Figure 2. Bland-Altman plot

Conclusion

The two methods for calculating Scond in MBW give similar results, and can be used interchangeably for assessment of distal conducting airway function. We could not find any reason to recommend the use of one over the other.

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[TBL 1]

#J160 – Shortened Multiple Breath Washout Is Not Suitable for Scnd Calculation in Patients with Cystic Fibrosis.

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“On behalf of the London CF Collaboration, Action Medical Research and Henry Smith Charity”

Background

Multiple Breath Washout (MBW) gives sensitive information about distal gas mixing in the lungs, which can be further refined by phase III slope analysis (figure 1).

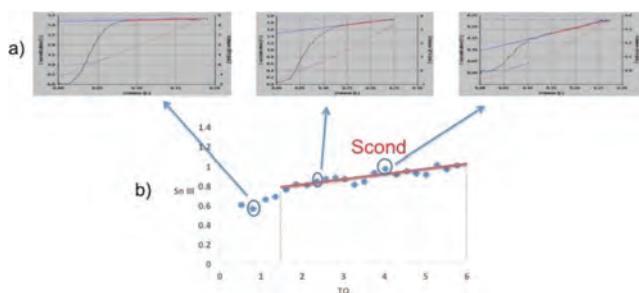


Figure 1 a) Phase III slope (red line) of 3 breaths in a MBW run b) Normalized phase III slope for each breath (SnIII) is plotted against its corresponding lung turnover (1 TO = cumulative expired volume that equals FRC). With ventilation inhomogeneity, SnIII gradually increases throughout the MBW. Scnd reflects abnormalities within conductive airways and it measures the SnIII increase per unit TO between ~1.5–6.0 TO

MBW is a time-consuming procedure. There are shortened protocols for MBW(1–2) but they have never been tested for Scnd calculations.

We aimed to compare Scnd obtained applying the standard endpoint for SF6 MBW (SF62.5%) and a shortened protocol.

Methods

Cystic fibrosis (CF) patients and healthy controls (HC) aged 6–18 years, studied for the LCF Collaboration performed SF6MBW with a mass spectrometer system, at tidal breathing.

Scnd was derived applying two different endpoints for calculation of Functional Residual Capacity (FRC):

1. SF62.5% (i.e. SF6 concentration 2.5% of the starting value)
2. SF6 Cn@TO6 (i.e. % of SF6 initial concentration when reaching 6 lung volume TO).

Scnd was automatically calculated, after elimination of small breaths with a tidal volume <3 Fowler dead space.(3) MBW runs with >1/3 of breaths excluded were removed. Subjects with Lung Clearance Index >14 were eliminated. Scnd was calculated from subjects with 3 valid runs, and was then volume corrected(4).

Results

In CF subjects Scnd was significantly higher applying the SF62.5% endpoint than the Cn@TO6 endpoint ($p < 0.01$; Table), while there were no significant differences in HC ($p = 0.4957$). Mean FRC by the SF62.5% protocol compared with the Cn@TO6 endpoint was higher both in CF (1.65 vs. 1.54 L; $p < 0.001$) and in HC (2.26 vs. 2.21 L; $p < 0.05$)

[TBL 0]

A Bland-Altman plot of the average Scnd by the two endpoints against the differences for every subject is shown in figure 2.

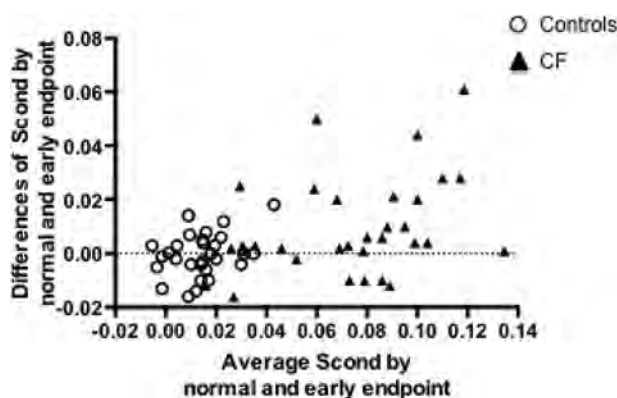


Figure 2. Bland-Altman plot

Conclusion

A shortened protocol for SF6MBW Scnd calculation may not be suitable for CF subjects with moderate-severe lung disease as it tends to underestimate FRC, and therefore also Scnd. In fact, a lower FRC anticipates the 1.5–6 TO interval in the MBW and excludes from Scnd calculation some late breaths that, in subjects with ventilation inhomogeneity, wash out the most abnormal lung units, whereas in controls, FRC underestimate does not affect Scnd since the SnIII has poor progression throughout MBW.

References

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#J170 – Impact of Video-fluoroscopic Swallow Studies on Feeding Management and Clinical Status of Children with Dysphagia.

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Purpose

To evaluate the impact of video-fluoroscopic swallow studies (VFSS) in children with suspected dysphagia on occupational therapists' (OT) management, feeding patterns and clinical respiratory status.

Methods

This is a retrospective case file review of 25 consecutive children with clinical suspicion of dysphagia, who underwent VFSS in a tertiary hospital setting. Evidence of pharyngeal pooling, laryngeal penetration and lung aspiration was sought from the VFSS. Data were collected on OT management strategies, feeding patterns and clinical respiratory status prior and following the VFSS.

Results

Demographics:

Twenty-five children, 14 (56%) males, underwent VFSS at a median age of 28 months (range 1–193). Their diagnoses were central nervous system dysfunction (n = 13, 52%), structural defects (n = 4, 16%), syndromic abnormalities (n = 4, 16%), neuromuscular disease (n = 3, 12%) and vocal cord palsy (n = 1, 4%).

VFSS Results:

Out of 22 children examined with thin liquids, 7 (32%) had pooling, 11 (50%) penetration, and 4 (18%) aspiration. With thick liquid, 5/16 (31%) had pooling, 13/16 (81%) penetration, and 2/16 (13%) aspiration. With thin puree, 3/11 (27%) had pooling, 3/11 (27%) penetration, and 1/11 (9%) aspiration. With thick puree, 5/18 (28%) had pooling, 5/18 (28%) penetration, and 0/18 (0%) aspiration. With soft solids, 2/9 (18%) had pooling, 1/9 (11%) penetration, and 0/9 aspiration. With firm solids, none of 8 had pooling, penetration or aspiration.

OT Intervention:

After VFSS, the following measures were advised by OTs that had not been suggested following clinical assessment alone: 8/25 (32%) thickening feeds, 3/25 (12%) feeding interface adaptation, 3/25 (12%) oro-motor stimulation and 3/25 (12%) change in positioning.

Change in Feeding Patterns:

Following the VFSS, 4 (16%) children who had been fed exclusively by naso-gastric tube (NGT) or percutaneous endoscopic gastrostomy (PEG), were allowed to eat orally. One (4%) was changed from NGT to oral and PEG feeds. Two (8%) children who ate orally before, were asked to remain nil by mouth after the VFSS, one changing to NGT and one to PEG.

Clinical Impact:

In the year preceding the VFSS, there were a total of 93 hospital admissions, falling to 65 in the year after, p = 0.003. Total days of admission were 530 before and 282 after, p < 0.001. Respiratory admissions fell from 42 to 25, p = 0.003. Pediatric intensive care unit admissions fell from 10 to 5, p = 0.017. The number of antibiotic courses fell from 66 to 40, p = 0.018. Total days of antibiotic treatment per year fell from 425 to 303, p = 0.014.

Conclusion

Penetration was most commonly observed with thick liquid, while aspiration was commonest with thin liquid. Clinical assessment of dysphagia resulted in incomplete ascertainment and valuable further information was gained by VFSS. Change in feeding strategies was associated with clinical improvement of respiratory status.

#J172 – Sonographic Evidence of Pulmonary Edema in Pediatric Patients With Congenital Heart Disease.

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Propose

Traditionally, real-time ultrasonography was used mainly for visualization of structures and functional abnormalities in congenital heart diseases (CHD). Significant advances in ultrasonography have made it a useful tool for the diagnosis of pulmonary complications associated with CHD. This study aims at highlighting the accuracy of lung ultrasound compared to chest radiography in pediatric CHD patients.

Method

We employed ultrasonography as a non-invasive method and an alternative tool for the diagnosis of pulmonary edema in patients with CHD. We enrolled 17 patients with CHD who were admitted consecutively to our ward with pulmonary edema from October 2009 to December 2011. Pulmonary edema was suspected due to increased infiltration and bilateral perihilar regions with engorged vascularity on chest radiography. The lung ultrasound was also performed to detect comet-tail artifacts arising from the pleural line. The sonographic findings of a control group of 30 patients without pulmonary edema were compared with the group with pulmonary edema. The performance of chest radiography and ultrasound findings were also compared.

Results

A total of 17 patients (M/F 9/8) identified with pulmonary edema ranging from 0.1–18 years of age and a mean and standard deviation of 5.47 ± 5.10 years old were examined. Chest X-ray revealed congestion with or without inflammatory changes in 4 patients and pulmonary alveolar edema in 13 patients. The lung ultrasound showed numerous comet-tail signs arising from the pleural line in all patients without sonographic inflammatory signs. The sensitivity and specificity of lung ultrasound was 100%.

Conclusion

Our results demonstrate that lung ultrasound is very useful in the diagnosis of cardiogenic pulmonary edema. In experienced hands, lung ultrasound can be used as an alternative real-time, non-invasive, non-irradiating and rapid tool in the diagnosis of pulmonary edema in children with CHD.

Reflections and Proposals

Lung ultrasound is a useful tool for the diagnosis of pulmonary edema in children with CHD.

K. THERAPEUTIC PROCEDURES

#K6 – Sublingual Atropine Sulfate Use for Sialorrhea in Pediatric Patients.

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Background

Sialorrhea is a frequent problem and may lead to aspiration in patients with swallow dysfunction. In this study we aimed to assess the effectiveness and safety of sublingual atropine sulfate treatment in pediatric patients with sialorrhea.

Method

The medical records of the patients who had received sublingual atropine sulfate 20 mcg/kg/dose for 4–6 times per day for seven consecutive days in our hospital during a period from January 2015 through January 2016 were reviewed retrospectively.

The demographic properties, diagnosis, need for invasive or noninvasive mechanical ventilation and the presence of tracheotomy were assessed.

Response rates to sublingual atropine were measured by the “Teacher Drooling Scale” (TDS), which is a metric for assessing level and frequency of drooling that ranges from 1 (no drooling) to 5 (profuse drooling all day) and recorded by nurses before and after treatment. Pre- and post-treatment drooling scores were compared.

Results

Thirty-five pediatric patients with sialorrhea who received sublingual atropine sulfate were identified, although TDS assessment was only performed in 21 of these patients.

The median age of the patients was 30 months (3–144 months) (7 girls, 14 boys). Seventeen (80%) patients were on invasive mechanical ventilation and seven (30%) had a tracheotomy. Twenty patients had a neurodevelopmental disorder and only one patient had oral and esophageal lesions due to corrosive material intake.

The median TDS prior to sublingual atropine sulfate treatment was 5, and decreased to 3 on the second day of treatment up to the end of seven days, a change that was statistically significant ($p < 0.001$). No side effects were observed during the treatment period.

Conclusion

Although sublingual atropine sulfate is safe and effective during short term usage for the treatment of sialorrhea, randomized placebo-controlled and long term follow-up studies are necessary.

#K120 - In vitro Characterization of Adding a Partition Separating Mouth from Nose in a Pediatric Facemask.

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Comparison of the in vitro properties of two pediatric masks for valved holding chambers of identical shape with one comprising a septum blocking nasal inhalation.

A newly designed mask with septum (MS, Or'hal[®], Laboratoire Protec'Som) was compared in vitro to a similar mask but without septum (MP, Protec'Som). Essential characteristics of child facemasks were measured *in vitro*: flexibility, volume and seal to the face, and their relationship to in vitro drug deposition. Both masks were used with the same valved-holding chamber (VHC, Tips-haler[®], Laboratoire Protec'Som). Flexibility, volume and seal of the masks were measured against 5 forces (0; 0.5; 1; 1.5; 2 kg). Flexibility was estimated as a force-dependent length reduction of the masks onto a hard and flat surface; and expressed as the slope of length versus force regression line. Mask volumes were determined by the water displacement method. Seal was evaluated by applying mask-VHC to a realistic 3D supple face model (Copley Scientific) and delivering constant airflow. Integrity of the seal was expressed as the ratio of airflow before and after the mask-VHC-face system. Aerosol delivery was assessed using an in vitro mouth inhalation model (Copley Scientific) at two clinically relevant application forces (0.5 and 1 kg) and a breathing simulator (Copley Scientific). Aerosol (Fluticasone propionate, Flixotide[®], GlaxoSmithKline) was captured on a filter (Copley Scientific) and drug concentration was assayed by spectrophotometry at 236 nm.

Logically, the addition of a septum inside the mask decreased flexibility (MP: -0.80 , $r^2 = 9894$; MS: -0.57 , $r^2 = 0.9758$). Despite initial volume reduction (27% at 0.5 kg) due to the partition, MP and MS volume were equivalent at higher application forces (above 1.5 kg) due to reduced flexibility. The septum also increased seal efficiency to the face model by 15% at 0.5 kg and 29% at 2 kg. However, for aerosol deposition, at the 2 application forces tested (0.5 and 1 kg), there was no statistically significant difference between the 2 masks. Increased application force increased the filter dose (MS: +7.2%; MP: +8.7%) and decreased drug deposited onto the mask (MS: -5% ; MP: -4.6%).

The results show that within the scope of our in vitro model, changes in volume and seal did not affect drug deposition.

The use of facemasks adds complexity to the design and assessment of VHCs. Despite 80% of VHCs (in France, in 2015) selling with pediatrics masks, research is still scarce. The primary function of this mask with septum is to block nasal breathing, oral inhalation being favored for lung treatment, and recommended by guidelines. However, mask design should not otherwise compromise drug delivery. Mask-to-face seal and dead space volume can affect

medication delivery, especially for children with low tidal volume. It is therefore essential to develop robust in vitro models to test these parameters when designing new masks.

#K126 – How Reliable Is the Internet for Treatment of a Child's Acute Cough?

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Background

The Internet is one of the leading sources of medical advice for parents, yet the guideline adherence and quality of the websites remain questionable. Given the rapid development of the Internet, results of previous studies on the quality of online information on pediatric acute cough treatment may be outdated. Aim: To evaluate the accuracy of information on acute cough treatment in children provided online. Methods: The three most common search phrases for each language (Arabic, English, French, German, Norwegian, Russian) were evaluated in the three most often used search engines. To avoid bias, the search in all languages was conducted on a laptop or tablet, in incognito mode, on 3 consecutive allotted days for each search engine (one day for one phrase). For each phrase and each search engine, the first 200 results were checked. Each website was evaluated based on adherence to advice, with technical appraisal and content completeness as secondary outcomes. BTS guidelines and AAP statements were used as the standard for advice. Websites were awarded 0 or 1 point for each piece of information provided (1 was assigned for standard-adherent information), with a maximum of 13 points. Each parameter was expressed in % of the websites that provided correct information. Technical appraisal included components such as author, references, functioning and relevant links and modification date. Content completeness focused on assessing the presence of information such as purpose of cough, its mechanism and possible types of treatment. Websites were given 1 point for the presence of each feature. Results: 6178 websites in 6 languages were evaluated, 1297 of which were relevant and therefore assessed. In the adherence of advice section, the information on correct hydration and the use of levodropropysine showed to be the most (46.5%) and least (0.8%) accurate respectively. Only one website received the maximum score. The total point score median was 2. German websites proved most reliable, while English websites were the least (total score median 4 vs. 1, respectively). For content completeness, with a maximum point score of 7 (achieved by 114 websites), the median point score was 4. The most commonly stated information was that on increased fluid demand and/or humid environment, which was provided by 51.8% of the assessed websites. Regarding technical appraisal, 4 websites received the maximum score of 11 points, with a median point score of 5. Lack of paywall/registration proved to be the highest scoring parameter (98.5% of websites).

Conclusion

The overall accuracy of adherence to advice was low. The technical aspects of the assessed websites scored higher than content completeness and much higher than adherence to advice. Proposal for future actions: As the Internet continues to be a major source of information, we propose an official, multilingual website containing updated and guideline adherent data.

#K130 – Effects of Specific Inspiratory Muscle Training Using an Individual Training Device in Children with Asthma.

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Introduction

In asthmatic pharmacological as well as self-management education and non-pharmacological therapy, respiratory physiotherapy (whole-body exercise training, inspiratory muscle training (IMT) and breathing retraining techniques) has an important role. There is a debate regarding the effectiveness of inspiratory muscle training in asthmatics, with no conclusive evidence to support or refute IMT for asthma.

Objective

The aim of this study was to evaluate the effects of specific IMT using an individual training device designed to increase the strength and endurance of the inspiratory muscles on pulmonary function, muscle strength and endurance in children with asthma.

Methods

In the randomized clinical study, we included 135 children (males = 82, aged 6–18 years, mean = 12.6) with mild to moderate asthma diagnosed by a physician, treated in the Children's Hospital Srebrnjak. One hundred and eight children underwent specific IMT with a special physiotherapy device during one month (at least 10 times/month). Twenty-seven children were given instructions how to perform diaphragmatic breathing exercises regularly at home during one month. The results were evaluated using Wilcoxon Signed Ranks Test and only values of $p < 0.05$ were considered statistically significant.

Results

The comparative analysis showed that the values of absolute and relative forced vital capacity (FVC_{rel} and FVC_{abs}, respectively), absolute peak expiratory flow (PEF_{abs}), peak expiratory flow measured by a peak flow meter (PFM) and absolute forced expiratory volume in the first second (FEV1_{abs}) had significantly increased in comparison to their initial values in the IMT group: FVC_{abs} from 2.93 ± 0.81 L to 2.99 ± 0.83 L ($p = 0.012$), FVC_{rel} from 87.86 ± 11.06 % to 89.48 ± 10.65 % ($p = 0.011$), PEF_{abs} from 5.65 ± 1.73 L/min to 5.81 ± 1.79 L/min ($p = 0.013$), PFM from 324.35 ± 99.21 L/min to 341.78 ± 112.82 L/min ($p = 0.003$) and FEV1_{abs}

from 2.54019 ± 0.734916 to 2.5933 ± 0.75554 ($p = 0.25$). On the other hand, the values of FVC_abs, FVC_rel and PEF_abs did not show a significant increase in the group of children who performed breathing exercises at home, although PFM significantly increased from 303.46 ± 94.27 L/min to 339.26 ± 75.74 L/min ($p = 0.011$). The results also revealed a significant increase in maximal inspiratory pressure (MIP) and inspiratory muscle endurance (Tlim), defined as the time the subject was able to sustain breathing against an inspiratory pressure load equivalent to 60% of the MIP, in both groups. In the IMT group, MIP increased from 79.88 ± 31.99 cmH₂O to 117.7 ± 29.33 cmH₂O ($p = 0.000$) and Tlim from 259.74 ± 361.74 s to 437.35 ± 413.28 s ($p = 0.000$).

Conclusion

Specific IMT, using an individual training device designed to increase the strength and endurance of the inspiratory muscles, may improve pulmonary function in children with asthma, as indicated by the increase in FVC, PEF, FEV₁, MIP and Tlim.

#K136 – High Flow Nasal Cannula Therapy for Infants with Severe Acute Bronchiolitis – First Experiences.

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Introduction

High flow nasal cannula therapy is a new and noninvasive method in treatment of infants with a severe form of bronchiolitis. In oxygenation, the air is humidified and heated, the use of respiratory muscles and instances of atelectasis are decreased, functional residual capacity is thus improved. The goal of this method is for shorter and more effective treatment of acute severe bronchiolitis in infants treated in pediatric intensive care unit and avoidance of invasive ventilation.

Subjects and Methods

A total of 15 patients (aged 2–24 months), previously healthy infants and toddlers, without accompanying diseases such as chronic respiratory diseases, bronchopulmonary dysplasia, congenital heart diseases, with clinical features of proven viral infection (RSV, adenovirus, or hMPV in nasal aspirate proven by PCR method), severe bronchial obstruction and laboratory results of respiratory acidosis (pH level below 7.3, pCO₂ level above 7 kPa, pO₂ below 7 kPa) were treated with high flow oxygen using nasal cannula in the period of 24–48 h in addition to other supportive pharmacotherapy (inhalation with hypertonic NaCl, bronchodilator and corticosteroid).

Results

The patients treated with high flow oxygen using nasal cannula during 24–48 h recovered significantly faster, with reduction in hypoxemia and CO₂ accumulation, reduction of breathing efforts, reduction in respiratory and heart rate. In all patients, after 48 h of treatment in acid-base status, there were no signs of respiratory acidosis (normal pH range (from 7.35 to 7.45 kPa, pO₂ from 7.3 to 10.6 and pCO₂ from 4.3 to 5.7 kPa), with mildly elevated bicarbonate level and slightly reduced SaO₂ values.

Conclusion

High flow oxygen therapy in infants with severe forms of acute viral bronchiolitis allowed for shorter and more effective non-invasive ventilation treatment with faster improvement of general and respiratory status. Our limited experience with the first application of a new non-invasive ventilation in children with severe acute bronchiolitis treated in intensive care unit is highly positive and encouraging and we can recommend this treatment as the therapy of choice in place of invasive methods. An increasing number of patients are necessary in further research for purposes of optimization and evaluation of the new intervention.

#K157 – Video-assisted Thoracic Surgery for Pediatric Spontaneous Pneumothorax – A Tertiary Children's Hospital Experience.

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The aim of this study was to review a tertiary children's hospital's experience with thoracic treatment of pediatric spontaneous pneumothorax (SP).

A retrospective review of all children undergoing Video-Assisted Thoracic Surgery (VATS) for SP between 2011 and 2015 was performed and data on demographics, diagnostic imaging, therapeutic approach, findings at surgery and outcomes were reviewed.

Ten patients, 7 males and 3 females, aged 13 to 17 years old (average 15.5) underwent VATS procedures for SP in a five-year period. SP was primary in 5 patients and secondary in 5 patients, in whom asthma was the primary disease in the majority. Eighty percent of patients were found to have apical abnormalities of the lung on CT scanning. The indications for surgery were as follows: a first episode with persistent air leak in 60% of patients and a recurrent ipsilateral pneumothorax in 40% of patients. Three different surgical techniques were used as follows: apical wedge resection plus mechanical pleurodesis (50%), apical wedge resection plus chemical pleurodesis with talc (40%) and apical wedge resection plus mechanical and chemical pleurodesis with talc (10%). Apical blebs were identified at the time of VATS in 100% of patients. There was an additional VATS procedure for contralateral pneumothoraces in 30% of patients. There were no recurrences during the study period. Hospital mean length of stay was 8.4 days, and postoperative chest tube duration was 3.6 days (range 2 to 6 days). Mean follow-up was 19 months (range, 2 months to 3 years). There were no deaths or postoperative complications.

The thoracoscopic approach for treatment of SP is safe and effective in children. Wedge resection plus either mechanical, chemical pleurodesis or combination of these techniques were all associated with acceptable outcomes. Due to a lack of evidence of which surgical approach is superior in children, there is still no agreement and consistency in pediatric spontaneous pneumothorax management. Given the relatively low incidence, we suggest a

multicenter approach for future research in order to generate the evidence required for informed management of SP in children.

#K213–Flexible Pediatric Bronchoscopy on Pulmonary Atelectasis: 10-Year Experience in an Adult Pulmonology Department.

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Introduction

In pediatric age, almost all cases of atelectasis are acquired and referred to as secondary; in rare cases, primary atelectasis caused by congenital abnormalities may be present from birth. Chest physiotherapy is the most common treatment in hospital setting, although there are limited data supporting the efficacy of this approach. Bronchoscopy is considered a “last resort” in atelectasis management. There are no data comparing non-invasive therapies with bronchoscopy.

Aims

Characterize children with atelectasis who were submitted to flexible bronchoscopy. Characterize endoscopic findings in these children.

Methods

Retrospective and observational analysis based on former medical records of patients aged under 18, submitted to flexible bronchoscopy in a bronchoscopy suite, over a 10-year period (2007–2016).

Results

We reviewed 52 flexible bronchoscopies in patients under 18 years old (newborn: 1; infant: 15; toddler: 20; pre-schooler: 6; schooler: 7; teenager: 3) with male predominance (59.6%) and a mean age of 3.2 years.

Sixty-nine percent of children had a pneumonia diagnosis, of which 14 were recurrent. Seven children had a neurological disturbance: Down syndrome (n = 2), Charge syndrome (n = 1), Rett syndrome (n = 1), anoxic encephalopathy (n = 2) and cerebral palsy (n = 1).

The presence of foreign-body was confirmed in 2 children, needing conversion to rigid bronchoscopy.

The right lung was the most affected (71.1%) and middle lobe atelectasis was the most frequent (n = 15).

The most frequent endoscopic findings were: 50% bronchorrhea with purulent and viscous secretions; 30.7% inflammatory findings with mucosal hyperemia and edema; 7.7% extrinsic compression due to vascular rings (n = 3) or lymphadenopathy (n = 1); 5.8% scarring lesions with bronchial stenosis.

The average delay to bronchoscopy was 19 days in children aged less than 1 year and 8.5 days in the remaining patients.

In patients with pneumonia (n = 36), only 22% had microbiological positive results (*Haemophilus influenzae* n = 7 and *Mycobacterium tuberculosis* n = 1)

All interventions were performed under general anesthesia. Intraprocedure complications occurred in 1 exam: severe bronchospasm with desaturation that was corrected immediately with no need for further intervention. The mortality rate was zero.

Conclusion

Flexible bronchoscopy in the pediatric age is important in the diagnosis and treatment of atelectasis. It can be useful in children with neurological impairment or airway clearance disorders. Flexible bronchoscopy allows identifying airway conditions that could need further endoscopic management such as bronchial stenosis with recurrent infections. Further studies comparing invasive and non-invasive procedures would be important.

#K214 – Pulmonary Wedge Resection in the Pediatric Population: Experience of a Surgical Department of a Tertiary Hospital.

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This study aims to characterize the patient population submitted to a pulmonary wedge resection in a tertiary pediatric hospital. This type of approach is used to avoid an anatomical resection and therefore is intended to spare healthy lung tissue, being performed by thoracotomy or thoracoscopy. Most of the patients suited for this approach suffer from secondary malignant metastasis (SMx) or pleural bleb/bullae associated with primary pneumothorax (PT). Although it is not a new technique, to our knowledge, little has been discussed regarding this surgical approach in the pediatric population, therefore we conducted this study to better understand our patient population in our tertiary pediatric hospital.

Online clinical files were searched for patients admitted in our hospital between January 2010 and November 2016 with the diagnosis of PT (ICD-9:5128) or SMx (ICD-9:1971) submitted to a surgical procedure, including those who were submitted to a pulmonary wedge resection. Overall 18 patients were identified, corresponding to 25 procedures; 14 male, 11 female (56%vs44%); 16 due to PT and 9 to SMx; 16 by thoracoscopy and 9 by thoracotomy (64%vs36%); the pre-op anesthetic evaluation of each case, according to the American Society of Anesthesiology, was from I to IV: 1, 16, 8, 0 (4%vs68%vs32%vs0%). The SMx cases were due to: 7 Wilms Tumor, 1 osteosarcoma, 1 testicular cancer (78%vs11%vs11%); 6 patients with PT had asthma (37.5%). No other relevant co-morbidities were recorded. 3 cases had SMx bilaterally and 2 cases had contralateral PT. There were no intra-operative complications in either group. Two relapses of the PT group were identified, submitted to another thoracoscopy wedge resection with good outcome. In the group with SMx, there were no identified relapses necessitating another surgery.

All patients with SMx were approached by thoracotomy and those with PT by thoracoscopy. Although thoracoscopy had gained more supporters along the years, much has been discussed if patients with SMx met good criteria for this approach. Nowadays, most authors acknowledge thoracotomy as the preferred choice in this setting for its important tactile characteristics. However this approach has a greater morbidity and thoracoscopy is considered as an excellent approach to

execute a wedge resection, with PT patients being the perfect candidates. Our data seem to reflect those mainstream surgical options with optimal results, and therefore we consider them to provide good care to our patients. However this study has a small sample and its design does not allow evaluating the long term outcome of our patients through adulthood, therefore further studies are warranted.

#K215 – Quality of Life of Home-Ventilated Children and Adolescents in a Tertiary Care Center.

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Introduction

Home mechanical ventilation represents a treatment option for patients with chronic respiratory failure, changing prognosis of many disorders in children and potentially improving their quality of life (QoL). This study intends to evaluate QoL of home-ventilated children of a tertiary pediatric hospital, according to children/adolescents and caregiver's perspectives.

Methods

We retrospectively studied families enrolled in a pediatric home ventilation program in a Portuguese tertiary pediatric hospital, for a period longer than 6 months. The Pediatric Quality of Life Inventory™ (PedsQL™), approved for the Portuguese population, was anonymously answered by children/adolescents and caregivers coming to outpatient appointments in the respiratory clinic. Period of study: June – December 2016. Written informed consent was obtained from caregivers. Several data, including demographic and clinical characteristics, were collected. Statistical analysis was performed using SPSS 21.0.

Results

Forty-four fully answered questionnaires were obtained (median age 12y; 57% male). Main diagnostic groups were: neuromuscular disease (10), mixed syndromic (7), obstructive syndromic (6), sleep obstructive disturbance (6), restrictive syndromic (4), cerebral palsy (2), spine bifida (2), severe obesity (2) and chronic pulmonary disease (2). Median time on ventilation was 3y7m. Most children were ventilated from 0-8h; good/very good compliance was reported in 66%. Sixty-six percent attended school in a full-time schedule.

QoL (score 0–100) reported by children and adolescents had a median score of 66 while the one reported by parents was 58. We verified a strong correlation between QoL scores reported by both groups ($r = 0.7$).

Median QoL scores reported by parents /children were the following for each age group: 2-4yo (42/-), 5-7yo (73/73.9), 8-12yo (63/67) and 13–18 (51/64).

There was no statistically significant difference between QoL values according to parents or to children based on the different diagnostic groups ($p = 0.671$ and $p = 0.679$), as well as type of interface used ($p = 0.192$ and $p = 0.152$), hours of ventilation per day ($p = 0.277$ and $p = 0.365$) or compliance ($p = 0.534$ and $p = 0.160$). There was also no statistical significant difference between QoL scores related to total duration of ventilation in years (parents – $p = 0.875$ and children – $p = 0.420$).

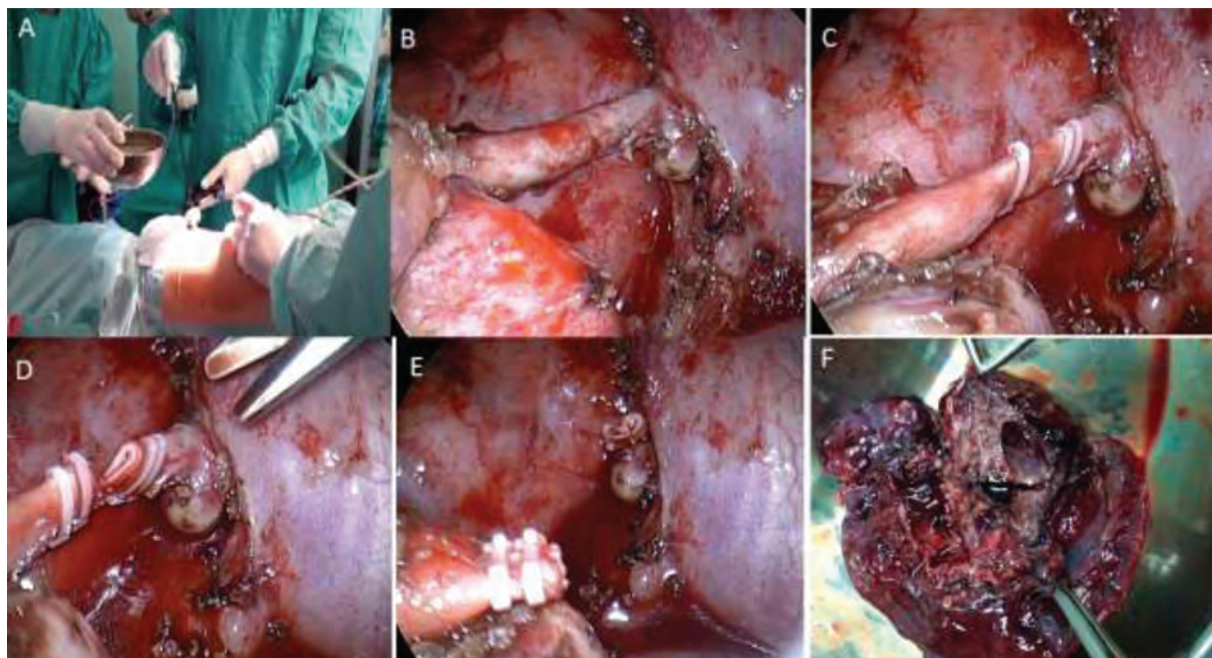
Conclusion

Life quality scores of HVC were similar between different types of diagnosis, duration and mode of ventilation.

We did not find significant differences between QoL scores in different groups of diagnosis, total duration of ventilation, ventilation mode, type of interface, hours of ventilation per day and levels of compliance.

There is a strong correlation between scores obtained from parents' and children's questionnaires.

Global results from QoL scores were higher than in other previously published reports.



L. CELLULAR AND MOLECULAR BIOLOGY

The two abstracts/manuscripts for the Cellular and Molecular Biology section will not appear in this issue

M. PEDIATRIC PULMONOLOGY IN DEVELOPING COUNTRIES

#M5 – VATS for CCAM: Report of Three Cases

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Two male and one female child, ages 7, 4 and 3 years, were treated for symptoms of cough, high temperature in district hospitals. In all three children, laboratory blood tests, chest radiograph, auscultatory findings showed the presence of pneumonia. Children were treated with appropriate doses of antibiotics. After the rehabilitation of inflammation, they were sent to the UCC Sarajevo to perform chest CT scan, which pointed to the CCAM and PS changes in lungs. This required surgical lobectomy of the affected part of a lung. In both patients with pulmonary sequestration, the aberrant systemic artery was originating from the most proximal part of the abdominal aorta. The operation was performed under a general anesthesia with one sided-lung ventilation and collapse of the lung with disease. Patients were positioned in the stable lateral decubitus position. Three small incisions in the chest approximately 1 cm long were performed in the 5th ICS mid-axillary line for the 5 mm 30° telescope to examine inside the chest. The other two incisions were performed for the working instruments, one in the 4th ICS front axillary line (5 mm port) and one in the 8th ICS front axillary line (10 mm port). In cases with pulmonary sequestration, the division of the aberrant artery was first performed. The artery was easily found in the lower pulmonary ligament which was divided and the artery freed over a length of 2–3 cm from adhesions and fibrotic sheath. In one case, the artery could be clipped using the Weck® Hem-o-lok® polymer locking ligation system and in the other case, the artery was more than 11 mm thick and the vascular stapler Endo-GIA™ 30–2.5 mm was used. Pulmonary ligament was further divided with hook cautery until exposure of the inferior pulmonary vein which was completely exposed. The segmental arterial branches to the lower lobe were identified and all were divided one by one from medial to lateral after positioning of the Weck® Hem-o-lok® clips through a 5 mm port. To allow for further resection of the lower lobe, the major fissure was completely divided using a LigaSure™ 5 mm blunt tip 37 cm sealer and divider.

A 6 cm skin incision was performed along the port in the 5th ICS and the soft tissues divided with the cautery. The chest was entered in the 5th ICS along the upper edge of the 6th rib. The final dissection between the lower lobe bronchus and the pulmonary vein was performed partially bluntly with the aid of Ligasure. The lower lobe bronchus was finally always divided using the stapler two times, once for segment 6 and once for the main part of the lower lobe bronchus before branching to other segments. Finally, the inferior pulmonary vein was divided using the vascular stapler. The mediastinal pleura was closed with Vicryl 4/0 stitches. This study suggests that patients who present with asymptomatic CCAM will subsequently become symptomatic. Early surgical referral and intervention may be beneficial to avoid the development of complications.

#M10 – Analysis on Surveillance of *Mycoplasma pneumoniae* Infection in Children

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Objective

Mycoplasma pneumoniae (*M. pneumoniae*) is an important pathogen causing respiratory tract infection in adults and children. In recent years, epidemiological characteristics of *M. pneumoniae* infection have changed. Further epidemiological studies are needed to find answers to this phenomenon.

Methods

- (1) Study population: patients consulting the fever clinic for on-site investigation of *M. pneumoniae* respiratory tract infections.
- (2) The clinical data of the subjects were obtained by questionnaire, medical history collection, physical examination and assistant examination.
- (3) Pharyngeal swab acquisition and DNA detection. For some subjects, we conducted long-time monitoring for *M. pneumoniae*-DNA in pharyngeal swabs to observe the carrying duration of *M. pneumoniae* after infection and to observe its relationship with the progression of the disease.
- (4) Culture and isolation of *M. pneumoniae*.
- (5) Drug resistance analysis and mutation detection of *M. pneumoniae* strains: isolated strains were detected and analyzed for macrolide-resistance, and the mutation points were confirmed.
- (6) Molecular typing of *M. pneumoniae* strains: all isolates were detected by MLVA molecular genotyping. Parts of the strains were also detected by P1 gene typing. The two types of molecular genotyping methods were compared. We also explored the significance of MLVA typing in molecular characters in *M. pneumoniae* infection.

Results

A total of 1025 patients were enrolled. Among these, 163 were *M. pneumoniae*-DNA positive, for a positive rate of 15.09%. We found that *M. pneumoniae* infection tended to occur in children over the age of 5 years, summer and autumn were the epidemic seasons, and pneumonia was the most common form of *M. pneumoniae* infection. Multiple regression analysis found that *M. pneumoniae* infection was positively correlated with age, severity of disease and multiple siblings, and was negatively correlated with runny nose, nasal symptoms, past history of pneumonia. *M. pneumoniae* carrying time varied according to the different areas of *M. pneumoniae* infection: pneumonia was the longest, bronchitis the second, and URI the shortest. A total of 94 *M. pneumoniae* strains were isolated from *M. pneumoniae*-DNA positive patients, with the isolation rate at 57.7%. MLVA typing distinguished the strains into 8 types. Except for 2 strains, all the other 92 strains (97.9%) were macrolide-resistant strains. The 2 macrolide-sensitive strains had a special MLVA type.

Conclusion

M. pneumoniae infection tended to occur in children over the age of 5 years, summer and autumn were epidemic seasons, and pneumonia was the most common form of *M. pneumoniae* infection. Age, severity of disease and multiple siblings were risk factors of *M. pneumoniae* infection. Macrolide-resistant strains are prevalent at present. MLVA genotyping may be a molecular epidemiologic method of predicting macrolide-resistant strains of *M. pneumoniae* infection.

#M22- Epidemiological Characteristics and Risk Factors of Complications of Severe Measles Pneumonia in Children.

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Background

Although the incidence of measles has dropped significantly, in 2014, a measles epidemic broke out in Hanoi and in some northern provinces with high mortality rates due to complications of severe pneumonia.

Objectives

To describe epidemiological characterizations and determine certain risk factors of severe measles pneumonia.

Patients and Method

Patients admitted to the Pediatric Department of Bach Mai Hospital for measles complications with pneumonia. Measles diagnosis based on epidemiological, clinical and IgM antibody test (+) with measles virus following Guidelines of the Ministry of Health in 2014. Diagnosis and classification of pneumonia based on WHO Guidelines in 2013.

Results and Discussion

From February to August 2014, there were 309 measles patients hospitalized with pneumonia complications. Of these, there were 205 males and 104 females with a male/female ratio of 1:1.97.

There were 111 cases of severe pneumonia, accounting for 35.9%. Of the latter, there were 56 (50.5%) cases with oxygen therapy, 55 (49.5%) cases with mechanical ventilation and 20 deaths. Mortality among pneumonia was 6.5%. There were 99 (32%) measles infants under 9 months and 268 (86.7%) had not been immunized with the measles vaccine. The risk factors related to severe measles pneumonia complications were: children under 9 months of age (OR = 2.66; 95% CI: 1.57 to 4.49; P = 0.000), children not immunized with measles vaccine (OR = 4.12; 95% CI: 1.47 to 12.44; P = 0.004), children with humeral IgA, IgG, IgM immunodeficiency. There was no correlation between bacterial or viral coinfection on severity of pneumonia. This means that the review of a number of previous studies on the direct role of the measles virus impact on the severity of pneumonia.

Conclusion

Measles complications of pneumonia in hospitalized children occurred more often in infants less than 9 months of age and children without measles vaccination. The risk factors which increased the severity of the disease were: children under 9 months of age, without measles vaccination and reduced immune factors IgA, IgG and IgM.

Key words: Measles; Pneumonia; children

#M61 – Factors that Negatively Affect the Prognosis of Pediatric Community-Acquired Pneumonia and Its Etiological Analysis in a Developing Country.

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Introduction and Aim of the Study

Community-acquired pneumonia (CAP) is still the most important cause of death in countries with scarce human and financial resources. The main purpose of our study was to identify the factors that negatively affect the clinical evolution of children hospitalized with CAP in a developing country and to explore infection etiology.

Methods

All patients (pts) discharged from the hospital Itigi-Tanzania with a diagnosis of CAP from August 2014 to April 2015 were enrolled. Clinical data until discharge were gathered and analyzed. Dried blood spots (DBS) for quantitative Real-time PCR for bacterial detection were collected. Moreover, clinical evolution of the disease was correlated with bacterial findings.

Results

100 children (M47%) of average age 33 months were included. 29% were classified as malnourished, with a weight for age Z score ≤ 2 . The average length of hospitalization was 10 days. 24% of pts were identified with severe CAP and 11% died. Surprisingly, 54% of pts had been hospitalized with a suspected diagnosis other than CAP. The wrong diagnosis at admission increased complications (15% vs. 2%

$p < 0.05$), treatment with ≥ 2 antibiotics (96% vs. 81% $p < 0.05$) and radiological investigations (34% vs. 15% $p < 0.05$), furthermore increasing the length of hospitalization by two days. The comorbidity (e.g. malaria, typhoid fever, anemia, meningitis), found in 32% of children, significantly increased severity, number of complications, deaths, need for chest x-rays and oxygen therapy ($p < 0.05$). Need for oxygen was significantly increased in pts with negative prognosis ($p < 0.01$). Children with malnutrition required more antibiotics ($p < 0.05$). In 52 (62%) of patients, *Streptococcus pneumoniae* (S.p.) was isolated; *Haemophilus influenzae* (Hi) was detected in 23 patients (27%), mainly type b (Hib) (74%), and *Staphylococcus aureus* (S.a.) in 17 of our cases (20%). 5 children had *Pseudomonas aeruginosa* (P.a.) (6%) and *Salmonella typhi* (S.t.) was detected in 3 patients (3%). 75% of patients had mono-infection, the remaining 25% showed bacterial co-infection, most frequently between S.p. and Hi (57%). Neither of these bacteria, in mono or co-infection, was isolated recurrently in children malnourished, younger or with comorbidities, nor was there a correlation found with severity, complications, deaths, oxygen demand or duration of hospitalization.

Conclusions

Our study highlights the difficulty of diagnosis and comorbidities as the main factors that negatively affect the clinical evolution of children hospitalized with CAP in a country with limited resources. S.p. and Hib still have a large role in childhood pneumonia in developing countries, therefore implementation of current vaccine strategies is needed to reduce preventable childhood morbidity and mortality. DBS is a simple and efficient diagnostic method for bacterial identification in countries with scarce medical resources.

#M72 – Evaluation of Children with Hydatid Cyst in the Middle Region of Turkey.

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Objective

Hydatid cyst is a chronic zoonotic infectious disease with poor prognosis and serious medical, social and economic consequences. Although it is widespread throughout the world, Turkey is one of the endemic areas. Early diagnosis is difficult due to being asymptomatic in early stages. Optimal therapeutic option is not clearly defined in the pediatric population. In this study, we aim to review demographic, clinical and laboratory findings, treatments and outcome of children with hydatid cyst disease in two pediatric pulmonology centers in the middle region of Turkey.

Method

Clinical records of patients with hydatid cyst disease, who were under 18 years of age, were reviewed between 2007–2015. Patient ages, involved organs, laboratory findings, treatments, follow-up and outcome were noted.

Results

During the 8-year period, 49 patients were followed in two pediatric pulmonology centers. Mean age was 9.3 ± 3.6 years, 17 (35 %) of whom were female and 32 (65 %) of whom were male. Fifteen (31 %) patients were living in rural areas and 34 (69 %) were living in urban areas. Fourteen (28 %) had a history of contact with a dog and 6 (12 %) had family history. Thirty-six (73 %) had lung, 25 (42 %) liver, 12 (24 %) both lung and liver, one lung, liver and brain, one lung, liver and gall bladder, one lung and adrenal gland, two (4 %) isolated spinal, and one isolated spleen involvement. Hydatid Cyst indirect hemagglutination positivity was detected in 24 patients, *Echinococcus granulosus*-specific IgG positivity in 9 patients and specific IgE positivity in 8 patients. Surgery was performed in 34 patients, PAIR in 13 patients. All patients were treated with albendazole of which 7 had additional praziquantel treatment. Mean albendazole treatment duration was 15.5 ± 13.2 months. Mean follow-up duration was 26.4 ± 24 months and relapse occurred in 7 patients in this duration.

Discussion

Hydatid cyst is an important public health problem in endemic areas. Although medical and family history, clinical and laboratory findings were negative in most patients, it must be kept in mind in suspected children in these regions. Although it usually presents in lung and liver in children, there could be atypical organ involvement without lung and liver involvement.

#M90 – Clinical Profile of Patients with Kartagener's Syndrome.

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Introduction

The need for early recognition of ciliary dyskinesia is being increasingly recognized worldwide[1]. While confirmatory diagnosis for ciliary dyskinesia is not easily available in developing countries, very often a clinical diagnosis can be made especially when it is part of Kartagener's syndrome[2,5]. However there is usually an unacceptable delay in instituting airway clearance therapy which could potentially prevent or delay the development of bronchiectasis [3,4,6]. This study was performed to look at the clinical profile of patients with Kartagener's syndrome with special attention to the delay in diagnosis.

Methods

Retrospective chart review of patients with a clinical diagnosis of Kartagener's syndrome attending the pediatric respiratory clinic in a tertiary care hospital over 7 years from 2009 to 2016.

Results

There were 7 patients, 4 males and 3 females, who had a clinical diagnosis of Kartagener's syndrome. Age ranged from 2 years to

19 years. Clinical criteria of situs inversus, bronchiectasis and sinusitis were fulfilled by all patients.

One patient had a complex cyanotic heart disease along with dextrocardia. While all had clinical bronchiectasis, 3 had nasal polyposis and 2 had chronic adeno-tonsillitis.

Onset of Symptoms

Documentation of onset of respiratory symptoms within 1 year of age in the medical records was noted in 86 % of these patients. Neonatal respiratory distress was reported in 2 children. Chronic wet cough and persistent nasal discharge was documented in 6 children.

Age of Diagnosis

Only 2 children were diagnosed within 1 year of age (at neonatal period and 3 months respectively). More than 70% had diagnosis delayed beyond infancy in spite of early onset of symptoms.

Conclusion

Kartagener's syndrome with typical features is not uncommon in pediatric practice in a tertiary care center. In spite of early onset of symptoms, diagnosis and initiation of treatment is delayed in the majority, leading to development of bronchiectasis and significant pulmonary morbidity[6].

#M96 – The Impact of Surgery on Growth, Pulmonary Functions and Acute Exacerbations in Children with Non-Cystic Fibrosis Bronchiectasis.

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Aim

Treatment decisions for the management of bronchiectasis include pharmacological agents and nonpharmacological approaches such as chest physiotherapy, and surgical procedures. There is no data regarding the outcome of surgery in children with non-CF bronchiectasis and the indications of surgery in these patients are unclear. In this study, we aimed to review the effect of lung resection on pulmonary exacerbations, lung function tests and nutritional conditions in patients with non-CF bronchiectasis; and to compare the results with patients managed with medical treatments.

Methods

The medical records of patients with non-CF bronchiectasis between December 1998 and October 2011 were retrospectively analyzed. Patients who underwent lobectomy and were followed for at least four years before surgery and four years after surgery were categorized as the "surgery group". Age- and gender-matched non-CF bronchiectasis patients who were medically treated without surgery in the same period for at least four years were selected as the "medical group". The medical data including age, body weight, body height, Body Mass

Index (BMI), z scores, number of pulmonary exacerbations and lung function tests were recorded for four years before surgery and four years after surgery in the surgery group; and four years from the initial evaluation in the medical group.

Results

There were 29 patients in the surgery group and 33 age- and gender-matched patients in the medical group. There was no statistical significance with regard to age, gender, lobar distribution of bronchiectasis, BMI, microbiological analysis and lung function tests of the patients between the surgery and medical groups at first admission. There was a statistically significant difference between the z scores for height within the surgery group after the surgery and medical group ($p = 0.003$); z scores for height improved in both groups. There was no statistical significance when comparing z scores for weight ($p = 0.45$) and BMI ($p = 0.52$) within the surgery group after the surgery and in the medical group during their follow up. Lung function tests including FEV1% ($p = 0.65$), FVC% ($p = 0.45$) and FEF25-75% ($p = 0.58$) also did not change significantly within years both in the surgery group after the surgery and in the medical group. There was also no statistical significance for total number of pulmonary exacerbations ($p = 0.29$), oral ($p = 0.52$) and intravenous ($p = 0.66$) antibiotic requirements of patients within the surgery group after the surgery and in the medical group.

Conclusion

Although there have not been any prospective randomized trials comparing the short- and long-term efficacy of surgical and medical treatment, our results show that surgical management of non-CF bronchiectasis has no significant effect on BMI, z scores, number of pulmonary exacerbations and lung function tests of patients. Surgical management has led to significant improvement on height of patients with non-CF bronchiectasis that was not previously explained in the literature.

#M113 – The Xpert MTB-RIF to Diagnose Tuberculosis in Adolescents from Rio de Janeiro, Brazil.

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Objectives

To describe the use of the Xpert MTB/RIF assay for the diagnosis of TB in adolescents aged 10 to 18 years from Rio de Janeiro between January 01, 2015 and December 31, 2015 in sputum and induced sputum samples.

Methods

This descriptive, cross-sectional study collected data from the Laboratory Environmental Management (GAL) database.

Results

A total of 772 tests were analyzed. Sputums were the most prevalent specimens with 746/772 samples (96.6%): 617/746 (82.7%) were not

detectable and 129/746 (17.3%) were positive. The mean age was 16 years, and males prevailed at 52% (67/129). A culture test was conducted in 105/772 samples (13.6%) and drug sensitivity test (ST) in 64/105 samples (60.9%). Most samples (125/129, 96.9%) were sensitive to Rifampicin (RIF); the resistance of 1/129 (0.8%) was inconclusive; and 3/129 (2.3%) were resistant to RIF. Of these, one resistant to isoniazid was confirmed by culture and ST. ST did not confirm resistance to RIF in the second sample. The third sample was culture negative. The mean time between sample collection and arrival at the laboratory for conducting the Xpert MTB/RIF assay was about four days, and the laboratory took a mean of eight days to provide the result.

Conclusion

Most sputum smear microscopy tests were justified as adolescents can produce sputum effectively, allowing sample collection for analysis. Bacilli were not detected in most cases (82.7%), unlike other countries, which have higher rates of positive results. The percentage of RIF-sensitive samples was 96.9%, demonstrating the high sensitivity of *M. tuberculosis* in our medium.

Reflections and Concrete Proposals

Xpert MTB/RIF assay proved to be effective for the diagnosis of TB in adolescents. However, it is important to conduct a culture test in addition to the Xpert MTB/RIF assay to confirm RIF resistance and to test sensitivity to other drugs, which would indicate whether drug replacement is actually necessary.

#M114 – Clinical Profile of Children and Adolescents with and without Comorbidities Hospitalized with Community Acquired Pneumonia.

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Objectives

To describe the clinical profile of children and adolescents hospitalized with community-acquired pneumonia (CAP), divided into two groups: with and without comorbidities.

Methods

Observational, longitudinal, descriptive study, with prospective data collection, in a cohort of patients aged 0–11 years, hospitalized with clinical and radiological diagnosis of CAP, from January 2010 to January 2012. Descriptive analysis was performed; the two groups were compared by logistic regression for possible risk factors for CAP using relative risk (RR) with 95% confidence interval (CI). The process of selection of independent variables was stepwise forward, level of 5%.

Results

Of the 121 cases evaluated, 47.9% had comorbidities. Of these patients with comorbidities, 6/58 (10%) had pneumonia complicated by chest radiography. In bivariate analysis, patients with comorbidities demonstrated higher chance for age > 60 months ($p = 0.005$), malnutrition

($p = 0.002$), previous use of antibiotics ($p = 0.008$) and previous hospitalization for CAP ($p = 0.004$). In multivariate analysis, these variables were independent predictors of CAP in patients with comorbidities: age > 60 months ($p = 0.002$, RR = 5.39, 95% CI: 1.89 to 15.4); malnutrition ($p = 0.008$; RR = 1.75, 95% CI: 1.75 to 44.6), previous use of antibiotics ($p = 0.013$, RR = 3.03, 95% CI 1.27 to 7.2), previous hospitalization for CAP ($p = 0.03$, RR = 2.91, 95% CI 1.08 to 7.9).

Conclusions

Most patients with CAP and comorbidities were aged > 60 months, were malnourished, had previous use of antimicrobials and had previous hospitalization for CAP; the comorbidities had a higher relationship with the probability of malnutrition and hospitalization for CAP in older age than in children without comorbidities.

Reflections and Concrete Proposals

Knowledge of this clinical profile may contribute to better assist CAP in hospitalized pediatric patients in referral centers.

#M150 – Azithromycin Administered at the time of Severe Bronchiolitis Has a Protective Effect on Subsequent Wheezing in Infants.

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Purpose

A significant proportion of infants develop recurrent wheezing after an acute viral bronchiolitis (AB) event. Despite extensive research, clinical trials could not show any intervention with a relevant clinical impact on AB. However, at least one recent study has demonstrated a prolonged protection for recurrent wheeze and lower respiratory morbidity in infants treated with azithromycin during an acute respiratory syncytial virus (RSV) bronchiolitis. The aim of the present study was to test the hypothesis that administration of Azithromycin during an AB event reduces subsequent wheezing and hospital re-admissions.

Methods

This is a secondary analysis of a randomized, double-blinded, placebo-controlled trial, including unpublished data on wheezing and hospitalizations during the initial 6 months following admission for acute viral bronchiolitis. The study was performed in a tertiary University hospital in Southern Brazil. Participants were infants (< 12 months of age) hospitalized with AB. Patients were randomized to receive either Azithromycin or placebo, administered orally, for 7 days. Assessment of clinical data included length of hospital stay and identification of respiratory viruses, described in a previous publication. In addition, secondary data from the initial study were registered in a follow-up during 6 months after the AB episode in order to identify recurrent wheezing and hospital readmissions. Families were contacted by telephone at 3 and 6 months after the initial acute event and responded to a standardized questionnaire.

Results

Eighty-three patients were included (Azithromycin group, $n = 46$; placebo group, $n = 37$). Kaplan-Meier analysis showed wheezing was significantly reduced in the Azithromycin group ($P = 0.022$). Acute events which were positive for RSV ($n = 38$) or not by RSV ($n = 30$) had a significant reduction for subsequent wheezing in both subgroups. Hospital re-admission during the period of follow-up was not significantly different between the two groups.

Conclusion

Azithromycin significantly reduces the risk of subsequent wheezing between 0 and 6 months after hospital admission due to acute viral bronchiolitis irrespective of the presence of respiratory syncytial virus. Considering the important clinical impact of our findings and the risk of increased use of macrolides in this group of patients, further studies should try to better define which infants could be better responders to macrolides and whether severity is also a factor associated with efficacy of treatment.

#M165 – Clinical Profile of Children with Tuberculosis with or without HIV Infection in a Pediatric Pneumology Outpatient Clinic in Rio de Janeiro, Brazil.

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Objective

To describe the clinical profile of patients with tuberculosis (TB) associated or not with HIV infection treated at a pediatric pneumology service.

Methodology

This descriptive, retrospective and cross-sectional study was conducted from 2004 to 2016. The following variables were analyzed: age, anti-HIV test, tuberculin skin test result (TST), chest radiograph, acid-fast bacilli smear (AFB smear), AFB culture, and presentation form: pulmonary (PTB) or extrapulmonary TB (EPTB).

Results

A total of 128 children and adolescents were studied, of which 96/128 (75%) were aged less than 10 years. In the 106 HIV-negative patients, PPD was positive in 65/106 (68.8%) and negative in 26/106 (24.5%); chest radiograph suggested TB in 73/106 (68.8%); AFB respiratory samples were positive in 13/81 (16%) and negative in 68/81 (84%); and culture was positive in 16/65 (24.6%) and negative in 49/65 (75.4%). With respect to disease presentation, 51/106 (48%) patients had exclusive PTB, 36/106 (34%) patients had EPTB, and 19/106 (18%) had PTB and EPTB.

In the 22 HIV-positive patients, TST was positive in 2/22 (11.8%) and negative in 15/22 (88.2%); chest radiograph suggested TB in 15/22 (68.1%); AFB respiratory samples was positive in 3/18 (16.6%) and negative in 16/18 (88.8%); and culture was positive in 1/18 (5.55%). In

the same group of patients, 11/22 (50%) had exclusive PTB, 8/22 (36%) had EPTB, and 3/22 (14%) had PTB and EPTB.

Conclusion

PTB was the most frequent TB manifestation in these patients. AFB respiratory samples and culture were negative in most patients, reinforcing the paucibacillary nature of the disease in children. These results were similar in both groups (HIV-positive and HIV-negative patients). However, positive TST results were 2.5 times higher ($F < 0.001$) in HIV-negative individuals probably because of their better immune response. The rate of TB/HIV coinfection was high because the study site is a reference center for both diseases.

Reflections

In patients treated at our reference center, the clinical profile of TB was similar in HIV-positive and in HIV-negative patients. TST was not very useful for the diagnosis of children with TB-HIV.

#M168 – Antipneumococcal Vaccine Status of Children Hospitalized for Community Acquired Pneumonia (CAP) at a Brazilian Pediatric Hospital.

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Objectives

To describe the pneumococcal 10-valent vaccine status of hospitalized patients due to community acquired pneumonia (CAP) at a University pediatric hospital in Rio de Janeiro, Brazil.

Methods

Cross-sectional retrospective study of patients from 0 to 13 years old hospitalized for CAP between January 2015 and September 2016. Data from the medical register and the vaccination card were analyzed. Those who received the appropriate number of pneumococcal 10-valent vaccine doses for age were considered vaccinated, and those with incomplete or absent vaccination were deemed not vaccinated. Patients without vaccine information were excluded. Descriptive statistics (frequency, percentages, mean, median and standard deviation) and calculation of p value by Fischer's test (p significant < 0.05) were performed.

Results

Of the 63 patients studied, 44 were vaccinated, 12 were not immunized and 7 had no information. Among those vaccinated, there were 26/44 (50.1%) female and 20/44 (45.5%) were between 1 and 4 years old. The most associated comorbidities were: neuropathies and asthma (7/44 each). The most frequent radiological changes were interstitial infiltrate (17 / 40–42.5%) and alveolar infiltrate (13 / 40–32.5%) ($p = 0.6$). Eight children had pleural effusion (8 / 40–20%). Penicillin G (PG) was the most frequently initial antibiotic prescribed (17 / 44–38.6%) ($p = 0.2$). Hospitalization time ranging between 7 and 14 days occurred in 31/44 (70.5%) patients ($p = 0.007$); median: 9 days.

Among the 12 patients not vaccinated, there were 6/12 (50%) of both sexes. The predominant age group was ≥ 5 years old (4/12–33.3%). There was no predominance of any comorbidity. The interstitial infiltrates were the most common changes in radiography (6/12, 50%), followed by alveolar changes (4/12, 33.3%). The most frequently initial antibiotic prescribed was PG (7/12, 58.3%). Hospitalization time ≤ 7 days occurred in 6/12 (50%); median: 8 days.

We found a greater number of hospitalizations among those < 6 months of age who were not vaccinated ($p = 0.06$) and that the hospitalization time was higher among those vaccinated ($p = 0.007$).

Conclusion

The antibiotic of choice in the treatment of CAP in both groups was PG. However, the predominant interstitial radiological pattern found in both groups was more suggestive of viral CAP. There was a lower frequency of hospitalizations among < 6 months vaccinated children.

Nevertheless, vaccinated children apparently had more severe CAPs, with longer hospitalizations than non-vaccinated ones.

Reflections and Concrete Proposals

It can be assumed that the presumed severity of PACs in children under 6 months may be due to the selection of strains not contained in the pneumococcal 10-valent vaccine.

N. MISCELLANEOUS

#N36 – Global Tracheostomy Collaborative Survey on Pediatric Tracheostomy Care.

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Introduction

There are an increasing number of children with complex health needs requiring tracheostomy. They experience lengthy and costly hospitalizations and there is variation in management practices for children following insertion of their tracheostomy. The International Pediatric Otolaryngology Group has recently published recommendations for perioperative pediatric tracheostomy care, but these do not address discharge planning or long-term tracheostomy care.

Aim

To investigate current pediatric tracheostomy management practices from the perioperative period to discharge planning and long-term care.

Methods

A survey was designed following a Global Tracheostomy Collaborative pediatric interest group meeting and distributed to all pediatric member hospitals using Typeform. Questions covered the clinical management surrounding the entire process from insertion of tracheostomy to discharge planning and long term care.

Results

There were 13 responses. Those responding performed a mean of 15 new pediatric tracheostomies per year and 69% of centers had a specialized pediatric tracheostomy service. All respondents agreed an emergency tracheostomy box needs to be with the child at all times and that this should contain: a spare tracheostomy tube of the same size and one a size smaller (100%), a suction catheter (100%), a water based lubricant (92%) and scissors (92%). Equipment felt essential at bedside included all above plus: resuscitation bag and mask (92%), spare ties (92%) and O₂ saturation monitoring (83%). Most (92%) used a process to regularly document this equipment.

42% of respondents performed routine inpatient tube changes weekly and other responses depended on clinical and parental training needs. Recommended frequency of outpatient tube changes varied from every two to four weeks.

There was no consensus over which ties or tapes to use. A quarter had a feeding policy after tracheostomy insertion. Indications for considering cuffed tracheostomy tubes included mechanical ventilation (75%), high leak without a cuffed tube (67%) and aspiration (42%); only 25% considered age. Common indications for suctioning were: inability to cough out secretions (100%), respiratory distress (100%), suspected blocked tube (100%), secretions in the tube (92%), request by the child for suction (75%), changes in ventilation pressures (58%), hypoxia (58%).

Most respondents (92%) had discharge criteria for children with newly inserted tracheostomies, 67% had a protocol for decannulation and 46% for transition from pediatric to adult care.

Conclusions

There is some consensus on tracheostomy management surrounding emergency equipment and indications for suctioning, frequency of tracheostomy tube changes and need for post-tracheostomy discharge criteria. Areas of debate surround types of tracheostomy ties and feeding after tracheostomy insertion. Areas for further development include decannulation protocols and transition from pediatric to adult care.

#N41 – Case Report: Late Presentation of Bochdalek-Type Congenital Diaphragmatic Hernia in an Adolescent.

Stachewski Verrone K¹, Nassar S², Bizon A³.

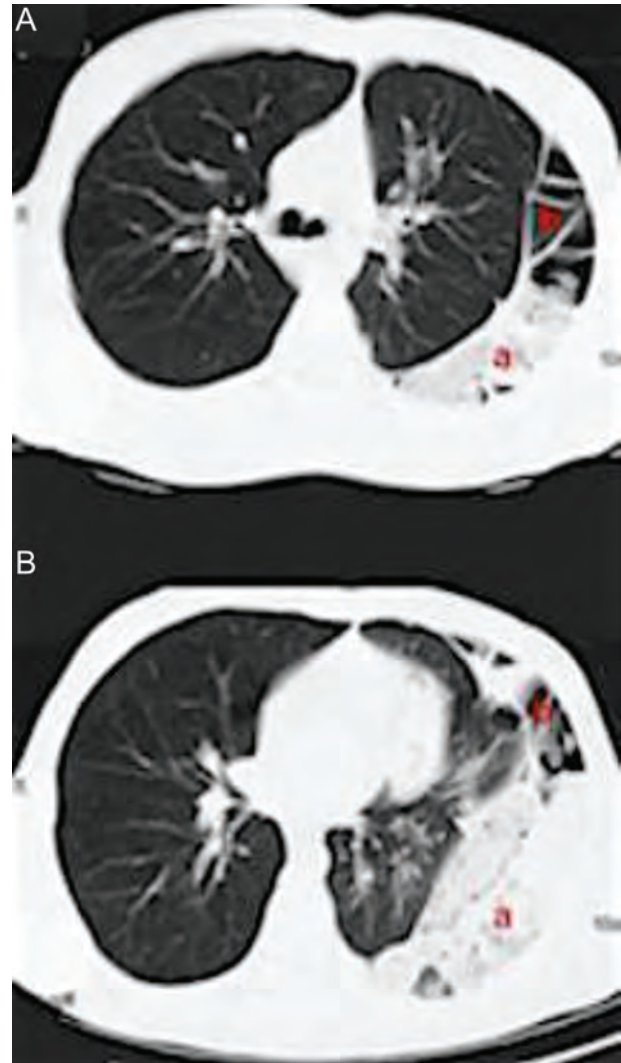
¹Pediatric Pulmonology, GPACI Hospital – Sorocaba, Brazil; ²Radiology, Centro Médico Diagnostic Centre – Sorocaba, Brazil; ³Thoracic Surgery, GPACI Hospital – Sorocaba, Brazil

Introduction

Late Presenting Congenital Diaphragmatic Hernia (CDH) beyond the neonatal period is rare and often misdiagnosed with delayed treatment. We report a case of Bochdalek Hernia (BH) with ipsilateral pulmonary hypoplasia in a 13-year-old boy without any respiratory symptoms.

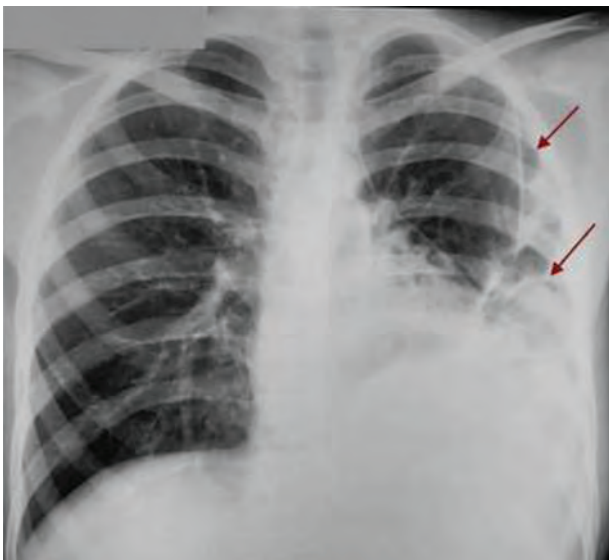
Case Presentation

A 13-year-old Caucasian boy was admitted to the hospital in January this year with severe vomiting and dehydration. These symptoms had gotten worse 1 month previously. During this period, he went to ER sometimes, but was dismissed with antiemetics. The boy started to present recurrent vomiting after meals 2 years ago. He had no respiratory symptoms or past trauma history whatsoever. Physical examination: he was very thin (height 1,63m, weight 33 kg). He had decreased sounds on the left hemithorax and scaphoid abdomen with rare sounds. Chest X-Ray: opacity at the lower left chest with bowel gas image (Image A). CT scan demonstrated loops of the colon and small intestine in the left thoracic cavity (Image B). MRI confirmed failure of diaphragm function besides intra-abdominal organs, mediastinal shift and pulmonary hypoplasia (Image C and D). A laparotomy followed by a thoracotomy revealed a typical Bochdalek hernia with the stomach, small intestine, transverse and ascending colon, spleen, cecum and appendix inside the left thoracic cavity. The contents were reduced manually into the abdominal cavity. At this moment the pulmonary hypoplasia could be seen. The suture of the diaphragm was done without prosthesis. Nowadays, the patient is well with good weight gain.



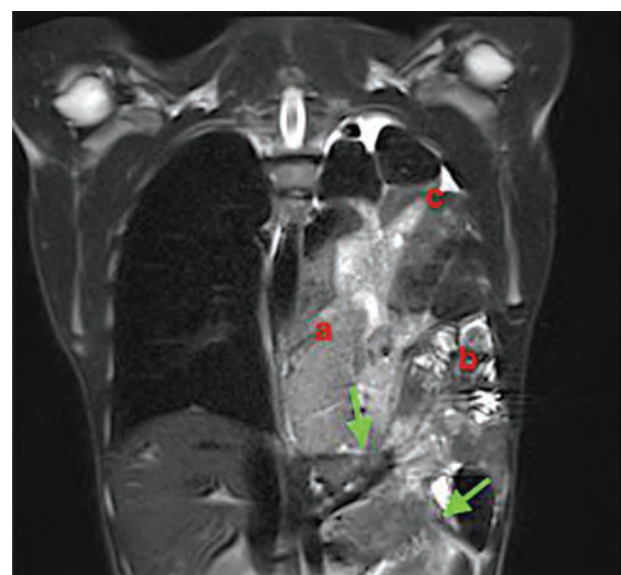
B

Image B shows small intestine (a) and colon (b)

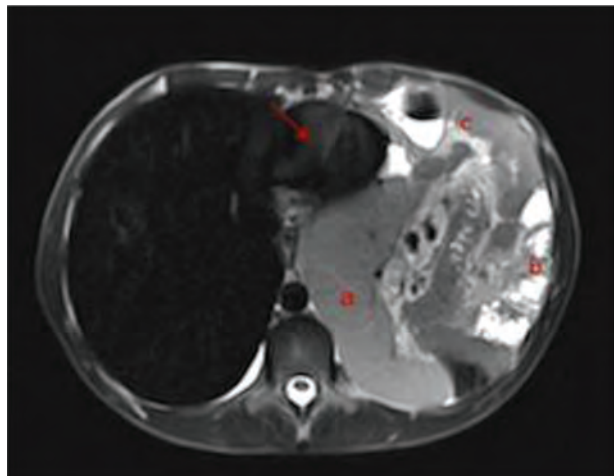


A

Image A shows bowel gas (arrows)



C



D

Images C and D show failure of diaphragm (green arrows), pulmonary hypoplasia (red arrow), spleen (a), small intestine (b) and colon (c)

Discussion

Bochdalek hernia (BH) is usually congenital, arising due to failed closure of pleuroperitoneal ducts and represents 2.5%-25% of all late presenting diaphragmatic hernias. It is generally present in neonates and is even diagnosed antenatally. By contrast, late presenting BH is associated with a much wider spectrum of clinical presentation which may be respiratory and/or gastrointestinal symptoms or, in some cases, asymptomatic. Pulmonary hypoplasia is one of the most common associated malformations. Diagnosis is often made by chest X-Ray, but is associated with a high risk of misdiagnosis because of the great variability in radiographic appearance. CT scan and MRI are specific in making the diagnosis. Once diagnosed, early surgical intervention is necessary for the prevention of any complication and can lead to a good prognosis.

Conclusion

Congenital diaphragmatic hernia present in late childhood is rare and shows nonspecific symptoms. Hence, a child with recurrent gastrointestinal or respiratory complaints should be assessed thoroughly and the suspicion of this presentation is needed to successfully diagnose and manage this condition properly.

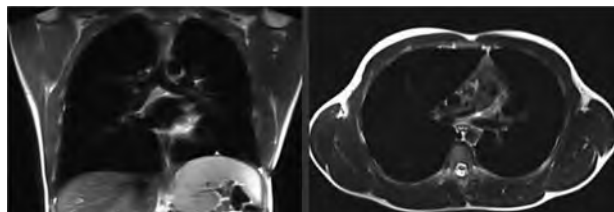


Image E: 6 months after the surgery

#N47 – Eosinophilic Granulomatosis with Polyangitis in Childhood: A Case Report.

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Eosinophilic granulomatosis with polyangitis (EGPA) – previously called Churg–Strauss syndrome – is a multisystem disorder characterized by allergic rhinitis, asthma and prominent peripheral blood eosinophilia. EGPA is classified as a vasculitis of the small and medium sized arteries, although the vasculitis is often not apparent in the initial phases of the disease.

In EGPA, the most commonly involved organ is the lung, followed by the skin. However, cardiovascular, gastrointestinal, renal and central nervous systems can also be affected. Vasculitis of extrapulmonary organs is largely responsible for the morbidity and mortality associated with EGPA.

An 11-year-old boy was admitted with cough and dyspnea to our hospital; he had been treated with high dose ICS + LABA combination for a year, but his asthma remained uncontrolled. Based on the laboratory data (peripheral eosinophilia), associated with severe asthma and nasal polyposis, the first suspected diagnosis was allergic bronchopulmonary aspergillosis, but the *Aspergillus* serological test was negative. After some weeks, new symptoms were observed: gastrointestinal signs, skin lesions with characteristic histological finding and facial paresis. Thus the patient fulfilled the diagnostic criteria of the American College of Rheumatology, and EGPA was eventually diagnosed.

Neither cardiac nor renal involvements were found. The patient showed favorable clinical progression after oral prednisone therapy.

In case of therapy-resistant asthma, we should think of systemic diseases with pulmonary manifestation and search for their symptoms.

#N63 – Comparison of Sleep Characteristics, Patterns and Problems in Young Children within the Southeast Asian Region.

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Background and Objectives

Optimal sleeping habits are important for the health and development of the young. Cross-cultural differences in sleep habits and practices have been described between Caucasians and Asian children. Our study aimed to characterize the sleep practices and patterns within the Southeast Asian (SEA) region to evaluate if there are differences within a region with fairly similar socio-cultural populations.

Participants

Parents and caregivers of infants and toddlers (birth to 36 months old) from countries in Southeast Asia participated in this study.

Methods

Data was collected using the Brief Infant Sleep Questionnaire from 5,987 children from 6 countries in the SEA region (967 Indonesia/ID, 997 Malaysia/MY, 1034 Philippines/PH, 1001 Singapore/SG, 988 Thailand/TH and 1000 Vietnam/VN). Results: The sleep variables varied amongst SEA children studied. Bedtimes and nighttime sleep varied across the region by as much as 1 hour 34 mins and 1 hour 15

mins respectively. There were also significant differences in sleep settings and parental perceptions of sleep problems in their children.

Conclusions

Despite being geographically very close together and having some common socio-cultural characteristics, sleep variables in the young child within the South East Asian region do differ in significant ways. This observation is important in evaluation of children within this region especially where there is substantial cross-boundary medical tourism.

#N84 – Clinical Analysis of Six Cases of Lung Tumors in Children.

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Objective

To discuss the clinical manifestation, imaging characteristics and outcomes of lung tumors in children.

Methods

We retrospectively collected information regarding six cases of lung tumors in children in a hospital from Jan 2010 to March 2016. The information included clinical manifestation, imaging characteristics, pathological results, treatment and reviews.

Results

(1) All six patients firstly visited pediatric internal medicine departments. Symptoms included cough (n = 6), dyspnea (n = 4), fever (n = 1), chest tightness (n = 1), chest pain (n = 1) and lameness (n = 1). We did not find hemoptysis, wheezing or weight loss in these patients. Physical examinations revealed unilateral decreased breath sounds (n = 4), moist rales and wheezes (n = 1), and normal (n = 1). We did not identify finger clubbing, anemic appearance, lymph node enlargement or hepatosplenomegaly, etc. (2) Laboratory examination showed all the parameters of complete blood count, liver functions, blood glucose, blood fatty and uric acid overlapped with 95% confidence interval. Two cases of increased tumor markers. (3) Imaging results showed multiple cystic lesions in lungs (n = 2) (both with pleuropulmonary blastoma), multiple nodes (n = 2), endobronchial soft tissue mass (n = 1) pulmonary round-shaped mass (n = 1), and mediastinal mass (n = 1). Imaging results also found atelectasis (n = 3), pneumonia (n = 2), pneumothorax (n = 2), longitudinal diaphragmatic hernia (n = 2), pleural effusion (n = 1), subcutaneous emphysema (n = 1). (4) All patients underwent tumor puncture biopsy or tumor resection. Pathology revealed the final diagnosis of pleuropulmonary blastoma (n = 3), squamous cell carcinoma of the lung (n = 1), thyroid papillary carcinoma (n = 1), malignant germ cell tumor (n = 1). All of the latter were malignant tumors. Patients were followed up. Two patients died (both with pleuropulmonary blastoma). Two patients survived (followed up for 7 months and 1 month, respectively). Two cases were lost to follow-up.

Conclusion

Lung tumors are rare diseases in children. Patients usually firstly visit the pediatric internal medicine department. Clinical signs and symptoms may be nonspecific. Tumor marker examination and imaging examination are helpful for the diagnosis of lung tumors. Biopsy should be performed to confirm the final diagnosis. The long-term prognosis of these patients is still needed to be followed-up.

#N88 – Malignant Thoracic Tumors: A 5-year Experience of an Oncology Reference Center

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Aim of the Study

To perform a survey of all malignant thoracic neoplasms operated at our center in the last 5 years; to evaluate the types of tumors, the intra- and postoperative complications as well as surgical mortality.

Malignant neoplasms in the pediatric population are rare, affecting about 2% of children. Of these, 30% are solid tumors. The most common types of solid tumors are CNS tumors, Neuroblastomas, Rhabdomyosarcomas, Nephroblastomas and Osteosarcomas.

Thoracic malignancies are divided into primary or secondary malignancies. The primary malignancies have as primitive location the thoracic cavity, from the thoracic wall to the mediastinum. Secondary tumors are distant metastases from other solid tumors.

Methods

A retrospective review of medical data of patients submitted to surgical resection of malignant thoracic neoplasms.

Main Results

In the last 5 years, 19 patients with thoracic malignancies have been operated in our center. Of these, thirteen patients had primary tumors (Neuroblastoma, Ganglioneuroblastoma, PNET/Ewing's sarcoma) and the remaining six had secondary tumors (Nephroblastoma, Testicular Sarcoma, Osteosarcoma of the Femur). Of the primary tumors, the most prevalent was Neuroblastoma. Of the secondary tumors, the most common was metastatic Nephroblastoma.

There were no complications associated with the surgical procedures performed.

Conclusion

Although rare, thoracic neoplasms should be considered as an integral part of the list of differential diagnoses in pathologies commonly observed in the emergency department.

From the surgical point of view, it requires the approach of varied and noble anatomical regions and it is therefore of utmost importance to concentrate the procedure in a reference center so that there can be an optimization of results with impact on survival.

#N95 – Etiology of Chronic Cough in Children: A Study of 370 Cases.

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Introduction

Chronic cough (CC) is frequent in children at any age and a diagnostic and therapeutic challenge to pediatricians. Published data show that it occurs in 5–10% of children at any time, despite different definitions: previously more than 4 weeks and recently more than 8 weeks.

Pediatric causes are particular and adult algorithms are useless. Viral infections, frequent in acute cough, can lead to CC by eliciting hyperreactivity of cough receptors (CRHR). Mycoplasma and Bordetella are causal in about 30% of CC in teenagers. Upper airways cough syndrome (UACS), formerly post-nasal drip, is common in atopic children with asthma, cough variant asthma, sinusitis and allergic rhinitis. Non-recognized aspirations such as inadequate feeding practices (IFP) are very common and usually underdiagnosed – even more frequent than gastroesophageal reflux disease (GERD) and dysphagias.

Objective

To verify the etiology of CC in the prontuaries of 370 children followed by pediatric pneumologists, whose diagnosis was based on a successful therapeutic trial or specific tests.

Methods

Inclusion criteria: 1) CC lasting >4 weeks, 2) Atopic status: atopic stigma, high IgE level, familiar atopy, specific IgE (blood or skin test). 3) CC resolved. We determined the main and the secondary causes of CC in this group.

• Diagnostic procedures: UACS: clinical + cure after antibiotics. • Asthma: ISAAC + responsive to β 2-agonist, peak-flow, resolution after

inhaled corticoids. • Cough variant asthma TEA: Diretrizes Bras TC, 2006. • GERD: pH-metry (ESPGAN, ZMD positive or temporal association), another test associated with resolution with treatment. • Minor aspiration after IFP: clinical picture, partial or total resolution with IFP correction and healthy sleeping rules.

Results

• IFP was the main cause of CC in 26.5% of this sample, and it was the single cause in 14% of cases.

Conclusion

In our study, approximately 80% of CC lasted \geq 8 weeks and 55% were non-atopic – these findings should be kept in mind when managing CC.

Two existing etiologies were frequent (>40%) in both groups (A and NA). The first cause of CC was asthma/CV asthma. Atopy was related to: older age, UACS and asthma but not to CRHR or wheezy baby syndrome.

IFP was the most important secondary cause (50%) and the other was CRHR.

Minor aspiration by IPF was the main etiology in 26.5% of cases and was underdiagnosed. It seems that GERD may be misdiagnosed with IFP – so we should be alert to feeding practices.

#N167 – Viral Bronchiolitis and Risk Factors for Severe Outcome.

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ATOPY	ATOPICS = 167(45%)	NON-ATOPICS = 203(55%)	TOTAL = 370
SEX ♂	94 (56%)	107 (59%)	
AGE (months, median)	44mo (4–146)	28mo (2–179)	
DURATION(wk, median)	16wk (\geq 8wk = 76%)	14wk (\geq 8 wk = 79%)	
# ETIOLOGIES: one	80 (47.9%)	96 (47.3%)	
two	71 (42.5%)	87 (42.9%)	
three	16 (9.6%)	20 (9.8%)	
ASTHMA	24.5%	5.4%	14%
CV ASTHMA	28%	22%	25%
IFP	27%	26%	26.5% *
GERD	25.7%	27.6%	27.6%
CRHR	12.6%	25.6%	19.7%
UACS	25.7%	11%	19%
POSTINFEC	17%	16%	16.5%
DYSFAGIA	2%	5%	3%
WHEEZY BABY SYND	2%	3.5%	2.7%
OTHERS	-	-	4%

Introduction

Viral bronchiolitis (VB) is a highly prevalent disease in children that carries great morbidity worldwide. We aimed to test the association between well-recognized risk factors for severe VB and hospitalization outcomes.

Methods

Retrospective study of hospitalizations for 1st episodes of community-acquired cases of VB in children aged ≤ 2 years, admitted between July 2010 and June 2016, in a tertiary center. Data on clinical variables: hypoxemia (peripheral O₂ saturation $< 92\%$) at admission, and risk factors for severe VB – age younger than 12 weeks, prematurity (gestational age < 37 weeks), pre-existent chronic disease (congenital heart defect, chronic lung disease of prematurity, neuromuscular disease and Down syndrome), early breastfeeding cessation (< 4 months) and tobacco smoke exposure – were collected. Total length of stay, days of oxygen supplementation, ICU admission and mechanical ventilation (MV) were the outcomes considered.

Results

602 children (55.8% male) were included with a median age of 3 (1–7) months. In 507 children, respiratory virus testing was performed: 66.5% respiratory syncytial virus, 11.0% rhinovirus, 9.3% adenovirus were identified. At least one risk factor was present in 91% of children, with age ≤ 12 weeks (59.1%), tobacco smoke exposure (55.3%) and early breastfeeding cessation (52.8%) being the most prevalent. The median (P₂₅-P₇₅) length of stay was 5 (3–7) days, increased in presence of chronic disease [(17 (9–45), $p < 0.001$)]. In a multivariable model, adjusted for sex and age, the presence of chronic disease, younger age and hypoxemia at admission significantly increased the length of stay by 6.8 (95% confidence interval (95% IC) 4.9–8.7), 1.6 (95% IC 0.6–2.7) and 1.8 (95% IC 0.7–2.8), respectively. The median days of oxygen supplementation was significantly higher in children with chronic disease (7 (1–10) vs. 6 (4–9), $p = 0.016$) and aged ≤ 12 -weeks (7 (4–10) vs. 5 (4–7), $p = 0.003$). In a multivariable model, adjusted for sex, age and hypoxemia, only the presence of chronic disease significantly increased the need for O₂ supplementation by 2.7 (95% IC 1.3–4.0). In the multivariable logistic regression models, adjusted for sex and age, ICU admission was significantly predicted by age ≤ 12 -weeks (odds ratio (OR) 5.2, 95% CI 2.7–10.1, $p < 0.001$), family atopy (OR 0.3, 95% CI 0.1–0.6, $p = 0.001$) and hypoxemia at admission (OR 6.2, 95% CI 3.3–11.6, $p < 0.001$) and the need for MV was significantly predicted by age ≤ 12 -weeks (OR 6.3, 95% CI 2.9–13.7; $p = 0.005$), family history of atopy (OR 0.3, 95% CI 0.1–0.7, $p < 0.001$) and hypoxemia at admission (OR 7.8, 95% CI 3.7–16.5, $p < 0.001$). Discussion: As expected, in this study, we identified the presence of chronic disease, younger age and hypoxemia at admission as being significantly associated with worse hospitalization outcomes. Despite not being considered a risk factor for severe VB, family atopy was shown to be associated with increased need for ICU and mechanical ventilation.

#N171 – A Rare Cause of Unilateral Hyperlucency on Chest X-ray (CXR) – Sawyer James Syndrome (SJS).

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Introduction

SJS is a rare disease that is frequently misdiagnosed as pneumothorax. We report a case of an adolescent who had SJS misdiagnosed as left pneumothorax for 10 years. We report this case to bring attention to SJS and the importance of careful consideration of differential diagnosis.

Method

Case report.

Case Report

We report a 15-year-old male patient who suffered from adenovirus pneumonia in 2001 and “spontaneous left pneumothorax” in 2005. He was otherwise well until Jan 2015 when he presented with persistent productive cough requiring antibiotics treatment. Physical examination found decreased left chest expansion, hyperresonant percussion, decreased breath sound, expiratory rhonchi and crepitation heard at lower zone. Other examination was unremarkable. CXR showed hyperinflated left chest with decreased vascular marking. HRCT showed small left lung with hyperinflation and decreased vasculature. Bronchiectasis was present. Bronchoscopy showed normal anatomy. BAL grew *Haemophilus influenzae*. Diagnosis was revised as pulmonary exacerbation on top of SJS with bronchiectasis. Bronchiectasis was concluded to be secondary to infection after investigation. Pulmonary function test showed fixed obstructive and restrictive physiology. ECHO showed no pulmonary hypertension. Radiologist’s comment on CXR in 2005 was SJS but not pneumothorax. Antibiotic was given for *Haemophilus influenzae* infection. Hypertonic saline nebulizer and chest physiotherapy were given for mucus clearance. Maintenance treatment for non-CF bronchiectasis was started. Our patient had a quick recovery and follow-up showed no clinical or lung function deterioration.

Discussion

SJS has a prevalence of 0.01%. It results from post-infectious BO which onsets in early childhood. Adenovirus is the most common causative organism. The salient features are hyperaeration due to air trapping and hypoperfusion due to vascular bed atrophy at the same region. SJS presentation varies from asymptomatic to that of bronchiectasis. Unilateral hyperlucency on CXR is universal. HRCT confirms the diagnosis. No active intervention is required but prompt treatment of infection prevents bronchiectasis. Prognosis is poor for those with saccular bronchiectasis. Unilateral hyperlucency on CXR is infrequently misdiagnosed as pneumothorax. Careful physical and radiological examination allows differentiation. Presence of pleural line on CXR, presence of breath sound and lack of respiratory distress despite significant pneumothorax speaks against the diagnosis. Bedside ultrasound showing sliding pleura rules out pneumothorax. Other differential diagnoses, including chest wall abnormality, lung

parenchymal abnormalities, pulmonary vasculature abnormalities, central airway abnormality and mediastinal abnormality require HRCT for confirmation.

Conclusion

SJS is a rare cause of unilateral hyperlucency on CXR. Careful examination with a systemic approach helps to tease out the correct diagnosis.

#N180 – Persistent Chest Pain in An Adolescent- Could Be a Bronchogenic Cyst?

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Introduction

Bronchogenic cysts (BC) are tracheobronchial tree developmental anomalies with an estimated incidence of 1 per 68 000 in the general population. Clinical presentation includes respiratory distress or recurrent infections secondary to airway compression. Differential diagnosis includes lung abscess, fungal disease, tuberculosis, hydatid cysts, vascular malformations and tumors.

Case Presentation

We describe the clinical case of a 15-year-old male with systemic lupus erythematosus (SLE) and a class IV diffuse lupus nephritis, medicated with mofetil mycophenolate, hydroxychloroquine and prednisolone. At 11 years of age, left superior lobe pneumatoceles were suspected as pneumonia sequelae. Three months before admission, he presented left pleuritic pain with a bilateral hilar infiltrate on chest x-ray and elevated C-reactive protein (CRP – 165 mg/L). One month later, he complained of fatigue and anorexia with 6.1% weight loss in one month, followed by nocturnal cough, night sweats and dyspnea for ordinary activities. There was no personal or family history of asthma or tuberculosis. Investigation showed leukocytosis (16040 leucocytes/ μ L and 13150 neutrophils), elevated CRP (97.4 mg/L) and erythrocyte sedimentation rate (40 mm/hr) and left upper lobe opacity on chest x-ray (image A). Electrocardiogram and echocardiogram were both normal. Thoracic CT scan depicted a parenchymal consolidation with air bronchogram, with multiple cystic cavitations at the anterior segment of the left upper lobe (image B), suggesting an infected BC. Flexible bronchoscopy showed reduction in the diameter of the left main bronchus in its terminal portion and hyperemic mucosa with abundant secretions. Microbiological studies were negative for bacterial, mycobacterial and fungal agents. He was medicated with amoxicillin and clavulanate for 14 days with gradual clinical improvement.

Conclusion

In infants and small children, bronchogenic cysts can present with respiratory distress but symptomatic older children may present with

recurrent infection and persistent/unexplained chest pain. Despite this, many infants and children are asymptomatic and the cystic lesion is found incidentally during routine chest radiograph. In the present case, the patient has a multisystemic disorder without a flare or recent adjustment of immunosuppressive therapy. It was documented as a parahilar cystic lesion in previous radiographs, and, after excluding an “atypical” respiratory infection, a pulmonary congenital malformation was considered. At clinical follow-up, the patient is asymptomatic. The definitive diagnosis of a BC depends on the histological study. The excision was considered and not accepted.



#N183 – Giant Pneumatocele as Late Evolution Mimics Pneumothorax.

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Introduction

Pulmonary Pneumatocele (PC) usually is asymptomatic and disappears spontaneously. Most often, it occurs as a sequela

from acute pneumonia, commonly caused by microbial agents and also by noninfectious etiologies. Incidence of post-infection pneumatocele formation ranges from 2% to 8% of all cases of pneumonia in children. It may be treated conservatively or surgically, depending upon the occurrence of complications, such as tension pneumatocele, pneumothorax or secondarily-infected pneumatocele.

Case Presentation

A six-year-old Brazilian boy previously healthy, followed-up as outpatient at a tertiary hospital for ten months, because of pneumatocele evolution after chest drainage. Thoracotomy with decortication was performed for complicated bacterial pneumonia with empyema. A follow-up chest Computerized Tomography (CT) disclosed a giant cystic lesion involving the entire anterior region of the right lung and mediastinum shift to the contralateral side. The patient was asymptomatic at hospital admission, with no distress. His physical examination revealed a peripheral O₂ saturation of 99% in room air, heart rate of 96 beats/min and respiratory rate of 26 breaths/min. His chest examination revealed decreased breath sounds on the right hemithorax and hyperresonance on chest percussion. He underwent water-seal thoracic drainage and the atelectatic lung was reexpanded. On day 21, he was discharged from the hospital with close follow-up.

Discussion

Pneumatocele develops as a consequence of localized bronchiolar and alveolar necrosis, which allows one-way-passage of air into the peripheral airways and alveoli. Late development of PC has been described after an acute inflammatory process. The diagnosis has often been made with simple posterior and/or lateral CX-Ray, but chest-CT scan might be helpful for differential diagnosis. Nonetheless, a giant pneumatocele could be misinterpreted as massive pneumothorax. Most often PC is symptomatic and usually regresses spontaneously with pneumonia process improvement, varying from weeks to more than one year; it requires surgical intervention for complications such as pneumothorax, secondarily-infected pneumatocele and tension PC, as in the present case.

Conclusions

The chest CT scan at first mimicked pneumothorax, however anamnesis and clinical features were essential for radiological conclusion. The treatment of PC is conservative in most circumstances, with close follow-up, because during the resolution period they may cause serious, sometimes fatal, complications requiring urgent intervention.

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#N192 – The Evaluation of the Acute Effect of a Single Use of Waterpipe Smoking on Lung Clearance Index.

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Background

Waterpipe smoking (WPS) has been spreading steadily from Eastern to Western countries especially among teenagers. A single session of WPS increases the levels of carboxyhemoglobin (COHb) in the blood, has a negative effect on cardiopulmonary parameters, and a controversial effect on lung function indices. Lung clearance index (LCI), an index of ventilation inhomogeneity, has not been evaluated in WPS subjects.

Purpose

To evaluate the acute effect of a single 30-minute session of WPS on LCI.

Methods

This prospective study evaluated the acute effects of a single session of WPS on LCI. Due to ethical concerns, the study was performed only in adults.

The primary outcome parameter was the change in LCI.

Carboxyhemoglobin (COHb) levels, pulmonary function tests and vital signs were evaluated in volunteer WPS group smokers before and after 30 min of WPS session.

Results

26 volunteers (21 men, 5 women), aged 25.6 ± 4.88 years, were recruited. Following one session of WPS, LCI values did not change ($6.52 \text{ lit} \pm 0.83$ vs. $6.30 \text{ lit} \pm 0.66$, $p = 0.22$). COHb levels rose significantly, from $2.66\% \pm 1.61\%$ (median 2.35) to $10.28\% \pm 4.42\%$ (median 9.80), $p < 0.001$. Heart rates increased from 86.5 ± 12.67 beats/min (median 83) to 92.92 ± 17.04 beats/min (median 91.5), $p < 0.05$. Respiratory rate increased from 14.85 ± 2.01 breaths/min to 19.39 ± 4.97 breaths/min, $p < 0.001$. There was a significant decrease in both FEV₁/FVC and FEF 25%-75%.

Conclusions

This first study evaluated the effect of WPS on LCI. In this small sample size, no significant changes in LCI values after one session of WPS were noted. Further larger studies evaluating the possible effect of WPS on LCI measurements with multiple clinical and physiological parameters should be performed to assess the clinical benefit of LCI measurement in WPS subjects.

#N193 – Necrotizing Pneumonia in Children: Open Issues.

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Necrotizing pneumonia (NP) is increasingly being identified as a complication of community-acquired pneumonia in children, for the last 20 years.

Aims

The purpose of this study was to analyze clinical presentation and management of NP from a single-center experience.

Methods

A retrospective chart review of cases of NP hospitalized in a Tertiary Care Pediatric Pulmonology Unit during a five-year period (October 2012–November 2016) was performed. Primary outcome variables were total duration of fever and hospital length of stay (LOS). A secondary outcome included imaging methods used. Demographic, clinical, etiology, treatment and imaging variables were summarized by standard descriptive statistics. Results were summarized as medians (min–max) for continuous variables and percentages for nominal variables. Children with comorbidities were excluded.

Results

Thirty-three children were included (45.5% males), median age 40 months (min. 1 month; max. 14 years). The median duration of disease before hospitalization was 5 days (1–15). Most children (78.8%) were referred from local hospitals; median timing of referral was day 2 of admission (1–16). Only one child did not comply with the national vaccination plan and 19 (57.6%) had pneumococcal vaccine.

Overall fever lasted for a median of 15 (9–33) days and median LOS at our unit was 12 (4–34) days. Children were hospitalized for a total of 16 (7–35) days. One child with *S. pyogenes* infection developed toxic shock syndrome. Eight (24.2%) children were already under oral antibiotic at admission, and 23 (69.7%) patients were initially prescribed intravenous ampicillin. Fifteen (51.5%) were admitted to the Intensive Care Unit, mostly (97.0%) for pleural drainage with fibrinolysis. No children needed ventilatory support. Nineteen (57.6%) children were submitted to oxygen supplementation, during a median time of 8 (2–25) days.

All children underwent chest X ray (CXR) diagnostic for NP on evolution, 26 (78.8%) also showed pleural effusion, 27 (81.8%) underwent lung ultrasound scan (USS) and seven (21.2%) chest computed tomography (CT) (5 before referral), which added nothing to previous knowledge.

Blood cultures (BC) were available for all cases and pleural fluid cultures (PFC) for 20 (60.6%). Bacterial yield was higher in PFC compared with BC (61.5% positive vs. 6%). The two positive BC isolated *Streptococcus spp.* and *S. pneumoniae*; regarding pleural liquid, *S. pneumoniae* serotype 3 was identified in 8 cases from PCR methods and 7 cultures were positive (3 *S. pneumoniae*, 3 *S. pyogenes* and 1 *S. aureus*). No deaths occurred, one child was re-admitted due to oral intolerance to antibiotic.

Comments

NP is a severe pulmonary complication with prolonged morbidity and a large amount of hospital resource use. CXR and USS for diagnosis are probably sufficient in the majority of cases. We discuss that NP must be referred to a tertiary care hospital early in the evolution of the disease.

#N210 – Domiciliary Overnight Oximetry Has a Role on Oxygen Weaning in Bronchopulmonary Dysplasia Infants on Long-term Oxygen Therapy.

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Long term oxygen therapy (LTOT) is indicated in bronchopulmonary dysplasia (BPD) to treat chronic or intermittent hypoxemia and its consequences. Discontinuation of oxygen therapy should be prompt when respiratory stability and ascending weight and height are achieved. As suggested in international guidelines, assessing oxygenation during sleep by continuous overnight oximetry (COO) or polysomnography is recommended when weaning infants from supplemental oxygen; for the comfort of children and families, monitoring should preferably be made at home, in the child's environment.

Aim

To describe the role of domiciliary COO on the weaning from LTOT in patients with BPD.

Methods

A retrospective chart review of patients on LTOT during a 7-year period (January 2010–December 2016) was performed. Data regarding demography, pulmonary disease, oxygen therapy and follow-up were collected. Clinical stability for daytime weaning was defined as adequate growth, stable respiratory frequency and stable levels of oxygen saturation (SpO₂) >92% on spot oximetry. A COO was performed when favorable weight gain was maintained and awake stable respiratory (according to different ages) frequency was referred; a minimum time of 6-hour recording was considered valid. Descriptive statistics were performed and the results are presented in medians (minimum – maximum).

Results

A total of 34 exams were performed with respect to 24 DBP patients. Five (14.7%) were inconclusive due to short recording time (< 1 hour) or due to artifacts and were excluded. The 29 valid exams concerned 19 patients (a median of 1.5 exams per patient), with a median age of 16 (5–69) months. The median of gestational age of patients was 26 (24–28) weeks and most children (13; 68.4%) had BPD grade 3 (severe). All children were accompanied by a domiciliary unit of respiratory care. The oxygen weaning during wake periods occurred when clinical stability as defined was achieved, being the median age 8 (3–28) months. A COO without oxygen support was performed when stability criteria were present, 5.5 (2–32) months after daytime weaning, at a median age of 15.5 (5–60) months; the median desaturation index was 3.7 (0.6–36.8)%, the median basal SpO₂ was 97.35 (94.3–99.6)% and the median minimum SpO₂ was 85 (77–90)%. After COO, two children still maintain oxygen therapy during sleep periods (currently with 16 and 29 months), and two children were lost to follow-up; in all the other

children, the weaning of LTOT was possible after COO and no children needed to resume the therapy. The frequency of clinical evaluations changed according to disease stage: every two months before oxygen withdrawal, monthly immediately after oxygen withdrawal and then every three months.

Comments

Domiciliary COO can provide relevant information in the weaning of supplemental oxygen in BPD patients, leading to a confirmation of clinical findings. A spot oximetry cannot cover all critical times of the day and night, such as all sleep stages.

#N192 – The Evaluation of the Acute Effect of a Single Use of Waterpipe Smoking on Lung Clearance Index.

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Background

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Conclusions

This first study evaluated the effect of WPS on LCI. In this small sample size, no significant changes in LCI values after one session of WPS were noted. Further larger studies evaluating the possible effect of WPS on LCI measurements with multiple clinical and physiological parameters should be performed to assess the clinical benefit of LCI measurement in WPS subjects.

How to cite this article: Abstracts from CIPP XVI Meeting.
Pediatric Pulmonology. 2017;52:S100–S176.
<https://doi.org/10.1002/ppul.23731>

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