Acknowledgment

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It is with such generous contributions and ethical collaboration with industry that a small yet highly committed organization that made it its mission to be the dedicated international voice of pediatric pulmonology could thrive for its 25th year.

Andrew Colin,
CIPP Founding Father

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Foreword

The International Congress of Pediatric Pulmonology (CIPP) is in its 17th highly successful edition this year, and is being held in beautiful Toledo, Spain. This is the largest and only truly international meeting of respiratory physicians.

The congress is known for its outstanding speakers delivering state of the art presentations covering all topics in our field. Science is at its best in CIPP.

The abstracts presented in this issue of Pediatric Pulmonology hail from all continents and the sessions in which these are presented are a fantastic showcase for young researchers. This is truly a great opportunity for these young physicians to discuss their findings in a friendly and constructive environment.

From this sample of abstracts and summaries of plenary sessions, one can gain a good awareness of the broad spectrum of the meeting.

Welcome to CIPP XVII.

Renato T. Stein, M.D., M.P.H.
President, CIPP XVII

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Keynote Lecture

How to Teach Medicine in the Present Times to Kids Who Are Online all the Time?

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Technology pervades 21st Century living and not always for the benefit of mankind as recent revelations about harvesting of personal Facebook data illustrate – Guardian UK/Cambridge Analytica. However, technology is here to stay and already impacts education from school age onwards. Medical curricula are generally slow to evolve and the pace of technological advancement risks leaving medical education languishing in the days of Osler. This presents several challenges for educators: 1. Access to and use of smart technology from a very early stage of development may influence learning behaviors and learning style; 2. Ease of access to boundless sources of information requires a different skill set from those of us who pored over textbooks late into the night; 3. Traditional learning methods may be perceived as old-fashioned and boring compared with more technological delivery of knowledge; 4. We need to equip doctors of tomorrow not just to learn using technology but to adapt to the increasing infiltration of technological solutions in the delivery of healthcare; what is the role of the physician when artificial intelligence can solve problems more accurately, faster and more consistently than a mere human?

How Much Time Do Kids Spend Online and How Does This Impact Their Learning?

Children aged 6–16 years spend an average of 6½ hours per day in front of screens (2015; up from 3½ hours per day in 1995). The Connected Kids report is an annual UK, nationally-representative survey of children aged 8–19 years. In 2017, it reported that tablet ownership among 8–12 year olds had dipped to 60% from 68% the previous 7 years, probably due to the increase in smartphones, which were owned by 66% of this age group. These devices are generally used to watch on-demand TV and films and to access social media. These trends are not confined to school-aged children; 27% of 5–6 year olds use a computer for up to 50 minutes/day and many young children have a television in their bedroom (43% of 3–4 year olds and 18% of 0–2 year olds in one survey).1 ‘Screen time’ refers to time spent with any screen, including smart phones, tablets, television, video games, computers or wearable technology. Although parents recognize that screen time can be educationally formative, they also express concerns about duration (how much is too much?), effects on health and wellbeing and optimal content.

There is evidence that well-designed and age-appropriate educational programs and interactive media can improve cognitive and language development and retention of taught information in children older than 2 years. However, evidence suggests that preschoolers still learn best from direct interaction with adults.2 Some studies associate prolonged TV viewing with lower cognitive abilities, especially related to short-term memory, early reading and math skills and language development. Beyond the preschool years, most television watched by children is entertainment programming. Research on interactive digital media, including online gaming has yielded disappointing results with regard to learning and educational outcomes. In contrast, experimental training studies have found short-term increases in cognitive skills from playing games but the effects on particular cognitive skills are specific to the games played, and there is no evidence that they would accrue from playing any electronic game that did not require practice of the skills.3 In general the evidence supports the judicious use of screen media-based educational experiences alongside adult interaction, except in very young children.

Medical Education in a Digital Age

It was estimated in the 1950s that the doubling-time of medicial knowledge was about 50 years; in 1980, it was down to 7 years and in
2010, just 3.5 years. By 2020, this is projected to be 73 days! This rate of change makes curriculum planning a challenge; only 6% of what was learned in the first 3 years of a medical curriculum in 2010 will still be relevant at the end of the following decade. Paradoxically, the expansion of knowledge will force medical schools to define those concepts that form the essential core of what students must learn. The practice of medicine requires students to master the application of knowledge to solving complicated clinical problems, which is enhanced by integrated understanding of homeostatic mechanisms at the cellular and whole organism level, rather than intimate knowledge of the individual components of these mechanisms. Curricula should be designed to foster deep learning of these concepts, which is enhanced by student-centered, active learning and spiral curricula that return to core topics at deeper and more complex levels of understanding and application throughout the curriculum. There should be an emphasis on developing the skills of problem-solving using the best available evidence acquired through searching, retrieving and critically evaluating the relevant medical literature. Blended learning approaches have been developed to accommodate variations in student learning styles; although favored by students, there is little evidence that this approach results in increased student competency compared with traditional didactic teaching.4

The learning environment is changing and technological solutions exist that can enhance and broaden students’ access to the curriculum and beyond. Technologies such as podcasts and videos with flipped classrooms, mobile devices with apps, video games, simulations (part-time trainers, integrated simulators, virtual reality), and wearable devices (google glass) are some of the techniques available to address the changing educational environment. The use of technology-supported learning has become a fundamental ingredient in the experience of students. A major part of that change has been through the widespread introduction and use of ‘virtual learning environments’ (VLEs), which combine a variety of tools and resources into a single integrated system.5 These challenge the traditional notion of students gathered in a geographical location to receive teaching and facilitate the ability of students to learn any time, any place, anywhere through the use of mobile technology. These also act as a portal to a much wider world of learning through networks with other students and doctors, e.g., through social networking applications6 and give access to massive open online courses. Medical education need no longer be confined within the walls of a university campus. Despite these innovations, evidence exists that students continue to value direct face-to-face contact with experienced teachers!7

Keeping It Real (and exciting)!

Video gaming as a leisure activity evolved from Pong, a simple, 2D table tennis game in the early 1970s, to sophisticated role player activities played globally by multiple players simultaneously using a range of platforms. Adolescent boys spend more time playing video games than girls; an average of 1-1½ hours/day. This did not impact on time spent in social interaction, although there was some evidence of displacement of school-related activities. However, there is little evidence that time spent playing video games has a negative impact on performance in educational outcomes.8

The gamification of learning is an educational approach to motivate students to learn by using video game design and game elements in learning environments. Serious games (SGs) are interactive and entertaining digital software with an educational purpose. Although these are gaining traction, their effectiveness in medical education has yet to be established possibly due to current heterogeneity of design elements between applications.9 Virtual reality (VR) is another application that has vast potential for medical education in addition to direct application to healthcare practice. VR is already in use in virtual anatomy classes, where students are able to dissect a body to see the structures of tissues and organs and their relations, including 4D imaging so that, for example, congenital heart defects can be inspected in a beating heart. It is also rapidly developing to simulate high-fidelity, virtual patient scenarios where multi-professional teams can be developed in a safe learning environment. There is also interest emerging in the use of VR in communication and social skills training in fields such as situations where it would be preferable to the use of actors, e.g., child protection scenarios, and for promoting behavioral change, e.g., in antibiotic stewardship.10

What Does the Future Look Like?

The future is now in digital healthcare, including using electronic health records, integrating more real-time data on patients, knowing how to use analytics as well as decision supports, delivering tests and treatments outside the healthcare setting, engaging in electronic communications with patients and their caregivers, and constant monitoring of activity. Doctors of the (near) future need to understand how to make sense of –omics scale data generated on their patients, e.g., how to counsel the patient who presents with a list of anxieties generated by a commercial genome screen.11 The mass of data that can be generated on patients’ samples by automated, high-throughput systems will require new approaches to interpretation of diagnostic tests. Personalized medicine is already a reality in the classification and treatment of cancer and rheumatological diseases. Therefore, an understanding of the biology underpinning these approaches is a fundamental requirement.

Advances in artificial intelligence (AI) beyond pattern recognition and decision support to intelligent decision-making raise the specter of redundancy of some of the traditional actions of the doctor. The missing link in the current debate around AI and machine learning in health care is understanding the key step of separating prediction from action and recommendation. This requires a change in how clinicians think about using models developed using machine learning.12 Properly managed and evaluated, computers and humans working together can bring benefits; better diagnostic algorithms providing more accurate diagnosis can reshape the traditional clinical problem-
solving exercise. This can free time for physician-to-patient interaction, which might both improve care and allow physicians to record, and accurately register, more phenotypes and more nuance in their patients’ problems. As Verghese and colleagues put it,12 “In the care of the sick, there is a key function played by physicians, referred to by Tinsley Harrison as the “priestly function of the physician.” Human intelligence working with artificial intelligence can bring physicians closer to fulfilling Peabody’s maxim that the secret of care is in “caring for the patient.”

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DIAGNOSIS OF OBSTRUCTIVE SLEEP-DISORDERED BREATHING

The worldwide shortage of pediatric sleep laboratories and the cost of polysomnography explain the very long waiting lists and the fact that most children are treated without polysomnography. The quest for other means to diagnose obstructive sleep apnea syndrome (OSAS) in children continues to be the focus of many publications.

Nocturnal oximetry

Contrarily to PSG, nocturnal home oximetry is widely available. A number of publications in the last year continued to propose in-depth analyses of oximetry recordings to diagnose OSAS and more accurately predict its severity. A very recent expert review on the subject elegantly summarized the state of the art on this topic (1). The authors conclude that, overall, nocturnal oximetry appears reasonably accurate in predicting moderate-to-severe OSA (apnea-hypopnea index>5/h), especially when using automated signal processing algorithms (2). A reliable screening test for mild OSAS however is still lacking (1). Finally, the authors remind us that nocturnal oximetry is less reliable in certain subgroups of children, such as those with obesity or Down syndrome.

Home sleep apnea tests for diagnosing obstructive sleep apnea in children

Conversely to adults, home-based sleep apnea tests are not yet recommended for OSAS diagnosis in children. Several recent articles have been published on the subject. The American Academy of Sleep Medicine again published a position paper stating that although the development of such tests must be continued, those currently available cannot be recommended at this time (3).

A new system, the Sonomat, could make a real difference if the first available results are confirmed (4). The Sonomat is a thin mattress overlay containing several vibration/sound sensors that can identify body movements, breathing movements, and both breathing and heart sounds. It enables the diagnosis of sleep-disordered breathing (apnea, hypopnea, snoring) without any attached sensor, making it especially attractive for children. The Sonomat has been validated in 76 children aged 2–17 years. Obstructive and central events were classified correctly. Notably, the time spent snoring was 10 times longer than the time spent with respiratory events. Hence, many children defined as normal by polysomnography were recognized as abnormal due to snoring and stertor. The authors conclude that the Sonomat accurately diagnoses sleep-disordered breathing in children. Moreover, it allows further quantification of partial airway obstruction, which appears especially relevant to a better understanding of sleep-disordered breathing in children (4).

Drug-induced sleep endoscopy (DISE)

Drug-induced sleep endoscopy enables a thorough evaluation of the site(s) of upper airway obstruction during sedation, mimicking sleep. By recognizing anomalies such as late-onset laryngomalacia or enlarged lingual tonsils, DISE can theoretically optimize surgical treatment in infants and children. Several articles on DISE were again published last year. A review on DISE in children concluded that it is a safe and useful technique, although the indications, anesthetic protocol and scoring system remain to be standardized (5). DISE is predominantly used in children with persistent OSAS after adenotonsillectomy (5). Several teams however use DISE in surgically-naïve infants and children, and have shown that it alters surgical treatment in ~33% of the cases (6,7).

ERS STATEMENT ON OBSTRUCTIVE SLEEP-DISORDERED BREATHING IN 1- TO 23-MONTH-OLD CHILDREN

This unique statement issued from an extensive literature review provides a useful stepwise approach to the management of obstructive SDB in 1- to 23-month-old children. The available diagnostic facilities and currently accepted treatments in various European countries were taken into account; a special consideration was given to the use of alternative diagnostic tests when polysomnography is not available. The statement also deals with malformations, either syndromic or not, and complex conditions, such as Prader-Willi and Down syndrome (8).

TREATMENT OF OBSTRUCTIVE SLEEP-DISORDERED BREATHING IN CHILDREN

Positional therapy

Avoiding supine position is well known and used in adults with obstructive sleep-disordered breathing. Few studies on the effect of supine position on obstructive sleep-disordered breathing have been performed in children, yielding conflicting results. Sleep position was studied in pre-school children (3–5 years) with or without obstructive sleep-disordered breathing. All children preferentially slept supine, and the apnea-hypopnea index was worse in supine compared to lateral...
and prone positions in nonREM and REM sleep. The authors conclude that further studies on the effect of positional therapy must be conducted (9).

Continuous Positive Airway Pressure

Review of the literature does not reveal any study using autotitrating CPAP (AutoPAP) for treatment initiation in children with OSAS. A retrospective study on 26 children aged 12 ± 3 years showed that AutoPAP was used 80% of the nights and ~6 hours/night, with a decrease in apnea-hypopnea index from 17 to 2/h. The authors conclude that CPAP initiation with AutoPAP is safe and an effective means to initiate CPAP in children (10).

REFERENCES


#2 What Sort of Asthma Do I Have?

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Introduction The Lancet asthma commission brought together experts from all over the world to address the question as to why for the most part asthma outcomes have stalled over the last decade [1]. The discovery of the efficacy of inhaled corticosteroids (ICS) undoubtedly transformed the lives of millions of patients suffering from asthma, but there have been no real major breakthroughs since. Pharmacotherapy is still the blue one and the brown one, albeit with a darker brown and a longer acting blue. Why? The Commission poses sharp questions and has some challenging answers, and some of the pediatric implications of the Commission will be reviewed.

Do I have asthma at all? There is no question that the approach to asthma diagnosis at all ages is lamentable. There is a reluctance to make any objective measurements before diagnosis, and as a result, the diagnosis is frequently wrong. In a group of academic general practices in the Netherlands [2], around 50% of children diagnosed with asthma, and prescribed sometimes high dose asthma medications, had no objective evidence supporting the diagnosis! In what other disease setting is a diagnosis made with no objective testing performed, even when simple tests are available? Given even this basic level of diagnostic competence is often not attained, small wonder that attempting phenotyping of airway disease is not considered (below).

What sort of asthma do I have (no other co-existing condition)? The Commission is predicated on the assumption that ‘asthma’ is no more a 21st century diagnosis than ‘arthritis’ or ‘anemia’. The term ‘asthma’ should be reserved for a clinical description – wheeze, breathlessness, chest tightness, cough – with no assumptions about the underlying pathology. Next, in order to answer the question in the abstract title, the airway is deconstructed into its component parts – in children, whether there is fixed and/or variable airflow obstruction, airway inflammation, or infection, and treatment is planned depending on the answer. There is nothing new in this; the late, very great Harry Morrow-Brown showed that prednisolone was effective only in patients with airway disease characterized by sputum eosinophilia (thus rescuing steroids from the dustbin of history to which they were in danger of being consigned by a large Medical Research Council trial which recruited all-comers irrespective of airway phenotype) [3]. This finding triggered a wave of steroid-fervor, but the lesson that Dr. Morrow-Brown taught us, that steroids should be used selectively, and were not a general panacea, was lost in history. So if, and only if,
there is evidence of airway eosinophilia, then ICS should be used. Similarly, variable airflow obstruction, if thought to be due to bronchospasm, is treated with short- or long-acting β-2 agonists. If there is irreversibly fixed airflow obstruction, there is no point in increasing treatment to try to reverse this. Finally, the airway disease should be seen in the context of any co-morbidities, and social and environmental factors, in particular adherence [4]. The emphasis should always be on detecting that for which a treatment exists.

This approach is of direct relevance to the vexed question of preschool wheeze. Instead of ‘diagnosing asthma’ at some wholly arbitrary age, we should be probing the nature of any airway disease as a preliminary to deciding how to treat it. Spirometry and acute bronchodilator reversibility can reproducibly be measured even in young children [5]; and there is increasing evidence that peripheral blood eosinophil count reflects lower airway eosinophilia [6], and, in conjunction with aeroallergen sensitization [7], can predict the response to ICS in preschoolers.

**Are the LMIC asthmas the same as developed world asthmas?** One of the most pernicious effects of the uncritical use of the umbrella term ‘asthma’ is the creeping assumption that the disease is the same the world over. This may not be the case, especially in LMIC settings with a high burden of infection and environmental pollution. Indeed, in Brazil, atopic asthma, so common in the UK, is very uncommon, and the phenotype is associated with bronchiolitis and helminth infections [8]. This of course means that what works in the UK may not work everywhere else in the world, and should not be uncritically adopted. However, the approach of deconstructing the airway works extremely well internationally, and the question ‘what sort of asthma does this child have?’ is globally relevant, and should be adopted rather than slavishly following the diktats from elsewhere.

**Is asthma a co-morbidity of a systemic or another respiratory condition?** The frequently asked question is, do children with, e.g. bronchopulmonary dysplasia (BPD) or sickle cell (SCD) have ‘asthma’? Post the Commission, this question should be discarded as meaningless, and instead, be replaced by, ‘does this child with e.g. BPD/SCD have an airway disease, and if so, what is its nature and how should it be treated. Thus BPD survivors have fixed and variable airflow obstruction, with no evidence of airway eosinophilia, and should be treated with short-acting β-2 agonists but not ICS [9]. SCD airway disease is of fixed airflow obstruction, with no airway reactivity or evidence of airway eosinophilia [10]. The same approach should be applied to the question of whether patients with cystic fibrosis (CF) or primary ciliary dyskinesia also have ‘asthma’.

**Beyond phenotyping: the importance of endotypes** As ever-increasing numbers of monoclonal antibodies become available, it will be important to go from treating phenotypes (the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment e.g. airway eosinophilia) to endotypes (a subtype of a condition, which is defined by a distinct functional or pathobiological mechanism). The importance of this is most clearly shown by cystic fibrosis; when the endotype (abnormal or absent CFTR function) was distinguished from the phenotype (chronic bronchopulmonary infection with airway neutrophilia) real progress was made, culminating in the use of designer molecules directly to correct CFTR dysfunction. Nowhere is this more important than in severe therapy resistant asthma; for example, although much eosinophilic airway disease is driven by classical Type 2 cytokines (IL-4, IL-5, IL-13), alternative pathways characterized by upregulation of genes concerned with metabolic pathways, ubiquitination and mitochondrial function have been discovered [11]. Airway eosinophilia is not synonymous with Type 2 inflammation [12], and should not necessarily be treated with anti-Type 2 monoclonal antibodies. It could be argued that endotypes are irrelevant to mild asthma which is easily controlled with low dose ICS, but I would argue that this is not the case; if we are to prevent the development of asthma, we surely need to understand pathways. Furthermore, we should not be complacent about ‘mild’ asthma; in the UK National Review of Asthma Deaths [https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills], only 40% of those who died had ‘severe’ asthma. Hence endotyping will ultimately be important for the asthmas of all severities.

**Summary and conclusions** The Lancet Commission is intended to trigger a new era of precision medicine for airway disease. In pediatrics, pulmonology, we have been guilty for far too long of failing to make measurements, uncritically accepting that one size fits all, and wasting time on irrelevant questions like ‘is it asthma, Dr?’. The challenge to us is to move into the age of true precision medicine, giving the right treatment to the right child, guided by objective measurements.

**References**


#3 Big Data and Multomics for Asthma Cure: The Case For

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Development of new methods for improving causal inference in large studies creates an opportunity for a step change in understanding mechanisms which underlie the development of different subtypes of asthma. Big data sets contain many thousands of variables (from clinical variables and objective tests such as lung function tests, to various "omics" data including genomics, proteomics, metabolomics, epigenetic data, etc.). The amount of data that is being generated is increasing exponentially, and as a consequence it is often not possible to define a priori hypotheses, or to know precisely what we are looking for.(1) In contrast to a traditional hypothesis-driven approach, big data methods involve the use of data-driven, hypothesis-generating techniques, which aim to uncover structure in the data to make predictions about important clinical outcomes, while remaining agnostic towards specific predictors, or an opinion of an investigator.(2) Limiting the inputs to such models based on preferences or opinions may limit the ability of a model to uncover the associations which do, in fact, exist. By developing algorithms to model a large number of potential associations in an unsupervised way, patterns can be identified that could not have been predicted in advance, even by experts in the field. Therefore, within the context of the "big data" research, data are allowed to speak for themselves. Combined with mathematical, bio-informatic, and computational techniques, systems biology can help to elucidate the directionality of relationships between variables at a more holistic level, thereby, moving away from associative to more causal analyses. However, the potential danger of this approach is that it may become divorced from rigorous scientific scrutiny and meaningful clinical interpretation.(1) Furthermore, machine learning techniques and their associated language inventory of "new" terms (for example hidden Markov models, random forest, Bayesian networks, latent variable modelling, clustering, etc..) may be complex for the clinical community to fully understand.

It is important to emphasize that big data can explain only a part of the picture, and clinical investigators and other domain experts can provide a deep understanding through their experience and clinical domain knowledge.(3,4) Integrating clinical expertise and experience with "big data" approach may allow external validation of what is experienced in the "real world". Examples of such approaches in the area of pediatric asthma and allergy include the refutation of the concept of "atopic march"(5), and debates on the causal relationship between asthma and different subtypes of allergic sensitization.(6)

Further examples include the use of data-driven hypothesis-generating techniques to discover different childhood "wheeze phenotypes”, using models which ascertained temporal patterns of symptoms in childhood. As a consequence of these and other studies, the conceptual framework of asthma heterogeneity is now widely accepted.(7) With the birth of genome-wide association studies (GWAS), researchers are able to investigate the relationship between hundreds of thousands of genetic markers with a phenotype. However, most large GWAS in the field of asthma use the broadest possible definition of the primary outcome (e.g. "doctor-diagnosed asthma"). Disaggregating asthma by using "big data" approach may improve genetic studies.(1, 8) By using "deep phenotyping", a recent comparatively small GWAS discovered the association of a specific asthma subtype (early-life onset asthma with severe exacerbations), with a functional variant in a novel susceptibility gene CDHR3 (rs6967330).(9) It is of note that this SNP is not associated with "doctor-diagnosed asthma" in any of the large-scale GWAS, but is strongly associated with persistent troublesome childhood wheezing. Functional studies have shown that rs6967330 may be a receptor for rhinovirus-C.(10) and this target is currently pursued for potential novel therapeutic agents for asthma.

One way of bridging the divide between hypothesis-generating big data methods and rigorous hypothesis-testing approaches is by creating a "team science" culture. There are examples of large collaborative groups which are working together in a synergistic fashion to ensure that there is a bridge between big data analytics, careful scientific process, and clinical interpretation. One such example is the UK Study Team for Early Life Asthma Research (STELAR) consortium,(8) which has pioneered the use of data-driven methodologies and machine learning in the analysis of complex longitudinal data in asthma, from the first use of the latent class analysis (LCA), principal component analysis, multilevel LCA using data from different sources, to the first use of machine learning in respiratory medicine. This large-scale collaboration and its underpinning shared e-infrastructure...
provided insights with clinical application. The mix of disciplines provides a collective contribution towards the interpretation of findings, and is an example of an approach where “big data” is coupled with “big reasoning” (1).

New possibilities for asthma research are emerging from personally tracked data from the ubiquitous use of digital devices, which can capture real-time information about daily behaviors, health status, and geographical locations, and which are widely accessible on an unprecedented scale. A challenge to modelling such data is distinguishing genuinely relevant data from “noise” arising from spam or searches not related to episodes of illness. Individually-generated data is also emerging from synergies between medical technology and smartphones. Bluetooth-enabled smart inhalers and peak flow meters, for example, allow monitoring of the adherence with medication, severity of symptoms, and lung function. These types of data have the potential to uncover different aspects of asthma heterogeneity. However, due to potential limitations, they should be viewed as complementary to, rather than a substitute for traditional or other forms of data. Without interpretive tools that can be readily incorporated in daily practice, there may be a risk of valuable research findings being overlooked as the consequent actions for decision-making may not be obvious.

One of the aims of asthma research is to understand disease heterogeneity to facilitate stratified approach to treatment. To achieve this, we need to move away from the artificial dichotomy of data-driven hypothesis-generating versus hypothesis-driven approaches, towards a more integrated one, whereby cross-disciplinary collaborations can facilitate rigorous scientific scrutiny and interpretation of findings. Steps need to be taken to improve the statistical literacy of healthcare professionals through greater education to bridge the divide with the big data “industry”. Ultimately, no single data source can uncover the complexity which drives asthma heterogeneity. There is huge potential to provide a more holistic understanding of the disease at a level of individual patients. A solution to the problem of asthma is an integrative approach whereby clinicians, statisticians, computer scientists, geneticists, physicists, basic scientists and epidemiologists work together to understand asthma heterogeneity.

To achieve this, we need to replace the current model of “selfish science” with its foundations of the “lead institutions” and “principal investigators”, with that of a genuine “Team science”.

References


#4 Pro-Con Debate: Big Data and Multi-omics for Asthma Cure

Con: Big Data and Multi-omics Alone Will Not Be Helpful to Cure Asthma: Hypothesis-Driven Mechanistic Research Is Essential

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We all accept and understand that “asthma” is simply a label given to an airway disease that in children is characterized by symptoms of wheeze, breathlessness, difficulty in breathing and/or cough. However, this label tells us nothing about the underlying pathophysiology. A Lancet Commission comprising expert opinion from world leading researchers and clinicians has proposed that asthma is “a heterogeneous mix of pathobiologically distinct mechanisms responsible for morbidity and mortality in patients” (1). It has been argued that airways diseases should be split into treatable traits, rather than being referred to using single “umbrella” terms such as asthma or chronic obstructive pulmonary disease (COPD). Given the heterogeneity of asthma, it has also been repeatedly proposed that the only way to advance management and achieve effective treatment for the individual patient is using personalized or precision medicine (2).

Pharmacogenomics, epigenomics, transcriptomics, proteomics and metabolomics are just some of the omics fields that are rapidly
advancing with the aim of providing tools to identify novel biomarkers to guide treatment (3). These techniques take an unbiased, hypothesis-generating approach whereby children with similar clinical features are grouped together with the aim of looking for potential patterns, “clusters” or gene signatures that may identify specific phenotypes. It is true that these approaches, together with advances in high-throughput technologies and statistical tools, are intended to expand our knowledge of distinct phenotypes, but it must be remembered that there are limitations to this approach if used in isolation. Some of the pitfalls are highlighted here.

The quality of the results obtained following unbiased, large data analyses is as good as the accuracy and reliability of the input data. Generating heat-maps, volcano plots and topographical diagrams is very pleasing to the eye, but really making sense of what is represented can be a huge challenge. It is essential that the right clinical parameters are used and equally important that the interpretation is undertaken with a clinical expert (4). Importantly, any patterns or disease phenotypes that may be uncovered need to be confirmed with mechanistic studies. It must be remembered that the data are hypothesis-generating, and need to be followed up with scientifically sound hypothesis-testing experimental studies. For example, although numerous genome wide association studies have been undertaken to identify asthma susceptibility genes, the translation of any of these genes to clinically meaningful functional effects is significantly lacking. Moreover, transcriptomics analysis of bronchial epithelial cells from patients with asthma was considered transformative when a “gene signature” for type 2 mediated asthma was identified from adult patients (5). But, the signature originally identified in airway cells was extrapolated to a peripheral blood biomarker, periostin, with a huge investment into stratifying patients according to serum periostin to decide response to anti-IL13 antibody therapy. The pilot data were promising, but the subsequent larger randomized trials have been so unrewarding that the anti-IL13 antibody Lebrikizumab is no longer being pursued by the company as a therapy for asthma (6). The key issue was a small alteration in range of serum periostin considered abnormal for the large phase III trials, with significant overlap between patients, the new biomarker definition resulted in a complete change in outcome. The problem of variability between patients, between trial designs and between response, or not, to treatments is a huge issue that needs to be considered before big data analyses are interpreted or translated.

Another factor that may have contributed to the negative outcome of the anti-IL13 antibody studies was the use of a serum biomarker that was originally found from airway epithelial cells. It is essential to ensure mechanisms are investigated in the most appropriate sample types. To extrapolate findings from airway cells to peripheral blood, or vice versa, may be hugely misleading. The immediate pitfall applicable to children is the proposed utility of blood eosinophils as a biomarker to determine which children may respond to anti-IL5 antibody therapy. Retrospective analyses of adult clinical trials have suggested peripheral blood eosinophil cut-offs that might identify patients most likely to respond to mepolizumab (7). However, it would be wrong to assume peripheral blood eosinophils may be helpful in children since there is ample data showing children with severe asthma have a persistent, steroid-resistant airway eosinophilia (8) which is often present in the absence of peripheral blood eosinophilia (9). Mechanisms underpinning pediatric asthma, specifically severe pediatric asthma (the group for whom novel treatments are needed) need to be investigated using airway cells. Despite knowing this, we shy away from investigating mechanisms in airway cells in children because of the difficulties inherent in obtaining airway samples. Moreover, mechanistic findings from adult studies cannot be extrapolated to children as has been demonstrated by the distinct role played by neutrophils in adult and pediatric severe disease (10). Translational approaches to uncover mechanisms underlying sub-phenotypes and to identify novel therapeutic targets must include age-specific disease models with primary airway cells from children.

References

ABSTRACT

Illnesses and subsequent asthma if they carried. Mothers had an increased risk of wheeze, hospitalization for wheezing. The COPSAC study reported that infants who were born to asthmatic circumstances, most of which we are just starting to unravel. Interest in this area of research has increased markedly since the paper from the ORChID children. In both studies, children recruited antenataly were closely followed to observe the pattern of acquisition of viruses and bacteria in early life. In CAS, every acute respiratory illness was reported to the study team, regardless of severity, the team visited and nasal secretions were collected. Secretions were also collected on two occasions each year when children were well. In ORChID, parents took a nose swab every week, which was posted to the laboratory for analysis. Parents in both studies kept daily symptom diaries. Twenty-nine ORChID children (18.5%) had viruses detected in nasal swabs during the neonatal period, with human rhinovirus (HRV) being the most common. Thirteen children had 14 symptomatic episodes associated with viral detection. The earliest symptomatic infections occurred at days 6 & 7 of postnatal life, both due to HRV-A. Most symptomatic infections were upper airway infections, with only 2 lower respiratory infections recorded during the neonatal period (4).

One age-old question that remains unanswered is whether viral infections cause asthma or asthma causes viral infections. Common genetic susceptibilities have been reported for asthma and viral respiratory infections. Epidemiological studies have associated infection with HRV-C with more severe illness, increased hospitalization and increased risk of subsequent asthma (5). CDHR3 is the surface receptor used by HRVc and is a susceptibility gene for childhood asthma (6, 7). Variations in ORMDL3 and GSDMB genes on 17q21 are associated with asthma and wheezing with HRV but not with RSV (7). Asthmatics are reported to respond differently to experimentally-induced viral infections, with less production of type 1 and type 3 interferons (8). However, data from studies infecting airway epithelial cells from children show that both viral-specific and host-specific factors are involved (9).

While viral lower respiratory infections are definite risk factors for subsequent asthma, especially those associated with fever and/or wheeze (2, 10, 11), the major risk comes when infections occur in the presence of allergic sensitization. In the CAS study, the increased risk of asthma was only seen in children who developed allergic sensitization before 2 years of age, with this risk persisting to 10 years of age (2, 10).

The role of bacteria in increasing or decreasing asthma risk is complex. The normal upper airway microbiome in healthy children is simple and dominated by Staphylococcus, Corynebacterium and Alloilococcus (Teo, 2015 #1). In the presence of a respiratory viral infection, the upper airway microbiome changes and is dominated by Streptococcus, Moraxella and Haemophilus (Teo, 2015 #1). To a real extent, the failure to "revert" to a healthy upper airway microbiome is associated with increased risk of subsequent asthma. In addition, asymptomatic carriage of Streptococcus was associated with earlier and more severe lower respiratory infections and increased asthma risk. However, the complexity of the situation is revealed by unpublished CAS data that show that an increase in Moraxella density before viral detection is associated with lower respiratory infections. This same increase is not seen with asymptomatic infections.

In summary, complex interactions between viruses, bacteria and allergic sensitization are at play in early life to modify asthma risk in children.

References

ABSTRACT


By virtue of the markedly different degree of attenuation of X-rays by air and soft tissue, chest radiography (CXR), fluoroscopy and computed tomography (CT) are effective methods for imaging the airways. Pathology may be directly visualized for large central airways or inferred for small peripheral airways on the basis of the imaging findings. Applications are broad and include suspected intraluminal obstruction (e.g. foreign body, bronchiolitis obliterans), intrinsic airway disease (e.g. tracheobronchomalacia, complete cartilaginous tracheal rings), or extrinsic compression (e.g. vascular rings and slings, crossing innominate artery, midline descending aorta).

The preferred imaging technique varies with the suspected pathology and available equipment. Dynamic imaging techniques such as inspiratory/expiratory CXR, fluoroscopy, and inspiratory/expiratory or cine CT permit the lungs and airways to be imaged at different phases of the respiratory cycle. Inspiratory/expiratory CXR and inspiratory/expiratory chest CT have long been the preferred initial imaging methods for detecting foreign body aspiration or bronchiolitis obliterans, respectively, on the basis of air trapping rather than direct visualization of the airway obstruction. Judicious use of airway CT in pediatric cases with an intermediate likelihood of foreign body aspiration may reduce the negative bronchoscopy rate. Fluoroscopy has historically been the preferred noninvasive method for diagnosing tracheobronchomalacia due to its ease of performance, even in uncooperative patients, and its high specificity, but it is limited by its subjective interpretation, low sensitivity, poor depiction of the paratracheal structures, and inability to simultaneously display the anteroposterior and lateral walls of the airway and quantify luminal cross-sectional area. In infants and children too young to comply with breath-hold instructions, inspiratory/expiratory phases can be simulated by imaging during right/left lateral decubitus or prone/supine positioning. Controlled-ventilation CT under sedation or anesthesia also permits inspiratory/expiratory imaging of the lungs and airways in uncooperative patients.

Dynamic cine CT technique allows the airways to be imaged rapidly and sequentially during successive phases of the respiratory cycle, and the airway findings on dynamic cine CT correlate well with those noted on bronchoscopy. Recent technologic advances including more rapid gantry rotation and wider detector arrays (up to 16 cm craniocaudal coverage) allow all or nearly all of the lungs and central airways to be imaged by CT throughout the respiratory cycle without the need for sedation or intubation. This technique is capable of generating multiplanar, 3D (volume-rendered and virtual bronchoscopy), and even 4D representations of the airways during normal tidal breathing or forced expiratory maneuvers, as well as depicting the relationship of the airways to the adjacent vasculature if intravenous contrast is administered, information that can be vital for therapeutic planning. With dynamic cine CT, intrinsic and extrinsic causes of airway narrowing can be distinguished and fixed airway stenosis can be differentiated from expiratory central airway collapse due to tracheobronchomalacia (softening of tracheobronchial cartilage) or excessive dynamic airway collapse (inward bulging of the posterior membrane).

Tracheobronchomalacia is primary (congenital) in approximately 1/2100 children and often resolves in isolated mild to moderate cases by 2 years of age as the cartilage geometry and composition matures and posterior membrane tone develops. Tracheobronchomalacia is often accompanied by gastroesophageal reflux disease and is associated with other foregut anomalies, especially esophageal atresia and tracheoesophageal fistula. Tracheobronchomalacia can be secondary to extrinsic compression, chronic airway inflammation, intubation, or positive pressure ventilation and is identified in about one-fourth of children with chronic respiratory symptoms or signs such as wheezing, barking cough, recurrent respiratory tract infection, apnea, cyanotic spells, or difficulty weaning from respiratory support. Tracheobronchomalacia was originally defined as >50% reduction in airway cross-sectional diameter during coughing, but false positives are very common with this definition, especially for the bronchi in which physiologic expiratory airway narrowing is more pronounced than for the trachea. The shape and cross-sectional area of the airway lumen can be precisely determined by CT, but there is no current consensus on the optimal threshold degree of expiratory airway collapse for a diagnosis of tracheobronchomalacia among children of varying ages with or without coexisting lung disease during either tidal breathing or forced expiration. Expiratory collapse of normal airways can occur in the setting of obstructive lung disease such as asthma or bronchopulmonary dysplasia due to increased pleural pressure and increased peripheral airways resistance that reduces airway transmural pressure.

Dynamic cine CT provides objective information to classify expiratory central airway collapse according to the FEMOS (functional status, extent,
morphology, origin, severity) system, but it should be noted that the degree of luminal narrowing is only one factor in airflow limitation. Evidence of airway compression or expiratory collapse on imaging does not necessarily indicate a condition requiring therapeutic intervention, and correlation with the clinical symptoms, signs, risk factors, and pulmonary function tests is necessary to determine the functional significance. In addition to the noninvasive nature, the advantages of dynamic cine CT over bronchoscopy include the ability to directly evaluate for vascular structures or soft tissue masses that impinge on the airway, depict airways too small to be passable by a bronchoscope, and assess the lungs for air trapping or other parenchymal disease.

A disadvantage of CT is the exposure to ionizing radiation. For perspective, CT virtual bronchoscopy can be performed with a radiation dose similar to a few months of natural background radiation. MRI avoids exposure to ionizing radiation and is capable of producing high resolution images of the central airways and vasculature during free breathing, but is limited by a longer scan time, more frequent need for sedation/anesthesia and less detailed depiction of the lung parenchyma compared to CT. Additional studies in children are needed to determine how the anatomic and functional information provided by dynamic CT and virtual bronchoscopy is best applied to the diagnosis, treatment planning, and post-therapeutic monitoring of pediatric airway disorders.

References

#7 Impact of Migration on Childhood Disease Manifestations

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Chronic respiratory diseases in children such as asthma are a major problem worldwide. International comparisons such as ISSAC (International Study of Asthma and Allergy in Childhood) have shown worldwide variation in disease prevalence with a large variability between continents, countries and regions. Also, within populations, big differences in disease manifestation exist. Social class and income, access to the health system, life style and environmental exposures play important roles. In addition, migration status seems to influence disease manifestation significantly, a fact which has been shown in migration studies around the world.

When in 1999 we first observed a protective migration effect in Turkish children growing up in Germany as the second generation of migrants, it was hard to understand why these children showed a lower prevalence of asthma than their German peers and children in Turkey. At the time, we postulated a healthy worker effect in these children, as their parents were especially fit and healthy when they applied to come to Germany for work. What we did not well understand at that time was that most of these families came from traditional backgrounds in rural parts of Turkey and thus, it is very likely that another potential explanation for these differences in asthma manifestation could be found in their exposure to microbial diversity, a well-known protective factor against asthma development nowadays.

Interestingly, the prevalence of asthma increased in Turkish children in correlation with their adaption to the lifestyle of their host country, which was measurable with their increasing German language skills. Similar effects of assimilation in disease prevalence were observed between children from East and West Germany, when asthma rates in East German children rose to West German levels within a generation. Further reasons for these differences in disease prevalence and manifestations between indigenous and migrant populations may be found in gene environment interactions or epigenetic mechanisms, either increasing or decreasing disease risk depending on changes in exposure and/or adaption to exposure from old to new environments and life styles.

However, one needs to be aware that current knowledge of migration effects on respiratory diseases are based on rather historical data and
not sufficient to understand current developments(6). Especially Europe has experienced unprecedented levels of migration from non-European countries such as Afghanistan, Syria, Eritrea and the south of the African continent within the last 3 years. The dimension of the current migration makes it difficult to understand the factors involved in disease development in these specific migrant populations who are rather diverse in genetic, social and cultural background. Prediction based on existing data may be difficult or impossible. A major challenge we face is the lack of knowledge we have on the living conditions of these children and the poor accessibility of these new migrant populations for medical studies. This is due to numerous facts: (1) a broad diversity of languages spoken in this heterogeneous group of immigrants, making it difficult to design study tools and achieve informed consent in potential study participants; (2) little affinity to science and the concept of studies, often driven by the fear that giving information may lead to expulsion by the government and (3) high mobility of these migrants due to political pressure. Having said that, it makes it even more important to get a better understanding of migrant populations if we want to serve all children equal and avoid missing out on the needs of an ever-increasing part of our future society.

References

#8 Steroid Refractory Inflammatory Phenotypes in Asthma for Pediatric Pulmonology

Stanley J. Szeftler, MD
managing asthma in children in order to prevent severe asthma and irrecoverable loss of pulmonary function as well as adverse respiratory outcomes in adolescence and adulthood.

**The Path to Severe Asthma**

Severe asthma in children is often associated with allergen sensitization, exacerbations associated with respiratory infections, sensitivity to irritants such as air pollution, smoking and indoor allergens, poor medication adherence, poor technique associated with delivery of inhaled medications and under-treatment. The potential consequences of poor management of severe asthma include mortality, repeated exacerbations requiring hospitalization, adverse effects to medications, the potential for disease progression and evolution to a pattern of COPD-like respiratory illness. Attention should now be directed toward minimizing risk and impairment with a goal to achieve optimal asthma control.

**Steps to Prevent Severe Asthma**

The varying patterns of lung function developing over time in children with mild to moderate persistent asthma were recently depicted by McGeachie et al. from the NHLBI Childhood Asthma Management Program (CAMP) (5). Four patterns were identified including two with reduced lung growth from early childhood and two patterns with evidence of early decline in pulmonary function after age 20 years. Approximately 11% of those participants met physiologic criteria for advanced levels of COPD in early adulthood. Therefore, children with persistent asthma should have ongoing measures of lung function to classify their lung function trajectory/phenotype and develop strategies for either recovering loss or preventing further loss in pulmonary function.

Steps should also be taken to assess the level of severity and burden of asthma. The Composite Asthma Severity Index (CASI) was developed by the NIAID Inner City Asthma Consortium (ICAC) (6). It is available free of charge at www.asthmaseverity.org and it can be used to assess the severity of asthma and the impact of an intervention.

The NIH Asthma Outcomes Task Force identified a set of biomarkers including allergen sensitization, blood and sputum eosinophils, exhaled nitric oxide and total serum IgE that should be considered in developing NIH-funded asthma research (7). These biomarkers have proven useful in identifying children who have more favorable response to inhaled corticosteroids as compared to other treatment options. These biomarkers can also be useful in considering the choice of immunomodulatory therapy.

The Seasonal Asthma Exacerbation Predictive Index (SAEPI) was also developed and validated by the NIAID ICAC to identify children at risk for an asthma exacerbation (8). This index can be used to identify children at risk for an asthma exacerbation and be assessed for potential intervention strategies, such as a step-up in treatment or a careful evaluation of medication adherence (9). Electronic adherence monitoring techniques are now available to monitor day to day rescue and long-term controller therapy. This assessment could lead to improved patient engagement to enhance adherence or perhaps justification to consider an immunomodulator therapy. In addition, the assessment of social determinants of health could lead to identification of important contributing factors to poor asthma management. The identification of these features could help to engage community support systems, such as school-centered asthma management programs, environmental assessment, and food resources that help to mitigate these conditions.

**Future Directions in Managing Severe Refractory Asthma in Children**

We now have a number of new treatment strategies to consider including a long-acting anticholinergic, tiotropium, and biologics such as omalizumab and anti-IL5 agents (mepolizumab, reslizumab and benralizumab) with varying levels of approval for use and clinical experience in children. Several other new medications, such as anti IL4/13 (dupilumab) and perhaps anti-TSLP, are currently being evaluated in adults with a plan for additional assessment in children based on their potential for managing severe asthma (10). It will important to define the role of each of these medications in preventing asthma exacerbations, preventing loss of pulmonary function or perhaps even improving pulmonary function, and improve the quality of life for children with severe asthma. It is also possible that these new therapies could alter the course of asthma and even prevent the development of severe asthma in children and reduce the potential for adverse respiratory outcomes in adulthood.

**References:**


#9 Vaccines to Prevent Pneumonia: Impact and Outcomes on Burden of Disease in Low and Middle Income Countries

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Pneumonia is the major single cause of mortality in children outside the neonatal period in low and middle income countries, accounting for approximately 900 000 deaths annually in children under 5 years. However, the incidence of childhood pneumonia has declined substantially in the last decade, with advances in immunization, improvements in socio-economic status and effective HIV preventative and treatment strategies. From 2000 to 2010, the incidence of childhood pneumonia decreased by approximately 25%, from 0.29 to 0.22 episodes per child year in low and middle income countries (LMICs). Similarly from 1990 to 2013, pneumonia-associated disability-adjusted life years (DALYs) decreased by 58%, from 186 million to 78 million. Most deaths and the majority of severe cases of LRTI occur in LMICs, especially Africa and South-east Asia, where the incidence and severity of disease is disproportionately high relative to the childhood population. The incidence in LMICs of 0.22 e/cy is more than 10-fold higher than that in high income countries estimated to be 0.015 e/cy. There is a very high prevalence of risk factors for severe disease in these settings including malnutrition and lack of breastfeeding, biomass exposure, HIV infection or exposure, poverty and poor living conditions. Early life pneumonia has also been associated with development of chronic lung disease into adulthood and substantial morbidity. Prevention of pneumonia may therefore be an important strategy not only to improve child survival but also to reduce the prevalence of chronic non-communicable lung diseases in children and adults, which also represent a substantial burden of disease in LMICs.

Advances in immunization against common pneumonia pathogens including measles, pertussis, *H. influenzae* type b (Hib) and pneumococcus [pneumococcal conjugate vaccines (PCV)] have resulted in important reductions in pneumonia-associated mortality, severity and incidence and have led to a changing spectrum of pneumonia from other pathogens. It is likely that even further reductions in pneumonia incidence, severity and mortality will occur in LMICs as uptake and accessibility to newer vaccines is strengthened.

Combined data from six studies of the effectiveness of HibCV in LMICs indicate a reduction of 18% in radiological pneumonia, of 6% in severe pneumonia and of 7% in pneumonia-associated mortality. For PCV, the estimated reduction was 29% in radiologically confirmed pneumonia, 11% in severe pneumonia and 18% in pneumonia-specific mortality. The effect of PCV has been especially prominent in children under 2 years of age with a more modest reduction in children aged 2 to 4 years. While PCV reduces severe invasive pneumococcal disease and bacteremia, prevention of non-bacteremic pneumococcal pneumonia is almost 20-fold greater compared to that of bacteremic pneumonia, due to the burden of disease. Further, the overall burden of disease prevented in HIV-infected children is much greater because of their susceptibility to severe disease. PCV has also led to a decline in hospitalization for adult pneumonia due to herd protection by reducing circulating pneumonia causing pneumococci serotypes. Widespread PCV immunization of infants has led to a dramatic decline in the rates of hospitalization for pneumonia in adults, especially the elderly. Replacement disease, with non-vaccine serotypes due to an increase in non-vaccine serotype disease requires ongoing surveillance as widespread coverage with PCV13 is attained in communities.

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

There has been a resurgence in pertussis pneumonia in children in high income countries, possibly due to waning pertussis immunity in pregnant women following acellular pertussis vaccination, with low antibody levels in babies. Babies are therefore susceptible to pertussis before completion of a primary vaccination series. This has not occurred in many LMICs where whole-cell pertussis vaccine is used. However, a rising incidence of pertussis in infants has been reported in South Africa where the acellular vaccine is used and where HIV infection increases susceptibility to disease; amongst children in the Drakenstein Child Health study, 3% of pneumonia cases were due to pertussis, while in another study in Cape Town, around 5% of children hospitalized with pneumonia had pertussis.

However, even in LMICs with high coverage for the 13-valent PCV, Hib and pertussis, the incidence of pneumonia remains high especially in the first 6 months of life. With high coverage for conjugate vaccines including PCV, the importance of vaccine-targeted pathogens can be anticipated to diminish while viruses and other bacteria, such as *S. aureus* are emerging as prominent causes of childhood pneumonia. In areas of high TB prevalence, *M. tuberculosis* has been reported to be associated with acute pneumonia in children, with culture confirmed
disease occurring in approximately 7–8% of cases. The role of mixed infections is increasingly being appreciated, associated with severe disease. RSV has been identified as a predominant pathogen particularly in the first few months of life in LMIC and high-income countries.

Immunization of pregnant women to protect against pneumonia in the first 3 months of life is gaining prominence as a potential effective strategy for pathogens such as pertussis, influenza and RSV. A randomized controlled trial of influenza immunization of pregnant women reported a vaccine efficacy of approximately 50% amongst immunized women and similar reductions in infants under 6 months of age for influenza proven infection. Recognition of the importance of RSV as an acute cause of morbidity and mortality has led to a surge in RSV vaccine and monoclonal antibody development, with several candidates currently being evaluated in clinical trials. These include RSV fusion (F) glycoprotein subunit vaccines for maternal immunization, live-attenuated RSV and adenovirus-vectorized RSV for infant immunization, and RSV F monoclonal antibody with extended half-life for neonatal or seasonal infant immunization.

References

#10 Impact of Early Lower Respiratory Tract Illnesses on Later Outcomes

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Sixty-five years ago, Oswald and coworkers made a seminal observation: subjects who were followed at the Brompton and other hospitals in London for debilitating chronic bronchitis were much more likely to recall having had prolonged school absenteeism, bronchitis and pneumonia as children than controls. Thirty-five years later, Benjamin Burrows, who founded the Center that I now direct and was a pioneer in respiratory epidemiology, refined and extended this finding: he and his coworkers reported that adults who recalled having had “childhood respiratory troubles” and smoked were more likely to have airflow limitation, assessed by spirometry, than smokers who did not recall such troubles. They noted that, although preferential recall could have biased their results, an alternative explanation might be that repeated respiratory infections during the growing years could predispose for the deleterious effects of smoking.

For the last thirty years, many birth cohorts have assessed the association between lower respiratory tract illnesses (LRTI) in early life and subsequent airway disease and lung function. Almost invariably, these longitudinal studies have found that children who have LRTI are at increased risk of having subsequent asthma and evidence of airflow limitation. In our own Tucson Children Respiratory Study, we initially reported that LRTIs occurring in the first 3 years of life increased the risk of having recurrent wheezing at the age of 6 years, but that the risk decreased with age and was absent after age 11. More recently, however, we reported that adults who smoked and had LRTI caused by the respiratory syncytial virus (RSV) in early life were more likely to have a diagnosis of asthma than those non-smokers who did not have a history of RSV-LRTI. However, those who had only one of these risk factors were as likely to have asthma as the no-RSV-non-smoking group. These results suggested that the risk for asthma associated with RSV-LRI “reappeared” in adult smokers, and two explanations are possible: either persons who have RSV-LRIs have a genetic/congenital predisposition that predisposes them for both RSV-LRTI and subsequent susceptibility to smoking; or RSV-LRTI somehow injures the Airways and/or conditions immune responses in a way that increases the likelihood of asthma-like symptoms in smokers.

As is often the case in biology, these two potential mechanisms may be at work in the population. Genome-wide association studies (GWAS)
performed in mice suggest an important genetic component to disease susceptibility associated with RSV\textsuperscript{6}, but unfortunately, there are no unbiased studies available that would support a similar conclusion in humans\textsuperscript{7}. However, Caliskan et al.\textsuperscript{8} confirmed that children who carried risk alleles at the 17q locus identified in GWAS of asthma were indeed at increased risk for the disease, but only if they had rhinovirus (RV) wheezing illnesses in the first 3 years of life. It is thus plausible to surmise that the asthma-LRTI connection is in part mediated by shared genetic predisposition.

GWAS studies are allowing a better understanding of the biological mechanisms that explain the interaction between 17q genes and RV-LRTI as determinants of asthma. A recent, very large GWAS of asthma showed that there are two separate loci associated with asthma in the 17q region: one close to the PGAP3/ERBB2 genes and a second one 3' from the first site and adjacent to the GSDMB/ORLMD3 genes\textsuperscript{9}. Since the later was more strongly associated with childhood asthma and increased expression of GSDMB/ORLMD3 in peripheral blood mononuclear cells after stimulation with RV\textsuperscript{9}, the results suggest that these two genes are somehow involved the LRTI-asthma interaction. A recent review has stressed the complexities of the possible genes gene-LRTI interactions that may influence asthma in the 17q region\textsuperscript{10}.

In support of a direct, injurious effect of the LRTI, a report based on the Drakenstein Child Birth Study in South Africa showed that, as compared with controls, children who developed an LRTI in the first year of life showed subsequent deterioration in parameters of airway function. To shed light on this issue, we studied immune responses in cells obtained by induced sputum during the exacerbation of chronic airflow obstruction. These findings are in concordance with previous reports showing decreased interferon type I and III responses to rhinovirus infection in epithelial cells obtained from adults with severe asthma\textsuperscript{13,14}. Taken together, these data provide strong support to the hypothesis that LRTI in infancy and early childhood are an important player among the factors that increase susceptibility to asthma and chronic obstructive pulmonary disease in adult life. Prevention of LRTI during the growing years, especially among subjects predisposed to the ill effects of these illnesses, could be a powerful strategy to improve respiratory throughout the life course.

References

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ABSTRACT

A. PEARLS

#1 Contribution of Large Animal Models to Pediatric Respiratory Medicine

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Introduction

Rodents are by far the most popular animal models of human diseases, including for pediatric respiratory medicine; one of the best examples is asthma. Rodents have several obvious advantages, including their small size and cost, short gestation and high number of littermates. Also, the number of diseases addressed by genetically-modified mice is unequalled in other species. There is an increasing awareness however that large animal models are physiologically closer to humans. For instance, the lung development of large animals such as the sheep and monkey corresponds to that of the human newborn at birth. This is different from the mouse or rat, whose lung is at the saccular stage of development. In addition, the size of large animals at birth allows to mimic the clinical conditions more closely and to perform more extensive physiological recording and tissue sampling than in rodents. Finally, the fetal lamb has been extensively used for chronic studies of fetal respiratory physiology in utero.

This short abstract summarizes a few contributions of large animal models to pediatric respiratory medicine.

Cystic fibrosis

In addition to murine models of cystic fibrosis (CF), a CFTR −/− piglet model has been designed a few years ago. The CF piglet airways lack normal CFTR protein and exhibit defective chloride and bicarbonate transport. Unlike mouse models, CF piglets develop lung disease like humans with CF (1). Experiments in CF piglets has allowed to challenge the dogma that the CF lung is normal at birth and that airway obstruction and air trapping is consequent to infection, mucus plugging or inflammation. Studies have indeed shown that on the day of birth, CF piglets already exhibit a decreased lumen size of proximal airways with airway obstruction and air trapping. The presence of such anomalies before any infection or inflammation suggests that CF is responsible for congenital airway anomalies (2). In addition, a sheep model of CF is being developed.

Acute viral bronchiolitis of infancy

Acute viral bronchiolitis of infancy, especially due to respiratory syncytial virus (RSV), continues to pose a great challenge worldwide, due to its very high incidence and severe forms, especially in preterm infants. While passive immunization can be given in specific conditions such as preterm newborns with bronchopulmonary dysplasia, no vaccine is yet available, and treatment is only supportive. Among the large animal models which have been used since many years, non-human primates and both the full-term and preterm lamb have yielded interesting results. However, all animals tested to date are only semi-permissive for human RSV replication and experimental infection with even large doses of virus results in little or no clinical signs of disease, and generally only mild pulmonary pathology (3). While they have been used to design and test candidate vaccines, they have not yet been responsible for any breakthrough with regard to anti-RSV vaccination. Overall, we unfortunately still lack a good animal model of acute viral bronchiolitis.

Bronchopulmonary dysplasia

Rodent models of bronchopulmonary dysplasia (BPD) have been studied for a long time. Meanwhile, the preterm lamb model has also been used for many years as a model of respiratory distress syndrome, including for prenatal prevention with betamethasone, for postnatal surfactant treatment and for mechanical ventilatory support. More recently, the preterm baboon and lamb have been used as animal models of BPD. Compared to rodent BPD models, they present distinct advantages. As already alluded to, their lung development at birth (= beginning of the alveolar stage at term) is identical to that of the human newborn. In addition, the preterm baboon and lamb have a similar respiratory distress than humans and need ventilatory support for days or weeks with oxygen-rich gas. To our knowledge, only the preterm lamb model is still active. Studies on the preterm lamb model of BPD have yielded important results, including the beneficial effects on alveolarization of vitamin A supplementation or non-invasive high frequency oscillatory ventilation (4).

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia is a rare congenital malformation which occurs in about 1/3300 live births. It is still responsible for mortality in about 20% of the infants due to a significant lung hypoplasia and vasculature maldevelopment. The lamb model with a surgically-induced diaphragmatic hernia in utero has led the field since many years. One especially important contribution of this model is the
FETO procedure (fetal endotracheal occlusion) which was designed and shown to promote pulmonary development in fetal lambs in utero. The FETO procedure is currently used in clinical trials involving several centers worldwide for the most severe forms of congenital diaphragmatic hernia (e.g., clinical trials NCT03138863, NCT00881660 and NCT02986087; https://totaltrial.eu) (5,6).

Non-invasive ventilation in newborns

Apart from two studies in newborn baboons and piglets, studies on the use of nRS have essentially been conducted in newborn lambs (see review in 7). Studies have shown that the early use of noninvasive respiratory support is generally associated with better respiratory outcomes in preterm lambs. Lambs with a more severe form of respiratory distress syndrome however showed a progressive deterioration while on bubble-CPAP.

We have been studying nRS in full-term and preterm lambs for more than 10 years. The various nRS modes we have studied include nasal CPAP (nCPAP), high-flow nasal cannula (HF), nasal intermittent positive pressure ventilation and nasal high frequency oscillatory ventilation. The nasal mask that we use has been specifically designed and molded for newborn lambs and allows the introduction of naso-esophageal catheters. Polysomnographic studies in lambs on any of the above nRS can be performed for several hours, including during the different states of alertness. In addition, lambs can readily bottle feed while on nCPAP or HF (8).

Our research program on nRS is mainly focused on two aims. First, we aim to better understand laryngeal behavior during nRS. We have shown that the larynx can actively close against ventilator insufflations during certain ventilatory modes (i.e., pressure support). On the contrary, the larynx does not close with nCPAP or HF, as well as during nasal high frequency oscillatory ventilation or nasal NAVA (neurally adjusted ventilatory assistance). These results can help individualize the type of nRS in a given patient. Secondly, we are interested by the interplay between nRS and aerodigestive problems, especially in newborns and infants. For this purpose, we have established the only neonatal animal model for studying gastroesophageal reflux disease. We have shown that nasal positive pressure ventilation, including CPAP, intermittent positive pressure ventilation and high frequency oscillatory ventilation, can efficiently inhibit gastrointestinal reflux (9). In addition, we have shown that nasal CPAP (but not HF), increases the rate of milk intake during bottle-feeding in preterm lambs, without inducing any cardiopulmonary events (10). Again, we believe these results can contribute to the ongoing heated debate on the relevance of bottle-feeding convalescing BPD infants still on nRS.

Conclusion

The contribution of large animal models to pediatric respiratory medicine has been and remains very important, especially in neonatology. Despite the cost and difficulty of maintaining such research, we hope that the above short summary brings convincing evidence that the responsible use of large animals in research can uniquely lead to a better understanding and treatment of pediatric respiratory diseases.

REFERENCES


#2 Microbiome – Does It Matter?

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The human microbiota is the aggregate of more than 10,000 species of micro-organisms (bacteria, viruses, archaea and fungi) that reside on or
within human tissue and fluids. There are estimated to be a ratio of 3:1 in terms of number of bacterial cells versus human cells in the body [100 trillion bacterial cells and 37 trillion cells respectively]. This vast amount of genetic material is strongly inferred to have a crucial role in human health and disease. The collective genomes of these microorganisms are referred to as the microbiome. Over the past two decades, molecular techniques, including those targeting the variable regions of the bacterial 16S ribosomal RNA (16S rRNA) gene, next generation sequencing and metagenomic analyses, have changed our understanding of the human microbiome, including the respiratory microbiome, in health and disease. At each body habitat, the microbiome is believed to have complex relationships both in the dynamics of its core and satellite organisms, and with its host, where it has potential interactions with the developing immune system and regulation of inflammatory responses [1].

In health, the microbiome has the potential to increase energy extracted from food, alter appetite signaling, provide a barrier against foreign pathogens and is essential in the development of the intestinal mucosa and the immune system. Dysbiosis of the microbiota has been associated with the development of infections (e.g. vaginosis and intestinal infection with *Clostridium difficile*), liver disease, gastrointestinal malignancy (gastric cancer), autoimmune disorders and metabolic disorders (obesity and type-2 diabetes). Perhaps the best studied is the gastrointestinal tract where the microbiome is altered in disease states compared with health, in 1 of 4 general ways [2]:

1. Dominance by pathogenic bacteria – it is in these conditions that there may be a causal relationship between the microbiome composition and disease, a possible example being colorectal cancer, although there is little evidence as of yet.
2. Depletion of health-associated bacteria – it is in these conditions that probiotics may be useful (that is, in order to replace the bacteria that are lost), for example, inflammatory bowel disease.
3. Broad restructuring of the microbial community, e.g. diarrheal illnesses
4. Disrupted homeostasis effected via the microbiota-gut-brain axis (this appears, for example, to be involved in the development of Parkinson’s disease). (http://www.nature.com/collections/dyhbnqhpzv)

Large scale multi’omics studies are underway (https://www.hmpdacc.org/ihmp/) to identify causal mechanisms and pathways in many of these areas, including how changes in the microbiome through pregnancy influence the establishment of the nascent microbiome in neonates and impact on premature birth, how changes in the gut microbiome in children and adults might be causal in inflammatory bowel disease, and the biological processes that occur in the microbiome and that may be linked to the subsequent development of type 2 D diabetes. For the gut at least, the microbiome clearly matters as restorative treatment targeting the microbiota has been shown to be effective in several recent studies. For example, probiotics restored patients with influenza to health more quickly; fecal microbiota transplantation (transposition) was more effective than antibiotics for treating infection with *Clostridium difficile* and probiotics also decreased the severity of liver disease and need for hospitalization in patients with cirrhosis.

The microbiota of the respiratory tract occupies several niche communities throughout the lung. Less is known of the respiratory microbiome than that of the gut, and certainly, in children at least, most studies have investigated the upper respiratory tract only. The microbiota likely serves as a defense against respiratory pathogens and data from animal models also suggest it has a role in lung maturation and in the development of mucosal immunity. For example, *Prevotella* spp. in mouse models decreases lung inflammation, neutrophil recruitment and pro-inflammatory cytokines. In germ-free mice, an increase in pro-inflammatory natural killer T cells was observed. However, this association was abrogated by transplantation of the microbiota from normal neonatal (but not adult) mice [3].

Recent data highlight a potential causal role of the microbiome in the development of preschool asthma and other atopic diseases, while linking these alterations in the gut microbiota with Western-style diets. Although it is currently difficult to implicate the respiratory microbiota in disease progression in cystic fibrosis, there are emerging data to suggest that the microbiota is very different in this condition and that it is profoundly affected by treatment with antibiotics and also that the microbiota, when dominated by individual pathogens, is associated with pulmonary inflammation and to the pathogens identified by standard microbiological culture [4].

Microbiome research is progressing rapidly and increasingly studies in large longitudinal cohorts and using multi’omics approaches are being conducted. The microbiome appears to matter but in order to determine just how much, we will need to improve how we analyze such combined and complex datasets utilizing machine-learning algorithms, time-resolved data modeling and other novel analytical strategies.


#3 Antenatal and Postnatal Corticosteroids for Preterm Infants

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Antenatal Corticosteroids

Evidence from a recent Cochrane review supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. Treatment with antenatal corticosteroids (compared with placebo or no treatment) is associated with a reduction in the most serious adverse outcomes related to prematurity, including: perinatal death (average risk ratio (RR) 0.72, 95% confidence interval (CI) 0.58 to 0.89; participants = 6729); neonatal death (RR 0.69, 95% CI 0.59 to 0.81; participants = 7188); RDS (RR 0.66, 95% CI 0.56 to 0.77; participants = 7764); intraventricular hemorrhage (IVH) (RR 0.55, 95% CI 0.40 to 0.76; participants = 6093); necrotizing enterocolitis (RR 0.50, 95% CI 0.32 to 0.78; participants = 4702); need for mechanical ventilation (RR 0.68, 95% CI 0.56 to 0.84; participants = 1368); and systemic infections in the first 48 hours of life (RR 0.60, 95% CI 0.41 to 0.88; participants = 1753). There was no obvious benefit for chronic lung disease (RR 0.86, 95% CI 0.42 to 1.79; participants = 818).

These findings are also correct for infants on the border of viability. Among infants born from 23 to 34 weeks’ gestation, antenatal exposure to corticosteroids compared with no exposure was associated with lower mortality and morbidity at most gestations. The effect size of exposure to antenatal corticosteroids on mortality seems to be larger in infants born at the lowest gestations.

The evidence for use of antenatal steroids at or after 34 weeks is still debatable. A recent systematic review and meta-analysis evaluated the effectiveness of antenatal corticosteroids given at or after 34 weeks to reduce neonatal respiratory morbidity. Three trials included 3200 women at 34 weeks’ gestation and at risk of imminent premature delivery at the time of hospital admission. Three other trials included 2498 women undergoing planned cesarean delivery at ≥37 weeks. Overall, infants of mothers who received antenatal corticosteroids at ≥34 weeks had a significantly lower risk of RDS (relative risk 0.74, 95% confidence interval 0.61 to 0.91), transient tachypnea of the newborn (0.56, 0.37 to 0.86), and higher Apgar scores compared with controls. Infants of mothers who received antenatal betamethasone at 34 weeks’ gestation had a significantly lower incidence of transient tachypnea of the newborn (relative risk 0.72, 95% confidence interval 0.56 to 0.92), severe RDS (0.60, 0.33 to 0.94), and use of surfactant (0.61, 0.38 to 0.99). Infants of mothers who received antenatal betamethasone at 34 weeks’ gestation had a significantly lower risk for bronchopulmonary dysplasia and those who received placebo, but the advantage may have been gained at the expense of increased mortality. Recently, the long-term outcome of this study was published. Among surviving extremely preterm infants, the rate of neurodevelopmental disability at 2 years did not differ significantly between infants who received early inhaled budesonide for the prevention of bronchopulmonary dysplasia and those who received placebo, but the mortality rate was higher among those who received budesonide.

In a recent meta-analysis, Shinwell et al. 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, P = 0.03; 6 trials, n = 1285). BPD was significantly reduced (RR = 0.77, 95% CI 0.65 to 0.91, 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 postnatal corticosteroids

The use of early systemic steroids in extremely preterm infants is not recommended because they may compromise brain development. New modalities of corticosteroid administration that will not affect neurodevelopmental outcome were recently explored.

Baud et al. randomly assigned extremely premature infants to early (within 24 hours of age) hydrocortisone or to placebo. Of the 255 infants assigned to hydrocortisone, 153 (60%) survived without bronchopulmonary dysplasia, compared with 136 (51%) of 266 infants assigned to placebo (odds ratio [OR] adjusted for gestational age group and interim analyses 1.48, 95% CI 1.02–2.16, p = 0.04). The number of patients needed to treat to gain one bronchopulmonary dysplasia-free survival was 12 (95% CI 6–200). In an exploratory analysis of neurodevelopmental outcomes of this trial cohort, early low-dose hydrocortisone was associated with a statistically significant improvement in neurodevelopmental outcomes in infants born at 24 and 25 weeks of gestation. In contrast, no statistically significant difference between treatment groups was observed in infants born at 26–27 weeks (p = 0.95) with a similar risk of moderate-to-severe NDI of 9% in both groups.

In the Neurosis study, 863 infants (gestational age, 23 weeks – 27 weeks) were randomly assigned to early (within 12 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. 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. Recently, the long-term outcome of this study was published. Among surviving extremely preterm infants, the rate of neurodevelopmental disability at 2 years did not differ significantly between infants who received early inhaled budesonide for the prevention of bronchopulmonary dysplasia and those who received placebo, but the mortality rate was higher among those who received budesonide.

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morbidities or adverse events. The role of inhaled corticosteroids in established BPD in spontaneously breathing infants was studied by Kugelman et al. They administered the inhaled steroid hydrofluorokane-beclomethasone dipropionate (QVAR) that is unique in its small particle size that results 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.

A recent meta-analysis 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 a 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 report concluded that intra-tracheal administration of budesonide-surfactant combination was associated with decreased incidence of BPD alone or composite outcome of death or BPD in very low birthweight infants.

Doyle et al. found no reduction in the rate of bronchopulmonary dysplasia and an increased rate of obstructive lung disease in a cohort of infants born in 2005, as compared with a cohort born in 1997. There was a striking decrease in the rate of use of postnatal glucocorticoids between these two periods, from 46% in the 1997 cohort to 23% in the 2005 cohort. These differences among eras could explain the reported results. The study conducted by Doyle et al. may suggest that we should try to adopt postnatal glucocorticoids policies, such as inhaled glucocorticoids, low-dose hydrocortisone, or intra-tracheal glucocorticoids with surfactant, that do not harm neurodevelopmental outcome.

References:

B. ARE ASTHMA GUIDELINES PREVENTING PROGRESS

Pro/Con debate (underlined)

#1 PRO: Importance of Implementing Asthma Guidelines: An Evidence-Based Approach that Helps Ensure Consistent Management

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Background:
The usefulness of clinical guidelines for the diagnosis and management of asthma in children has recently been scrutinized. It is suggested that guidelines simply serve to add to confusion, are very restrictive, prevent the clinician from using clinical acumen when making therapeutic decisions, and most importantly, do not serve to improve asthma outcomes(1). Cause for concern is further enhanced because some countries, such as the UK, have national guidelines in addition to the available international guidelines, such as the Global Initiative for Asthma (GINA)(2). Moreover, there are currently two sets of national guidelines in the UK, the National Institute of Clinical Excellence (NICE) guidelines(3) and the British Thoracic Society (BTS/SIGN) guidelines(4), both of which have some marked differences in recommendations(5).
So, are asthma guidelines really necessary, or do they just muddy waters?
A guideline provides guidance: deviations in management for individuals are expected

It is important to remember that guidelines are simply that; they provide guidance and advice to clinicians about the approach to the diagnosis and management of a condition. They should be referred to when making decisions, but are not set in stone. Indeed, when adherence to asthma guidelines was assessed in the pediatric emergency department, it became apparent that more than 90% of healthcare professionals believed in their use for children with mild to moderate asthma, but this number reduced to less than 80% for severe asthma. The majority (99%) of healthcare professionals believed the advantages of guidelines for asthma management out-weighed the disadvantages, even though two-thirds admitted to deviating from guidelines(6). Therefore, although it may be much less useful to have guidelines for the small proportion of children with severe and problematic asthma, it is apparent that their utility for milder disease is beneficial.

Clinicians’ agreement with, and implementation of guidelines

A key point to consider in the importance and need for guidelines for asthma, is that asthma is a very common condition in children. It is therefore as frequently managed by primary and secondary care clinicians as by specialists in pediatric pulmonology. It would be unreasonable to expect non-specialists to remain up to date with the latest evidence for the diagnosis and management of a condition, hence guidelines are helpful in providing a summary framework for management of a common condition. However, when adherence to guidelines was assessed among asthma specialists and primary care physicians in the U.S. less than half of primary care physicians either agreed with or implemented the national guidelines associated with asthma assessment and treatment(7). Even though asthma specialists expressed stronger agreement and adherence to guidelines than primary care physicians, actual adherence for several core recommendations was low in both groups. Only 30% of asthma specialists and 16% of primary care physicians were administering an asthma action plan, spirometry was undertaken by 44% of specialists compared to only 10% of primary care physicians, and assessment of inhaler technique was undertaken by 40% of asthma specialists and 16% of primary care physicians(7). Therefore, although time and energy are spent in developing guidelines, clinicians need to be convinced of both the benefit of their implementation and to adhere to them. Although clinicians may agree with the need for guidelines, this does not necessarily equate to adherence and implementation(7). A potential way to achieve better adherence to guidelines is to provide financial incentives for physicians. A systematic review of the impact of financial incentives on the implementation of guidelines for asthma or diabetes, showed an increase in the provision of asthma self-management action plans from 4% to 88%, and fewer emergency department visits and hospitalizations(8). An alternative strategy is to implement quality improvement (QI) methods that produce sustainable changes in health care delivery. The American Academy of Pediatrics implemented a statewide project incorporating leadership teams which provided coaching for individual pediatric practices through 2 nested learning collaboratives(9). The key aim of the project was to improve care for children with asthma across multiple practice settings. Following the QI initiative, optimal asthma care improved from 42% to 81% and the proportion of patients rated by clinicians as having good asthma control rose from 59% to 74%. Thus practice change was achieved by statewide QI programs(9).

Similarities and differences between guidelines for asthma

Key issues that are pertinent to asthma and have been highlighted in both sets of national guidelines in the UK, include recent increasing concerns about both over and under diagnosis of asthma in children(5). Thus both sets of guidelines have addressed the importance of making an accurate diagnosis in some detail. This includes, where possible, performance of objective tests that may support a diagnosis, such as exhaled nitric oxide and spirometry. Both the BTS/SIGN and NICE guidelines also emphasize the need for all clinicians to encourage and support self-management of asthma. All children must be provided with a clear, written asthma management plan which includes advice on actions to take if asthma control deteriorates. Action plans should include advice on short-term increase (e.g., short-term quadrupling of dose) of inhaled corticosteroids, when to commence oral steroids, and when to seek emergency medical advice(10). There is now good evidence that confirms the use of supported, self-management for people with asthma (written action plans) can reduce unscheduled healthcare use and improve asthma control. Moreover, supported self-management can be delivered effectively for diverse demographic and cultural groups and does not increase total healthcare costs(10). Although the majority of the content relating to the management of asthma is very similar in guidelines currently available, some key differences do exist. These are mainly determined by the search strategies used to generate the evidence for the guidelines. For example, the strategy used for the BTS/SIGN guidance includes a critical appraisal of the literature, but also takes into account pragmatic studies to ensure that guidelines provide clinically relevant recommendations. In contrast, the NICE guidelines include health economic modeling in the literature appraisal(5). A very practical difference that has resulted from these two approaches is that the NICE guidelines for the management of pediatric asthma recommend adding a leukotriene receptor antagonist (LTRA) to low-dose inhaled corticosteroids, while the BTS guidelines suggest adding a long-acting beta agonist (LABA) to low-dose inhaled steroids as the second step in escalation of therapy when there is inadequate control with inhaled corticosteroids alone. Although the current literature suggests equivocal evidence for both approaches, the recommendation by NICE is driven by lower costs of LTRA, while the BTS guidelines are driven by the advantage of keeping a single inhaler and device to avoid confusion and help adherence. The different priority for each guideline therefore directs the final recommendation, but it is with such discrepancies that the clinician must remember these are merely guidelines, and the correct approach for an individual patient must be what is finally chosen.

Summary

Asthma is the commonest, chronic respiratory condition suffered by children in the Western world, and is therefore managed in all clinical settings ranging from primary care to specialist tertiary care. Guidelines are generated in order to ensure consistency is maintained in the
approach to the diagnosis and management of such a common, chronic disease. They should be regularly updated and take account of the evidence base, thus ensuring practice changes in line with emerging research findings. Even though most countries will have their own guidelines for asthma management, the overall content is broadly very similar, and small adjustments are made to account for features specific to that population. Not all children with asthma can be managed by specialist clinicians, and therefore in order to provide a basic level of acceptable care for each child, asthma guidelines are necessary, beneficial and important. Admittedly, their implementation is variable, but perhaps the way forward is to spend some time and resources in assuring clinicians adhere to, and implement guidelines, rather than generating more variations of the same guidelines. Finally, the single most important point that must not be forgotten; guidelines are generated for children with asthma as a group, they are not intended to be individualized, thus deviation when making management decisions for each patient is expected and is the norm.

References

#2 CON: Asthma Guidelines are Harmful to Asthma Care
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With many decades of research, we have now come to the understanding that asthma is a syndrome comprised of many different phenotypes and endotypes with different underlying pathophysiologies such that treatment has to be individualized in order to maximize the level of control in our asthmatic patients (1, 2). Airway hyperactivity was once believed to be a major component of asthma and the main state of treatment was the use of bronchodilators. With further understanding that underlying airway inflammation is the main component, asthma treatment has shifted from bronchodilation to anti-inflammation. Asthma guidelines were developed in different regions in order to help physicians around the world to diagnose and to provide the optimal treatment (3–5). It has been pivotal in improving asthma worldwide. However, they have major limitations in application in the real world. Firstly, recommendations from these guidelines are primarily derived from results of randomized control trials, once believed to be the good standard for assessing treatment (6). It is increasingly clear that the “ideal situation” of a RCT may not reflect patients’ behavior in the clinical setting. Secondly, the more recently conducted RCTs on asthma have confirmed that the majority of asthma patients exhibit differential responses to various treatments such that a simple guideline-dictated approach will not provide the best possible care for all patients (7). As the underlying airway inflammation varies from one patient to another, a standard approach to all patients will not be optimal. With the increasing availability of different biologics, it is even more important to characterize our patients and select the most appropriate care for the individual patients. I would argue for a patient-oriented care pathway rather than a guideline-based treatment strategy as the era of guideline should be history given what we know about the complexity of the asthma syndrome.

References:
Asthma is the most common chronic disease in children and a leading cause of childhood morbidity worldwide. WHO estimates that 300 million people currently suffer from asthma. The global burden of asthma is rising, particularly in children in low- and middle-income countries (LMICs), where infectious diseases and other priority illnesses often predominate. Sadly, decades of research on causal pathways have had limited impact on the development of effective prevention strategies. [1] Low accessibility to basic medications, weak healthcare services, poor compliance with prescribed therapy, lack of asthma education, and social and cultural factors have been proposed causes for the lack of control of the disease. [2]

Prevalence of Asthma in LMICs:

The results from the International Study of Asthma and Allergies in Childhood (ISSAC) phase III demonstrated a worldwide prevalence of asthma in children that varies from 1.6% to 36.8%. [3] In some countries the prevalence increased, in others it plateaued, whilst in others the numbers of affected children decreased. Overall, the last report showed that the prevalence of asthma in LMICs has increased, particularly in South America and some areas of Africa and Asia. But more interestingly, the severity of asthma was greater in lower income countries. [4] Like many chronic diseases, asthma likely results from complex gene-environment interactions. The diversity of genetic and environmental exposures between populations probably explains the heterogeneity in the prevalence, phenotypes, and severity of asthma around the world.

Risk factors and asthma in LMICs

Several studies within these regions have shown how risk factors described in developed countries also affect the underprivileged. Moreover, other factors related to poverty, high risk conduct exposures and urbanization may be determinant of the trends of increased asthma prevalence. In LMICs, those who spent a large part of their lives in an urban setting tended to have unhealthier lifestyles and therefore a high risk of chronic respiratory diseases compared with their less urbanized counterparts. In a recent ecological study in Ecuador, Rodriguez et al. [5] showed that the prevalence of asthma increases with increasing levels of urbanization (p = 0.006). Although this rural-urban gradient in asthma is poorly understood, it could be due to levels of outdoor and indoor pollution, microbial or parasitic infections, or changes in lifestyle (e.g. diet).

It has been estimated that children spend most of their time indoors. Thus, indoor air pollution may be relevant to the development of childhood asthma. Passive exposure to tobacco smoke (ETS) is considered the most important source. ETS prevalence in developing countries varies significantly from 10 to 60%. In most countries, active smoking is common and may be due to cultural factors, lack of regulation and poor law enforcement. Prenatal and postnatal exposures to cigarette smoking are associated with asthma and asthma morbidity in childhood. WHO estimates that more than 3 billion people rely on solid fuels as a source of energy. Coal and wood combustion indoors have been reported to increase the risk of upper and lower respiratory infections in infants and preschool children. But also, it is associated with increased asthma prevalence. A global analysis of ISAAC reported an association between open-fire cooking and asthma symptoms. [6]

Outdoor pollution from motor vehicles, very common in urban areas, is associated with persistent respiratory symptoms and higher prevalence of asthma. Recent findings suggest joint detrimental effects of vitamin D insufficiency and traffic-related air pollution on severe asthma exacerbations in Puerto Ricans. [7]

Exposure and sensitization to common allergens is one of the major triggers in sensitized individuals with asthma. Allergens originate from a wide range of dust mite allergens, animals, indoor fungi or mold and cockroaches. Exposure to these allergens have been associated with asthma symptoms, airway hyperresponsiveness and severe asthma exacerbations in several cross-sectional studies in LMICs. [8]

Lifestyle changes such as diet and obesity have been related with the increase of asthma prevalence worldwide. Vitamin D deficiency has been associated with asthma in several LMICs. A study in Costa Rica showed that low vitamin D levels were associated with increased odds of asthma-related ED visits or hospitalizations in the previous year. But also, it was the first epidemiological study demonstrating an
association between low vitamin D levels and increased serum IgE levels and eosinophil counts.[9] Other studies focused on diet patterns have shown that fast food or a “Western” dietary pattern is associated with higher risk of asthma and also asthma severity. Similarly, to high income countries, overweight and obesity in LMICs have been associated with asthma or asthma severity.

The role of guidelines in LMICs

In developing countries, chronic respiratory diseases represent a challenge to public health because of their prevalence, severity, projected trends, and economic impact. In addition, there is limited access to essential drugs and close follow-up. The financial burden for persons with asthma and their families, as well as for healthcare systems and governments, is very high. Global asthma guidelines have been an important advance in raising awareness of childhood asthma and improving diagnosis and management, particularly in LMICs. Practical guidelines addressing the management of asthma in children have pointed out various aspects important in the development of this condition: medication issues, the environment, asthma education, comorbidity, and psychological problems. To be effective, guidelines must be relevant to the specific population, must be culturally acceptable and must be adapted to each health system.

Therefore, asthma control is not obtained in most patients, despite available management guidelines and evidence of ICS as controllers. Several surveys performed in LMICs have shown that close to 2.4% of all patients met all the GINA criteria for total asthma control, proposing under-recognition of uncontrolled asthma, underuse of appropriate controller treatment, inadequate patient education, and patient denial as possible explanations.

Since the development of worldwide guidelines on the diagnosis and management of asthma, special attention on achieving and maintaining asthma control as the key goal in asthma treatment has been a priority. In clinical studies of children with asthma in LMICs, the most cost-effective intervention for asthma control is secondary prevention of symptoms and acute exacerbations through controller medications, such as inhaled corticosteroids for mild asthma, and associated with long-acting B2 agonist for moderate asthma. Comprehensive approaches are critical for asthma control. Unfortunately, there is limited information on the impact of population-based interventions for asthma control, but some studies from developed and developing countries indicate it is cost-effective. Public health efforts have improved management in some countries. In Brazil, an ecologic study showed that those municipalities that were offering free medication for asthma had 45% higher odds to decrease hospital admission rates from asthma and, in addition, tripled their chances of reducing death rates due to asthma. In a recent study in Costa Rica, marked decrement in hospitalizations (53%) and mortality (80%) was seen following a National Asthma Plan (NAP) and the use of beclomethasone as a preventive medication. This NAP consisted of education meetings at all major public health care centers, emphasizing early diagnosis, early treatment using ICS as first-line therapy for asthma control, early use of reliever medication to treat exacerbations, appropriate referral to specialists for asthma care, and avoidance of common allergen sources (e.g. dust-mite and cockroaches) or tobacco smoke.[10]

Obstacles to implementation of asthma guidelines include poor health system infrastructure, limited or no availability of effective asthma therapy, poor capacity to adapt and implement guidelines, lack of asthma education for health care professionals, cultural and language barriers and use of non-traditional medical personnel as health care providers. Some problems may be unique to particular countries, but most LMICs share barriers to asthma management. Thus, collaborative public health and research efforts could have a major impact at a regional level. Such efforts should include vigorous campaigns to control and eliminate tobacco use, asthma education and non-pharmacological interventions (e.g. replacing biomass fuels, reducing allergen exposure, psychological support and weight loss).

In summary, asthma prevalence in deprived regions is high and shows increased severity. Worldwide, but particularly in LMICs, both intrinsic (race, ethnicity, weight, genetic) and extrinsic (exposure to allergens, indoor or outdoor pollutants, diet) factors may overlap in a single child to enhance or diminish asthma control and severity. Reasons for inadequate asthma control in poor populations include low accessibility to effective controller medications, weak infrastructure of health services for the management of chronic disease, poor adherence to therapy, lack of educational approaches, persistent exposure to risk factors and social, cultural and language barriers. Nevertheless, there is abundant evidence that access to proper diagnosis and adequate treatment reduces symptoms, health resource utilization, improves quality of life, and avoids hospitalizations and deaths from asthma.

C. ADVANCES IN THE NICU/PICU

#1 Utility of High-flow Nasal Cannula Therapy in the NICU

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The use of high-flow nasal cannulae (HFNC) is an alternative means of providing noninvasive respiratory support to preterm infants. A review published five years ago concluded that there remains uncertainty about the efficacy and safety of HFNC in this population and until the results of larger randomized trials are known, widespread use of HFNC to treat preterm infants cannot be recommended.1 Since then, much progress has been made and there is growing evidence of the feasibility of HFNC in preterm infants.

High flows result in washout of anatomical and physiological dead space and contribute to improved fractional 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 nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV). The PEEP is not monitored during HFNC; this raised concerns regarding the safety of HFNC in terms of air leak.

HFNC cannulae deliver heated and humidified gas at flow rates of more than 1 liter per minute through small binasal prongs. Because HFNC has a simpler interface with the infant and smaller prongs than nasal CPAP, the cannulae are perceived as easier to use, more comfortable for the infant, and advantageous for mother–infant bonding. However, the efficacy of HFNC in different clinical conditions needs to be evaluated and compared to other forms of non-invasive ventilatory (NIV) support; NCPAP and NIPPV.

A Cochrane review2 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. However, most of the evidence is available for the use of HFNC as post-extubation support and in infants with a birth weight above 1000 g.

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).3

The international HIPSTER multicenter, randomized, noninferiority trial,4 recruited 564 preterm infants (gestational age ≥28 weeks 0 days) with early respiratory distress who had not received surfactant replacement and 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 [90% CI], 5.8 to 18.7; P < 0.001). Infants were allowed to be rescued by NCPAP in treatment failure. 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.

Yoder et al.5 conducted a large RCT on HFNC vs. NCPAP in infants between 28 and 42 weeks GA, either as primary therapy or following extubation. Despite the high number of infants enrolled, the heterogeneity in stages of respiratory failure and diagnoses and treatment (before and after extubation) of the study population may have limited the interpretation of the results.

Lavizzari et al.6, in a randomized clinical non-inferiority trial, assigned infants 29 weeks 0 days to 36 weeks 6 days of GA with mild to moderate RDS to either HFNC or NCPAP. A total of 316 infants were enrolled: 158 in the HFNC group (mean [SD] GA, 33.1 [1.9] weeks) and 158 in the NCPAP/BiPAP group (mean [SD] GA, 33.0 [2.1] weeks). The use of HFNC was non inferior to NCPAP with regard to the primary outcome: failure occurred in 10.8% vs. 9.5% of infants, respectively (p = 0.71). In this study surfactant was administered using the INSURE technique, and this may explain the difference from the HIPSTER trial.

A recent meta-analysis7 enrolling a total of 1061 infants, showed significantly reduced risk of meeting respiratory failure criteria (risk ratio [RR] 0.65, 95% confidence interval [90% 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 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. Thus, HFNC should also be compared to NIPPV as an initial mode of support.

Kugelman et al.8, in a controlled, prospective, single-center pilot study, randomized infants (gestational age [GA] <35 weeks, birth weight [BW] >1000g) to receive HFNC (38 infants) or NIPPV (38 infants). There was no significant difference in the need for endotracheal ventilation (28.9% vs. 34.2%) between HFNC and NIPPV groups. Duration of nasal support was longer with HFNC compared with NIPPV. The study suggested that HFNC may be as effective as NIPPV in preventing endotracheal ventilation in the primary treatment of RDS in premature infants (<35 weeks GA and BW >1000g).

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.9 Following extubation, HFNC is associated with less nasal trauma, and may be associated with reduced pneumothorax compared with NCPAP.
For post extubation, in very preterm infants, Manley et al. in a multicenter, randomized, non-inferiority 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 non-inferior 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.

Consensus agreement was reached for many aspects of HFNC including: need for adequate heating and humidification, need to prevent nares occlusion, maximum flow rate of 8 l/min, assessment of fraction of inspired oxygen (FiO2) and work of breathing for either flow escalation or weaning, equivalence of HFNC to nasal NCPAP for noninvasive support of infants of ≥28 weeks with resolving respiratory distress and use of HFNC for noninvasive support of stable infants on NCPAP. There was general agreement for initial gas flow rates in the range of 4 to 6 l/min and for HFNC as primary therapy for mild respiratory distress.

To summarize, NCPAP is still the most common mode of non-invasive respiratory support worldwide. The available evidence supports the use of HFNC as initial therapy for mild RDS or post extubation for infants >1000 g. In infants < 1000 g, NCPAP or NIPPV appears to be more beneficial due to a better support for functional residual capacity. More studies are needed in these infants, especially for the initial therapy.

References

#2 NIV in Developing Countries: Is It Feasible?

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Introduction

Mechanical ventilation is one of the major therapies in pediatric intensive care units. It is usually delivered through an endotracheal tube and occasionally tracheostomy tube: this “invasive” ventilation is associated with complications including mechanical obstruction and infections, along with airway complications. It also requires infrastructure including equipments, training, and meticulous nursing care. Over past few years, non-invasive ventilation is getting more popular across the ICUs as well as for long-term ventilatory support at home (1).

Non-invasive ventilation (NIV) consists of ventilator support without endotracheal intubation. It provides support with an interface. Based on the interface being used, NIV may be delivered by using nasal prongs, nasal or face mask or a helmet (2).

High flow nasal cannula (HFNC) oxygen therapy is one of most commonly used form of NIV in all infants and children. It improves gas exchange by multiple mechanisms including: better tolerance by patients as it allows patients to clear airways by active participation, prevents drying of airways as it provides heated humidified air, provides high FiO2 up to 100% as body parts act as a reservoir, minimizes dead space due to high flow of oxygen and it provides positive airway pressure. It decreases claustrophobic sensation. HFNC is being used as an alternative to mechanical ventilation in neonatal respiratory distress syndrome and apnea, impending respiratory failure in children and adolescents, during weaning (post extubation respiratory distress), post surgical care, and in patients where intubation is avoided. Equipment for providing HFNC consists of different sizes of nasal cannulae, blender, humidifier and inline oxygen analyzer. The equipment is relatively less expensive and can be used easily after training residents/ nursing staff. The important part of training includes not only about providing respiratory support but to identify failure of improvement and need for intubation without delay (3).
By using a nasal or face mask as interface may be able to provide continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP). CPAP improves ventilation, and decreases work of breathing. However, it may increase the possibility of aspiration. BiPAP resembles the pressure support mode used in conventional ventilation. It permits setting of inspiratory and expiratory positive pressure. This mode may help in ventilation of neuromuscular illnesses, obesity hypoventilation syndrome and acute respiratory failure.

**Indications for NIV**

NIV is indicated in acute respiratory failure caused by asthma, acute bronchiolitis or pneumonia. It is indicated in children with obstructive sleep apnea, congenital central hypoventilation, chronic respiratory failure in conditions such as cystic fibrosis and in children having poor systolic ventricular function after cardiac surgery (4).

NIV is not suitable for infants and children with severe hemodynamic instability, high risk of aspiration, or need for high positive end expiratory pressure (PEEP). NIV should be avoided in children with recent cardiorespiratory arrest, shock, multi-organ dysfunction, and severe neurological dysfunction (5).

**Feasibility of NIV in developing countries**

We will discuss feasibility of NIV in developing countries under the following headings: indications, infrastructure (equipment, trained manpower), advantages and risks.

**Indications**

NIV is commonly used successfully in children with acute respiratory failure due to pneumonia, bronchiolitis, etc. These conditions are common in developing countries and are the major cause of mortality in under-five year olds. There is a high burden of severe disease requiring hospitalization and a sizeable number would need respiratory support. In addition, children with other conditions that are common in developing countries such as severe dengue, malaria, may also need respiratory support. The recent guidelines for pediatric acute respiratory distress syndrome (PARDS) also recommend the use of NIV for mild PARDS (6). Use of NIV reduces complications due to intubation; thus we may conclude that there are sufficient indications for NIV in developing countries.

**Infrastructure (equipment and trained manpower)**

Equipment for HFNC, CPAP and BiPAP are relatively less expensive and available or can be made available in pediatric intensive care units/pediatric wards. A properly fitting interface in the form of nasal or face mask may be a problem. Indigenously-made CPAP equipment and bubble CPAP have been used successfully in Indian ICUs. Kinikar et al. (7) used an indigenously-assembled Nasal Bubble CPAP (NB-CPAP) in 60 children (median age 18 months) with acute hypoxemic respiratory failure during the H1N1 pandemic. The equipment provided an expiratory positive airway pressure of 5 cm water and delivered FiO₂ of about 70%. All patients tolerated CPAP and none required endotracheal intubation.

Anitha et al. (8) used a modified system of Mapleson D or F circuits and face mask as interface. They treated 214 children with CPAP through a flow inflating device successfully in 89.7% of cases. The most successful outcome was observed in infants with acute bronchiolitis. Children with pneumonia required longer duration of CPAP. CPAP failed in 10.3% of cases and reasons for failure were: children <1 year and pneumonia with septic shock (8).

A recently published systematic review has evaluated the effects of NIV for acute respiratory failure (ARF) in low- and low-middle income countries (9). The authors included 10 pediatric studies with 1099 subjects. The primary diagnoses in the pediatric studies were pneumonia, malaria, and dengue shock syndrome. The median age was 9.0 months (IQR 2.6–27.6) and 34.2% were female. The most common modes used were ventilator CPAP and Bubble CPAP. In these children, the pooled risks for mortality were 9.5% (95%CI 4.6–14.5), NIV failure 10.5% (4.6–16.5), and for endotracheal intubation 5.3% (0.8–9.7). The authors attributed a lower pooled intubation rate relative to NIV failure rate to the following reasons: patients with NIV failure receiving a trial of high flow oxygen prior to intubation, transfer of patients who failed NIV to another facility, and death while on NIV (9).

Training of health care personnel is equally important for successful outcome of NIV in intensive care. Health care personnel are relatively better trained in conventional ventilation and they need training in early identification of failure of NIV. Training should be feasible.

**Advantages**

The major advantage of NIV includes avoidance of intubation. Intubation may be associated with increased risk of ventilator-associated infections, specifically ventilator-associated pneumonia (VAP). The rate of VAP is between 20 and 30% in developing countries. Use of NIV is expected to reduce the incidence of VAP (10).

**Risks**

NIV may be associated with a false sense of security and may delay intubation. A proper training of health care personnel may reduce this risk. As mentioned above, the meta-analysis suggests a risk of NIV failure in about 10% (9). In this study, in 5 pediatric studies, the pooled risk of facial skin sores was 2.4% (95%CI 0.8–3.9) and that of pneumothorax was 1.9% (0.1–3.9).

We conclude that NIV is feasible in developing countries and may be associated with major advantages.

**References**


#3 Advances in Non-invasive Respiratory Support in the ICU.

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The first report about using non-invasive ventilation (NIV) support in a PICU was published more than 20 years ago. Since then, several advances have been observed in this field, especially in the last five years. This is a review of what has changed during these years.

When teaching NIV in the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) courses, we are using the acronym ICEMAN to help attendees follow a proper pathway. We will review the advances in the field using this acronym.

IC stands for Indications and Contraindications:

Indications have grown despite the low level of evidence available: post-extubation respiratory failure, bronchiolitis, pneumonia, upper airway obstruction, acute chest syndrome and asthma. At the moment there is no study reporting mortality associated with NIV use in Pediatrics in spite of its generalized use. CPAP has already shown its superiority to low-flow oxygen by reducing mortality in pneumonia patients in Bangladesh. CPAP has also been shown to be superior to high-flow nasal cannulae (HFNC) in moderate/severe bronchiolitis.

Some Contraindications have disappeared such as being younger than six months; others have been better defined such as moderate/severe ARDS with P/F ratio below 150.

Children and mainly small infants and neonates are the patients demanding cutting-edge technology because of their high respiratory rates and short inspiratory times; additionally, synchrony issues are challenging in a scenario where leaks are common. Thus, advances in NIV technology are probably the most relevant ones.

E stands for Equipment:

Surprising developments in interfaces, ventilators and modes have occurred. Nowadays, interfaces such as the helmet and total face mask (TFM) are available in different pediatric sizes. Some RCTs and large observational studies suggest these interfaces are more efficient and comfortable in the acute setting. The TFM interface was introduced in our center five years ago for the management of respiratory failure in patients diagnosed with bronchiolitis. From 2010 to 2016, the intubation rate has diminished from 40 to 20%, and the use of TFM was the only independent predictive factor identified in preventing intubation.

Both compressor-based conventional ventilators and turbine-based NIV-specific ventilators have improved their capabilities to detect the inspiratory efforts of infants and neonates and to compensate leaks, so the patient’s median age or weight is progressively being reduced in cohort studies. Nowadays, some transport and ICU ventilators are turbine-based and theoretically perform better than NIV. Home ventilators are used in the PICU setting in some European countries (8.5% in a recently accepted paper). Its reduced cost is making the technique more available to children. Nevertheless, a recent ongoing bench study shows important differences in pressurization capabilities compared to Hospital NIV-specific ventilators. Cautious use should be recommended for children younger than one year.

M stands for Modes:

The S/T and Pressure support modes are still the most popular modes. Improvements in the S/T mode trigger sensitivity (Autotrack plus®) have been added but unfortunately, there are no data published confirming its advantages. Unpublished data from my Unit (n = 22) showed a 95% success rate in bronchiolitis patients with an average age of 44 days. NIV NAVA®, a mode with a neural trigger only available in one conventional ventilator, has shown promising results with improvements in synchrony, albeit anecdotal. As neonates and infants younger than three months are those who commonly suffer asynchrony, this, in my opinion, the population expected to benefit most from this mode.

Volume-targeted modes like AVAPS, i-VAPS available in hospital and home NIV ventilators are not approved for use in children weighing less than 30 kg. It seems that this technological advance is not going to be beneficial for children in the acute setting unless refined algorithms for smaller patients are developed in the future.

Regarding the A, Analysis of failure:

Non-invasive oxygen monitoring with SpO2/FIO2 (S/F) ratio is becoming more popular, after its early predictive value for NIV failure at 1 and 6 hours was confirmed. Moving away from a traditional blood-
gases paradigm to monitor awake patients with spontaneous breathing receiving NIV is a significant advance.

Cohort studies with multivariate analysis have identified variables indirectly measuring the work of breathing such as heart rate (HR) and respiratory rate (RR) at 2 hours or maximum pressure setting as predictors of NIV failure.

N stands for Next steps:

There is no available research trying to pinpoint when to stop or how to wean patients from NIV. Future research in this aspect is necessary to make advances.

In conclusion, several advances related to the use of NIV in Pediatrics have been reviewed in most of the relevant aspects of the technique, including the improvement of the ESPNIC blended courses using the acronym ICEMAN.


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D. PULMONARY FUNCTION AND EXERCISE TESTING

#1 Utility of Exercise Testing in CF and Suppurative Lung Disease

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Cystic Fibrosis (CF) and other suppurative lung diseases share characteristics that can negatively affect exercise capacity. These diseases result in airflow limitation and dynamic hyperinflation, limiting ventilatory capacity, and the associated chronic inflammation can result in malnutrition and reduced muscle mass, and decreased skeletal muscle function. Dyspnea from chronic lung disease results in decreased physical activity, further contributing to exercise limitation. Formal exercise testing can be used to assess symptoms related to exercise, exercise capacity and responses to exercise, response to intervention, and prognosis of underlying disease (1). With respect to CF, older literature demonstrated that exercise capacity was an independent prognostic factor (2,3). More recently, an international consortium has confirmed that exercise is an important prognostic factor for CF. Exercise capacity is also an important predictor of short-term survival following lung transplantation, and can be used to evaluate readiness for transplantation (4).

The factors contributing to exercise limitation are sometimes amenable to treatment. Changes in these parameters may then be reflected in exercise ability and the responses to exercise. Exercise capacity is a reflection of structural lung damage (5). Further, a combination of lung function and peripheral skeletal muscle function (maximal force or short-term work capacity) explain most of the variability in exercise ability in both health and disease (6,7). Thus factors that alter lung or muscle function can alter exercise capacity. As muscle mass is the main determinant of muscle function, and patients with suppurative disease have many metabolically active inflammatory cells in their submucosa and airway, produce a lot of mucus, a glycoprotein, patients with suppurative lung disease have increased caloric and protein requirements.

The gold standard for exercise testing is a progressive exercise test using a modified Godfrey protocol on a cycle ergometer while measuring gas exchange (8). A Godfrey protocol increases the
workload every minute in a stepwise fashion, with the size of the increments selected make that the test is completed in 8–12 minutes. These tests can be used to evaluate maximal capacity and responses and delineate the causes of exercise limitation. They can be used to also evaluate the response to intervention such as nutritional supplementation or exercise training.

A brief primer on exercise responses (the reader is referred to Clinical Exercise Testing 4th ed by NL Jones, Published by Saunders, 1997 for a more comprehensive review). At maximal exercise, the respiratory rate in late adolescence and adults is about 40 breaths per minute. Considering the duty cycle (inspiratory time plus expiratory time), meaning that at a respiratory rate of 40, the duty cycle is 1.5 seconds, it is not surprising that the FEV₁ (Forced expiratory volume in 1-second), or the amount of gas that can be maximally exhaled in 1-second, is a major determinant of exercise ability, typically explaining about a third of the variability in maximal exercise ability. During progressive exercise, minute ventilation (the product of respiratory rate and tidal volume) increases. Respiratory rate increases almost linearly, while tidal volume increases in an asymptotic manner, such that early on, tidal volume contributes more than respiratory rate to minute ventilation, but later on, especially in the second half of an exercise test, respiratory rate contributes more. Minute ventilation increases to match the carbon dioxide being delivered to the lungs. At a certain point, minute ventilation and alveolar ventilation increase disproportionately to the delivered carbon dioxide, resulting in a decrease in arterial carbon dioxide, in other words, the exercising individual begins to hyperventilate. With exercise, both the tidal volume and dead space volume increase, but alveolar volume is recruited proportionately more, such that the ratio of dead space to tidal volume normally falls from 33% to less than 20%, under normal conditions. Tidal volumes are normally recruited from both the inspiratory and expiratory reserve volumes, such that the end-expiratory lung volume is reduced compared to resting conditions. Typically, individuals breathe within the confines of their flow-volume loops. Patients with suppurative disease typically have expiratory flow limitation, meaning that flow is reduced on exhalation. At higher respiratory rates, there is not time to exhale all the inhaled gas, and this results in air trapping, so-called dynamic hyperinflation (9). It must be realized that total lung capacity does not change with exercise, so that dynamic hyperinflation means that there is less lung volume to draw from. Further, although the individual who has dynamic hyperinflation can profit from the decreased resistance at high lung volumes to be able to take larger breaths, this comes at the cost of increased elastic work of breathing.

Cardiac output, the product of stroke volume and heart rate, is there to meet the oxygen delivery needs of the exercising muscle and can largely meet these needs (10). Like tidal volume, stroke volume increases in an asymptotic fashion during progressive exercise, while heart rate increases in a linear fashion. Early on in progressive exercise, stroke volume contributes more than heart rate to cardiac output, but there is a progressively larger contribution from heart rate as work loads increase. With endurance or aerobic training, resting heart rate is decreased, the rate of rise of heart rate with exercise and the maximal heart rate is lower, and there is an increase in stroke volume, without a change in cardiac output for work performed. Ventricular dysfunction has been observed in patients with CF and chronic bronchiectasis (11), but there can be a contribution from increased dead space breathing, leading to wider pleural pressure swings, and hypoxia leading to pulmonary hypertension (12).

Another factor influencing exercise capacity in suppurative lung disease is deconditioning brought on by physical inactivity. While overall activity levels in CF patients appears normal, the amount of time spent in moderate to vigorous activity, which contributes to fitness, is reduced (13).

In summary, exercise testing provides an integrated view of the individual and the synergy between cardiopulmonary function and peripheral muscle function. Exercise testing can be used to assess symptoms, exercise tolerance, and the contributing factors. Patients with suppurative lung disease typically have obstructive lung disease and nutritional deficiencies. These can contribute to pulmonary and peripheral muscle limitations, and in more advanced disease, cardiovascular limitations. These limitations are compounded by decreased habitual physical activity, placing further limitations on exercise capacity.

Exercise-induced breathlessness is a common finding in children with asthma; however not all symptoms during exercise are due to asthma and other causes must be considered, particularly when symptoms only occur with exercise. Children and young people who present with exercise-induced breathlessness are frequently started on asthma treatment. When the symptoms are refractory to treatment, rather than revisiting the diagnosis, treatment is simply escalated, affording no relief to the patient and instead exposing them to the side effects of inhaled, and in some cases oral, corticosteroids.

Exercise-induced laryngeal obstruction (EILO) is an important differential diagnosis. This describes a condition where there is narrowing of the larynx during maximal exercise, leading to breathlessness and inspiratory wheeze, or stridor. This can include vocal cord dysfunction (glottic EILO) but more commonly laryngeal narrowing occurs as a result of closure of the supraglottic structures. The larynx is usually wide open during exercise to allow for maximal airflow. It is not fully understood why narrowing occurs in some individuals. The larynx is highly innervated and has many important functions, including phonation; however its most important role is to protect the airway and is therefore primed for closure. It is possible that irritants such as acid reflux, caffeine or poor hydration lead to hypersensitivity and either cause or exacerbate EILO. The peak age of onset is during early adolescence and is more commonly seen in females, suggesting that structural changes during puberty may have a role to play. Finally, the speed of airflow increases during maximal exercise leading to pressure changes across the larynx (Bernouille’s principle), potentially causing laryngeal collapse.

EILO is commonly found in athletes and may also co-exist with asthma. In a study of elite athletes with a diagnostic label of asthma, the diagnosis was only confirmed in 43% following objective testing; 35% had EILO; 13% had evidence of both EILO and asthma. In a cross-sectional population study of adolescents in Sweden, the prevalence was 6%.

Clinical Features of EILO
EILO occurs at peak exercise and usually resolves within a short time of stopping. An inspiratory noise is frequently heard and patients may complain of throat tightness or discomfort. It is usually not responsive to bronchodilators, however correct inhaler technique may provide a form of breathing control (see below) leading to some relief. Exercise-induced bronchoconstriction (EIB) on the other hand usually peaks after exercise, is characterized by chest tightness and expiratory wheeze and is generally responsive to bronchodilators although the symptoms can be prolonged.

Diagnostic Tests
Filming an episode on a mobile phone can be informative and help to guide further investigations. Spirometry is usually normal and exhaled nitric oxide (FENO) low, unless there is co-existent asthma. Occasionally blunted inspiratory flow volume loops are seen, however the sensitivity of these findings is low and they are generally non reproducible. An exercise-induced asthma test or other indirect challenge test such as a mannitol or eucapnic voluntary hyperventilation may be helpful to exclude EIB, but less so in the presence of both conditions.

The gold standard test is continuous laryngoscopy during exercise. A laryngoscope is positioned just above the larynx, fixed in place and left in situ during exercise. It is generally well tolerated, even by young children. The type of exercise can be tailored to the individual depending on what precipitates symptoms and can include running on a treadmill, ergometer cycling, rowing or even swimming. Direct visualization of the larynx can not only confirm the diagnosis and help to grade severity but also provide biofeedback and potentially pick up other pathologies such as vocal cord damage.

Management
Expert physiotherapy or speech and language therapist input and instruction in breathing control exercises is the mainstay of management. In a small number of cases, particularly severe EILO where conservative management has failed, laser supraglottoplasty can be carried out.

Conclusion
EILO is a common but overlooked cause of exercise-induced breathlessness. Correct diagnosis can lead to implementation of appropriate management strategies and avoidance of unnecessary treatment.

References


E. NON-INVASIVE MONITORING OF LUNG DISEASES

#1 Digital Technology to Monitor Respiratory Diseases

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In the beginning of 2018, Apple Inc. announced that it will now build its own hospitals, at this point focused on Apple Inc. employees where “medicine of the future for technology-affine people will be developed”. Digital technology has only started to revolutionize our world and that of our patients and their families. Interestingly, this perception has not reached medicine in a uniform wave but rather, fields like pediatrics are much more exposed to this change today than internal medicine or classic surgery where most patients are not digital natives. In general, digital technology has or will affect different areas of medicine such as information and communication with patients, retrieval of medical knowledge faster and more individualized, measuring biological data remotely, big data analysis and algorithms for data interpretation as well as self-empowerment of patients to address their needs directly.

While some of these developments are already part of daily life and some may even have bypassed their first hype (such as social networks), others may just be on the rise and open new possibilities to improve patient’s lives. One of these areas is the use of digital technology to promote knowledge on how to handle pediatric emergency situations for emergency physicians in the field, where they are guided through a specific emergency situation such as anaphylaxis in the child step by step and with individualized pediatric dosing recommendations (such as okinoby in Germany, www.okinoby.de). One can easily imagine that this will develop into augmented reality applications in the near future. Another promising area is the development of specific search engines to crawl the internet for rare diseases based on symptoms and signs, such as on www.findzebra.com, which is based on algorithms that search the net for the rare rather than for the common as it would happen for normal search engines such as Google and alike.

Digital technology may as well be used to measure lung function remotely in patients and allow for telemetric analysis of data. However, one has to say that home spirometry, especially in children and young adults, has limited success only as commitment and determination in performing these tests are crucial for result and its value for interpretation. Thus, other technologies less dependent on cooperation have been developed measuring breathing sounds over a longer period of time allowing for the analysis of respiratory symptoms during the night in the patient’s home environment (1,2,3). Indeed, these technologies primarily designed for adults are also very feasible in children after adjusting the analyzing algorithms and the first tests are extremely promising. Such technologies have a great potential to broaden our horizon on how patients are doing in real life and to adapt therapy accordingly.

The more data are available on our patients, such as longitudinal parameters on breathing patterns and lung function, the more information could potentially also be extracted from these data to make predictions. A fine example on how that can put to work for the patient was given by Urs Frey and his group. When they analyzed the time series of peak expiratory flows, asthma patients using bronchodilators showed long-range correlations that change significantly with disease severity, approaching a random process with increased variability in the most severe cases. Using a nonlinear stochastic model, both the increased variability and the loss of correlations augmented the risk of unstable airway function predicting the occurrence of severe exacerbations within a 30-day window (4).

Finally, digital natives have started to take their fate in their own hands. A fine example of what can be achieved in respiratory medicine is an initiative where people started to build their own sensors for PM2.5 and PM10 measurements when they became fed up with restrictive policies from officials that determined where and what air pollutants are measured. Thus, a video manual was published on how to build your own (actual reliably-working) sensor for particulate matter (at a price of 25€) and a website where these data are connected and publically available. With this system going viral, it is now possible for anybody in Europe, e.g., affected by respiratory diseases such as asthma, to get real-time information on air pollution for their
neighborhood, truly addressing the personal need of patients for individualized information (www.deutschland.maps.lufterdaten.info).

References


#2 Sputum: Infection and Inflammation

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Lower airway samples in children can provide an invaluable insight into lung pathology, both in terms of infection and inflammation. Lower airway samples can most reliably be collected bronchoscopically, however this only provides a snapshot at a single time point, invariably involves a general anesthetic, can only be carried out for clinical purposes and can have associated morbidity. Many of these problems can be overcome using sputum samples. Sputum is considered the gold standard non-invasive measure of lower airway inflammation and infection and affords the opportunity for longitudinal monitoring of treatment response and disease progression in the outpatient setting. However, obtaining sputum samples can provide its own challenges.

Sputum induction

Sputum production is characteristic of chronic supportive lung diseases (CSLD), such as cystic fibrosis, particularly at the time of an infective exacerbation and increased mucus production is frequently seen in asthma. However, children cannot always expectorate sputum spontaneously. Hypertonic saline can be used to induce sputum, even in very young, preschool children. Samples can be tested for the presence of infection, both bacterial and viral, the number and type of cells can be measured as can fluid phase inflammatory mediators including cytokines, chemokines and proteases.

Airway infection

Infection surveillance of children with cystic fibrosis and other chronic suppurrative lung diseases using sputum samples is an essential part of routine management. Accurate pathogen detection and antibiotic sensitivity pattern have important implications for management. Until recently obtaining samples from younger children has been challenging and instead cough swabs have been used, with their far lower sensitivity. Protocols for sputum induction in preschool children have yielded promising results and negate the need for bronchoscopy in some.

Smear positive sputum samples have been the cornerstone of tuberculosis (TB) diagnosis for many years. Induced sputum can be carried out even in very young children to obtain samples; however, the low number of bacilli makes diagnosis difficult in the pediatric population. Rapid diagnostic tests such as Xpert® MTB/RIF have excellent sensitivity in a range of care settings in low- and middle-income countries; therefore, obtaining good sputum samples is even more vital.

Respiratory infection surveillance using sputum samples is also an essential component of management in children with primary or acquired immunodeficiency to detect potentially life-threatening organisms such as Pneumocystis jirovecii.

Airway inflammation

Collection of sputum samples to measure airway inflammation is generally limited to specialist clinics and remains largely in the research arena. However, airway inflammation is not only a key pathological process in asthma but an important therapeutic target. Sputum samples can help to elucidate the underlying pathobiology of inflammatory airways disease and identify novel therapeutic targets.

Sputum eosinophils are the hallmark of steroid responsive disease and their presence helps to identify a group of patients who will respond well to inhaled corticosteroids, particularly if their symptoms are discordant. Furthermore, novel biologicals such as mepolizumab which targets IL-5 (a key mediator of eosinophil activation) are only effective in those with airway eosinophilia. Incorporating measurement of sputum eosinophils into management algorithms for adults has shown promising results; however, there is insufficient evidence in children to support this strategy.

Drawbacks

Sputum monitoring for infection has been a key component of the care of children with cystic fibrosis and other chronic suppurative lung diseases for many years; however sputum induction for measuring inflammation is more difficult to incorporate into clinical practice. It is time consuming, requires expertise and appropriate laboratory facilities to process the sputum and a result is not available immediately. Sputum induction can cause unwanted effects such as cough and bronchoconstriction and the taste is unpleasant. However, it is generally well tolerated and induction is successful in 70–90%, with success increasing with age.

Summary

Despite the constraints of sputum induction, obtaining a sputum sample can be vital in diagnosing and appropriately managing infections and a useful adjunct in inflammatory airways diseases, for children of all ages.
Exhaled breath contains thousands of biomarkers, many of which are relevant to the respiratory clinician and researcher. Exhaled breath can be collected non-invasively from patients, making it particularly useful in the pediatric setting in which invasive procedures are particularly stressful. It has three fractions: gaseous breath, which is composed mainly of nitrogen and oxygen but includes lower levels of oxygen, carbon dioxide, carbon monoxide, nitric oxide, and other gaseous molecules; exhaled breath condensate, which is a biofluid consisting of the distilled water that humidifies exhaled breath and also aerosolized droplets of airway lining fluid; and exhaled breath volatile, which consists of compounds that are volatile at body temperature (∼37°C).

While the clinical use of breath biomarkers has been reported for over a century, interest and advances in their use has dramatically increased in the past two decades, particularly in exhaled volatile organic compounds (VOCs). This session aims to provide a concise review of the study and recent clinical/clinical research applications of breath VOCs, also known as "breathomics".

Breathomics usually does not involve the study of a specific biomarker. Rather, hundreds (perhaps thousands) of breath VOCs are usually measured concurrently and the “fingerprint” provided by the relative signals of these VOCs is compared between conditions. Spectrometry is the usual method of analysis for these compounds, with gas chromatography/mass spectrometry (GC/MS) being the current gold standard of analysis. Along with analytical methods, collection techniques and devices have been evaluated for stability and reproducibility; currently, there are collection devices for breathomics capable of storing VOC signals for up to three months which allow for gold standard breathomics to take place anywhere in the world, regardless of proximity to a GC/MS center.

Using these techniques, researchers have now been able to identify unique VOC fingerprints for specific bacteria. Applying these fingerprints to breathomics may allow for non-invasive detection and monitoring of respiratory disease states.


#3 Breathomics for Infection and Inflammation.

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The use of morphological features and ancillary findings to narrow a differential etiology, and the ability to accurately assess the distribution and severity of large airways diseases, has given medical imaging a central role in the diagnosis and monitoring of chronic suppurative lung diseases. There is, however, great variation in imaging practice across the globe. Chest radiography is cheap, readily available and easily reproducible, with a low enough ionizing radiation exposure to allow repeated imaging follow-up. However, the increased sensitivity to pathology and better localization in three-dimensional space, makes computed tomography (CT) a particularly powerful tool.

Semi-quantitative visual scoring systems have been applied to both chest radiography and CT, with measures of bronchial wall thickening, mucus plugging and consolidation found to correlate with quality of life scores and subsequent rates of pulmonary exacerbation. The drive toward personalized medicine is fuelling a desire for fully automated, quantitative measures of disease, independent of observer experience and without the limitations of inter- and intra-observer variation encountered in visual scoring systems.

Whilst relatively high exposures to ionizing radiation previously limited CT use as a follow-up tool, technological developments have led to significant reductions in dose, with simultaneous increases in image quality. Alongside significant improvements in computing, this improved image quality, and a shift from interspaced CT sections to volumetric acquisitions of the whole chest, have led to successful implementation of both semi-automated and fully automated airway measurements from clinical CT examinations in the research setting. As a result, several groups now advocate regular follow-up of suppurative lung diseases (particularly cystic fibrosis) via CT. However, significant differences in opinion persist (how frequently to CT, whether to include a second acquisition at end-expiration as routine, the use of spirometer-guidance for acquisition timing, etc) and are driving renewed interest in structural imaging via magnetic resonance imaging (MRI), as an ionizing radiation-free, alternative cross-sectional imaging modality.

Improvements in both MRI hardware and software (coil technology, parallel imaging, respiratory-gating techniques, non-Cartesian reconstruction algorithms, etc) have led to far-increased sensitivity to both parenchymal and airway pathology. There has been particular interest in respiratory-triggered PROPELLER (Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction) and similar sequences and ultrashort echotime (UTE) sequences such as PETRA (Pointwise Encoding Time reduction with Radial Acquisition). These can produce images with isotropic spatial resolutions of 0.86 mm (compared to 0.22 mm from the current state of the art clinical CT systems) with good agreement on structural scores between CT and MRI.

Although MRI is likely to remain the less impressive structural imaging alternative to CT for the foreseeable future, its inherently quantitative and functional imaging capabilities offer far more exciting possibilities. Numerous publications have demonstrated the promise of ventilation imaging via MRI using hyperpolarized noble gasses as contrast agents. Hyperpolarized helium does not diffuse across the alveolar membrane thus allowing measures of regional ventilation and dynamic ventilatory measures (e.g. wash-in and washout times). Xenon has similar pharmacokinetic properties to oxygen, and when inhaled in hyperpolarized form, allows additional visualization and quantification of gaseous diffusion at the alveolar level. Studies have demonstrated roles for these techniques in COPD exacerbation prediction and outcome prediction in asthma.

Whilst hyperpolarized gas MRI offers an impressive array of new methods of visualizing and quantifying respiratory function in vivo, the cost and complexity of producing, administering and visualizing hyperpolarized gases limits its application to a very small number of specialist centers. Other more widely applicable methods are currently under investigation, perhaps most notably oxygen-enhanced MRI and Fourier-decomposition ventilation:perfusion MRI. Rather than obtaining signal directly from hyperpolarized gas, oxygen-enhanced MRI uses the slight T1 shortening effect of inhaled 100% oxygen, in its dissolved state, on adjacent tissues to demonstrate regional ventilation. Depending on the oxygen administration protocol, this technique can be used to assess regional ventilation (enhancement fraction) and dynamic parameters such as wash in and washout times. Fourier decomposition is an even newer technique which utilizes change in lung signal related to the mechanics of ventilation, and the pulsatility of pulmonary perfusion, to produce maps of ventilation and pulmonary perfusion without the use of inhaled or injected contrast agents. With further investigation of the clinical applicability of these techniques, it is clear that MRI will play an increasing role in vivo imaging of pulmonary physiology, both in research and clinical settings.

References:
Mucus overproduction and retention, chronic and recurrent respiratory infections, and intense airway inflammation associated with airway distortion and impaired mucociliary clearance is at the core pathology of bronchiectasis. Investigation of treatment options to address these pathologies have been lacking behind other respiratory diseases such as cystic fibrosis (CF), asthma and (in adults) chronic obstructive pulmonary disease (COPD). More recently a number of trials have been undertaken for bronchiectasis but predominantly in adults with severe disease; often requiring more than two exacerbations in the previous 12 months and/or chronic Pseudomonas aeruginosa infection for enrolment. Many of these have struggled to recruit and/or reach designated trial endpoints. Treatment for pediatric bronchiectasis remains a largely evidence-free field. There remain no therapies specifically approved by regulatory authorities for this group of patients. Guidelines for management are available with recommendations based on some evidence but largely ‘expert opinion’.1–3

**Antibiotics.** Prolonged macrolide therapy: Three prospective trials in adults using oral azithromycin (in two) and erythromycin (in one) for either six or twelve months consistently showed a 43–62% reduction in exacerbation frequency, a longer time to first exacerbation and improvement in symptom scores in the treatment group.(4) This was confirmed in a trial using a single weekly azithromycin dose for a mean of 20 months in children with reductions in exacerbations by 50%, hospitalizations by 30%, use of additional antibiotics by 50% and an increase in weight-for-age in the treatment group.(5) The medications were well tolerated with the main concern being evolution of antimicrobial resistance, although good adherence was associated with bacteria eradication.

Inhaled or nebulized antibiotics: Fifteen randomized controlled trials since 2000 investigating tobramycin, gentamicin, colistin and more recently aztreonam (6) or ciprofloxacin (7,8) in adults with variable antibiotic duration from two weeks or one month (on/off) for three cycles to 12 months continuous. Findings have been inconsistent with some reporting improvement in symptoms and quality of life (QoL) as well as reduced exacerbations but no improvement in lung function. Studies measuring sputum bacterial density (usually Pseudomonas aeruginosa) showed a significant reduction in colony-forming units with clearance described in 30–35%. Reductions in sputum myeloperoxidase, free elastase, and IL1β were also recorded. We conducted a pilot trial of nebulized gentamicin in children showing reduction in Haemophilus influenza with eradication in 60% and reduced IL8, IL1β and tumor necrosis factor α (TNFα) in sputum. However, these inflammatory and infective changes only occasionally translated to clinical response. Even when positive, the improvements were small compared to results of similar studies in CF with significantly more adverse events often necessitating stopping the treatment.

**Anti-inflammatory treatments:** Of two studies of inhaled corticosteroids (and long-acting bronchodilator) in adults with bronchiectasis and without co-existing asthma, one showed reduced 24 hours sputum volumes, improved QoL and an increase in cough-free days.(9) Specific anti-inflammatory agents have been explored. Cysteine-X-cysteine chemokine receptor-2, which binds IL8 and encourages neutrophil migration, was blocked with an antagonist AZD5069 which reduced sputum neutrophils but had no clinical benefit.(10) A trial of arvostatin, a statin drug known to modulate inflammation by an unknown mechanism, also reduced neutrophil activation and was associated with improved QoL.(11) However, caution has been advised as trials of inhaled corticosteroids and TNFα antagonists in COPD, and a leukotriene receptor antagonist in CF were all associated with an increase in pneumonia.

**Mucoactive therapies:** There have been two large trials of inhaled mannitol in adults. The first over 12 weeks showed an improvement in sputum weight in the placebo group associated with increased antibiotic use and no other differences. The second over 12 months showed no difference in exacerbation rates but an increased time to first exacerbation and an improvement in QoL scores in the treatment group.(12) One small study using nebulized hypertonic saline in adults showed no difference in outcomes after 12 months (13), although single doses have been associated with increased sputum clearance. Trials of mucoactive treatment have been cautious given the first using nebulized DNase was detrimental for bronchiectasis unlike its positive effects in CF.

**Physiotherapy:** Chest physiotherapy continues to be recommended as a mainstay of treatment though, in fact, has very little trial evidence behind it.(14) Comparisons between types of physiotherapy (positive expiratory pressure devices versus active cycle of breathing) has not consistently favored one over another. One recent small study showed using a slow expiration with glottis open in the lateral position compared to placebo exercises resulted in reduced exacerbations and improved QoL over 12 months. How easy this would be to undertake in children is unknown.

**Exercise:** A number of studies in adults have shown that exercise training for three to eight weeks shows improvements in exercise tolerance and QoL.(15) The benefits remain over the placebo group after the programs have finished at 20 weeks and at one year. This may well be an overlooked therapy available for children.
Treatment trials will be assisted with the establishment of the new Bronchiectasis Registries and increased international collaboration. Trials of treatment for children are desperately needed.

References:

#3 Management and Prevention of Chronic Suppurative Lung Diseases and Bronchiolitis Obliterans

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Chronic suppurative lung disease
The term includes bronchiectasis, empyema thoracis, lung abscess and necrotizing pneumonia. Protracted bacterial bronchitis is a newly described chronic suppurative condition in children (1). We will discuss non-cystic fibrosis bronchiectasis in detail.

Epidemiology
Bronchiectasis is a pathological term which denotes permanent dilated and thickened airways as a result of chronic inflammation and recurrent infection due to multiple underlying illnesses.

The global burden of bronchiectasis is not very well documented. It is more common in poor and disadvantaged children from indigenous and low- and middle-income populations and more severe than high-income countries.

Various estimates indicate variation in incidence and underlying illness in different geographic regions. Data from England and Wales suggest that between 2001 and 2007, mortality rates due to bronchiectasis in adults increased at 3%/year. A survey in New Zealand estimated an overall incidence of 3.7 per 100 000 in under 15-y-old children per year. In the Central Australian indigenous population, prevalence in children below 15 y was estimated to be 1470/100,000. There are no data on the magnitude of the problem of bronchiectasis from the developing countries. General impression is that it is a common cause of morbidity and mortality in the developing countries. It is estimated that almost 0.9% (0.7–0.8%) of children admitted with pneumonia may develop bronchiectasis. These figures suggest an estimated 212 to 2646 children developing bronchiectasis per one million children below 4 y of age in India (2).

Etiology
Common etiologies from low- as well as high-income countries include post infectious (specifically post pneumonia, measles, pertussis, etc). Other causes include: aspiration syndromes, malformations, primary ciliary dyskinesia, primary or secondary immune deficiency disorders. Causes could not be identified between 30 and 50% of children with bronchiectasis. Primary immune deficiency disorders and primary ciliary dyskinesia were more commonly reported from high-income group countries as compared to low-income group as various investigations were difficult to obtain in resource-poor settings (3).
Clinical manifestations

Clinical features are nonspecific and consist of chronic respiratory symptoms. Depending on the severity/extent of illness, children may present with wet cough associated with exertional dyspnea and chest wall deformity. Some patients may have wheezing, hemoptysis and clubbing. Course of illness is variable and is dependent on the underlying illness and treatment received. Children with generalized disease and experiencing recurrent exacerbations may have progressive decline in pulmonary function test and respiratory failure.

Definition of exacerbations in a child with bronchiectasis is unclear. A recent study reported clinical features such as increase in frequency of cough, expectoration and increase in crepitations and/or wheezing on auscultation indicating exacerbation. As infections are a common cause of exacerbation, there may be associated systemic manifestations such as fever, impaired appetite, etc.

Diagnosis

With compatible clinical phenotype, the first imaging should be X-ray film of the chest. Findings may be nonspecific varying from completely normal to increased bronchovascular marking and peribronchial thickening. It is believed that it is unlikely to be completely normal in children with bronchiectasis. With clinical phenotype and clues from chest radiography, high resolution CT scan (HRCT) may be performed to confirm a diagnosis of bronchiectasis. HRCT is the gold standard for diagnosis of bronchiectasis. Findings on HRCT include: bronchial dilatation (broncho-arterial ratio >0.8), bronchial wall thickening, lack of normal bronchial tapering, any bronchi with an internal diameter greater than the diameter of the accompanying pulmonary artery (signet ring sign) and bronchi visible closer than two centimeters to the pleural surface.

Other findings (nonspecific) include air trapping and mosaic perfusion defect. HRCT findings can help in assessment of the distribution and extent of bronchiectasis. Involvement of a particular lobe or distribution may give some clue about the underlying illness. Scoring systems (Bhalla, Nathanson, Reiff, and Webb’s scores) have been developed for assessment of severity and extent of illness.

A commonly accepted scoring system for children is the Bhalla score. It includes multiple items to assess severity and extent. Items include: a) severity of bronchiectasis; b) peribronchial thickening; c) extent of bronchiectasis (number of lung segments); d) extent of mucus plugs; e) abscesses or sacculations; f) generalities of the bronchial division involved (bronchiectasis/plug); g) number of bubbles; h) emphysema (number of lung segments); i) collapse/consolidation.

While HRCT remains the gold standard for diagnosis, it should be kept in mind that some lesions highlighted with HRCT may improve or regress.

Management

The outline of treatment of bronchiectasis includes: antibiotic administration, airway clearance, mucolytic agents, inhaled corticosteroids and bronchodilators, and surgical intervention.

It is important to identify etiological agents to optimize treatment according to pathogens. Antibiotics can be given for 7–10 days. Extended course of antibiotics to 4–6 weeks has been shown to improve outcome but associated with development of drug resistance.

Prolonged course of macrolides, specifically 2–3 times a week of azithromycin, has shown to improve outcome. Experience is limited for inhaled antibiotics in non-CF bronchiectasis. They can be used in children colonized with pseudomonas and experiencing frequent exacerbations. Use of mucolytic agents has not been shown to be effective and may be associated with worsening. The role of hypertonic saline as mucolytic agent is unclear.

Long acting beta 2 agonists and low dose inhaled steroids have shown some benefit in adult patients but not much data are available for children.

Most children with bronchiectasis can be managed successfully with medical management. Surgical intervention may be considered in localized disease that is uncontrolled with medical treatment or having uncontrolled hemoptysis.

Protracted bacterial bronchitis

This is a recently described clinical condition, not very well known amongst pediatricians. However, some people consider it to be the commonest cause of wet cough in preschool children.

Clinical definition includes: child with chronic wet cough for more than four weeks with absence of symptoms or signs of other chronic pulmonary disease and perceptible improvement in 14 days of antibiotic treatment. A bacterial spp of >10^4 colony-forming units/ml in bronchial lavage fluid or airway secretion classifies it as microbiology-based PBB. If it recurs more than thrice in a year, it is labeled as recurrent PBB.

The magnitude of the problem is not clearly documented. A proportion of children with persistent wet cough after ruling out genetic predisposition (cystic fibrosis, immune deficiency, primary ciliary dyskinesia) were labeled as PBB in most studies. A review of studies reporting chronic wet cough suggests a prevalence of 5–40% among children.

However this approach may also include children with uncontrolled asthma.

Diagnosis of PBB involves clinical phenotype with documentation of bacterial pathogen by invasive procedure for obtaining BAL. It is further complicated by reporting of bacterial pathogens differently by laboratory. Almost 30% of clinically-diagnosed PBB may not show an organism in BAL due to multiple reasons.

Most physicians treat PBB with antibiotics for 2–3 weeks. However some centers extend the latter up to 6 months. There is no evidence to support the beneficial role of physiotherapy.

To summarize: PBB is a recently described clinical condition, caused by persistent infection due to pathogenic organisms producing chronic inflammation. Its relation with development into bronchiectasis is unclear. There is a need to perform studies for diagnostic algorithm and treatment.
Prevention of chronic suppurative lung disease and its exacerbations

Due to lack of robust data, it is difficult to state effective strategies for prevention of suppurative lung disease and bronchiectasis. Consensus guidelines for same include: early diagnosis, regular follow-up, airway clearance in consultation with a trained physiotherapist, optimize nutrition, encourage physical activity, monitor growth, vaccination to prevent respiratory infections, clean environment. Early diagnosis of exacerbation should institute appropriate antibiotics. Selected patients may be given hypertonic saline, long-term antibiotics such as azithromycin or inhaled tobramycin (8).

Bronchiolitis obliterans

Bronchiolitis obliterans (BO) is a disease of terminal bronchioles that occurs following a severe viral infection. There is inflammation and fibrosis of terminal bronchioles. Common viruses that are associated with BO include respiratory syncytial virus, parainfluenza, influenza, and adenovirus. It may occur in children with HIV infection, post-transplant or gastroesophageal reflux (9).

Initially, BO starts like acute bronchiolitis and manifests with fever, cough, tachypnea and wheezing. The course is unusual, instead of recovery in 7–10 days, clinical features persist or worsen over a few weeks to months. The infant/child may continue to have tachypnea, dyspnea, hypoxemia, crackles, wheezing and air trapping leading to hyperinflation of the chest.

Imaging abnormalities include: hyperinflation on X-ray film, HRCT chest may show: hyperinflation, mosaic pattern of perfusion, bronchial wall thickening and bronchiectasis and atelectasis. Rarely, CT scan may show unilateral hyperinflated lung suggestive of Macleod/Swayer-James syndrome.

Diagnosis is based on clinicoradiological findings. Proposed criteria consist of i) History of acute bronchiolitis in previously healthy child, ii) Airway obstruction detected either by physical examination and/or by lung function tests that persists for over 6 weeks after the initial event despite the use of bronchodilators and steroids; iii) HRCT exhibiting bronchiectasis and/or a mosaic pattern; iv) Exclusion of other chronic obstructive pulmonary diseases (9).

Treatment consists of supportive care including oxygen inhalation, nutritional support, prevention of infections. For wheezing, bronchodilators can be used although it may not show response on expected lines as there is fixed obstruction. Tiotropium, a long acting antimuscarinic agent (LAMA), has been used in a small study with some benefit. The role of steroids in BO remains controversial. Systemic steroids, methyl prednisolone pulse and inhaled steroids have been used with variable response (9).

Long term azithromycin has been studied as an immunomodulator in BO (10).

References


B. DIFFICULT CASES

#1 C101 – An Unusual Germ in a Tachypneic Infant.

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Background: Atypical pneumonia in infants can be concerning for underlying pathologies, including congenital immunodeficiency. Clinicians often suspect Pneumocystis jirovecii (PCP) in this setting. We present a case of an infant with an atypical pneumonia caused by a very unusual germ, Pasteurella dagmatis, which led to the diagnosis of severe combined immunodeficiency.

Clinical case: A one-month-old full-term Caucasian infant was referred to our pediatric pulmonology clinic for persistent tachypnea since birth. Perinatal history was remarkable for mild respiratory distress at birth, which was diagnosed as transient tachypnea of the newborn. At the time of his discharge from
the maternity ward at five days of life, he remained mildly
tachypneic from time to time, but was otherwise thriving. At
3 weeks old, he presented an afebrile respiratory illness.
Clinical examination and radiographic findings at the time were
consistent with a viral respiratory infection, but the mother
reported a history of intermittent tachypnea since birth. An
outpatient appointment in pediatric pulmonology was thus
scheduled a week later.

At follow-up, the baby was found to be irritable, increasingly
nervous with a worsening cough and had lost weight. Ausculta-
tion demonstrated fine crackles and a diffuse alveolar-interstitial
pneumopathy was found on chest X-ray. He was then admitted for
further investigations. Diagnostic bronchoscopy with bronchoalveo-
lar lavage (BAL) was performed. Purulent respiratory secretions were
retrieved and antibiotic therapy with piperacillin-tazobactam and
therapeutic TMP-SMX was started to cover for Pneumocystis jirovecii
(PCP) pneumonia.

BAL culture was strongly positive for Pasteurella dagmatis, a gram-
negative coccobacillus usually described in dog bite-associated
infections. It is to our knowledge the first report of a pulmonary
infection with this germ in the pediatric population. The patient had no
history of dog bite but was in contact with a domestic dog in his home
environment. Upon confirmation of negative PCP testing and after
receiving antibiotic susceptibilities, antibiotic treatment was changed
for ampicillin with a good clinical response.

Profound lymphopenia (0.2 × 10^9/L) with undetectable IgM, IgA and
IgE led to the diagnosis of severe combined immunodeficiency
(SCID). BAL pathology was suspicious for alveolar proteinosis, and a
diagnosis of adenosine deaminase (ADA) deficiency was later made
by enzymatic essay with genetic testing confirmation. Treatment
with IV immunoglobulins, enzymatic replacement with PEG-ADA
and antibioprophylaxis (fluconazole and TMP-SMX) was started. The
patient responded well and is now waiting to start a gene therapy
protocol.

Conclusion: This case emphasizes the need to consider congenital
immunodeficiency in infants presenting with an atypical pneumonia
and even more so with the finding of an atypical germ. It also illustrates
the role of Pasteurella dagmatis as a cause of atypical pneumonia in
immunocompromised infants. Further research is needed to establish
the epidemiology of this germ in the pediatric population and the
possible role of domestic animal exposure in its transmission.

#2 D191 – An Unusual Story of Endobronchial
Hemangioma.

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We report the case of a 9-year-old girl with no medical background
who had repeated pneumonia in the past few months treated by
antibiotics. A chest radiography was performed and showed an
alveolar consolidation on the lower-right lobe, persistent on the
control X-ray after an adapted antibiotic therapy.

The chest CT-scan showed bronchiectasis of the entire lower right
lobe associated with an obstruction of the right-inferior lobar
bronchus.

There was no history of inhalation of a foreign body or previous chest
X-ray.

A bronchial fibroscopy was performed. It revealed a tumour-like mass
obstructing the entire right-inferior lobar bronchus. The anatomopa-
thological examination of the sample showed a pattern of a benign
vascular lesion (lobulated capillary hemangioma).

It was decided to treat by thermocoagulation associated with a
curative excision of the lesion.

On the control bronchial fibroscopy performed one month later, we
observed a recurrence of the lesion in the right main bronchus with
complete obstruction of the right-inferior lobar bronchus. This
recurrence was also observed on the new thoracic computed
computed tomography showing the endobronchial angiomatous lesion sitting
under the origin of the middle lobar bronchus, with a worsening of the
bronchiectasis of the lower right lobe.

A treatment with a beta-blocker was introduced (propanolol,
1 mg/kg/d). This treatment was well tolerated, and there was no
further pulmonary infection or cough. On the several computed
tomographies performed, we observed a stabilization of the lesion, and
after one year of beta-blockers, an improvement of the radiological
lesions with reremeabilization of the right-inferior lobar bronchus.

After two years of treatment, the fibroscopy showed a discrete curve
of the beginning of the Fowler, with a discrete thickening of the
bronchial spur of the right-inferior lobar bronchus. There were still no
clinical symptoms.

After three years of treatment, the fibroscopy showed an increase of
the angiomatous lesion, causing a partial obstruction of the Fowler.
The ventilation/perfusion lung scan showed hypooxygenation (47%) and
hyperoxygenation (42%) of the right inferior lobe. It was then decided to
increase the beta-blocker treatment at 3 mg/kg/d, even if there was
still no associated clinical manifestation.

After five years of treatment, the fibroscopy showed a discrete improvement: 48.75% ventilation and 43.7%
perfusion of the right inferior lobe. The lung function test showed a functional vital capacity at 82%, a forced expiratory volume in one
second at 85% and a maximum mid-expiratory flow 25–75 at 91%.

After seven years of treatment, the girl still had no clinical
manifestation, no cough or pulmonary infection and practiced
sports. The fibroscopy was normal, with no recurrence of the
hemangioma and no more curve on the Fowler. The tomography
showed a perfect stability of the bronchiectasis of the right inferior
lobe without any endobronchial image. The lung function test
showed an improvement, with a functional vital capacity at 91%, a
forced expiratory volume in one second at 93% and a maximum mid-
expiratory flow 25–75 at 94%. The ventilation/perfusion lung scan
showed a stability of the hypoventilation and hypoperfusion of the right inferior lobe.

Considering the improvement on all of the tests and without any symptoms, the beta-blocker treatment was stopped.

The beta-blocker treatment of this unusual localization of endobronchial hemangiom had allowed an improvement and avoid a lobectomy; this medical treatment has not been previously described in the literature in children.

Introduction: Plastic bronchitis (PB) is a rare complication in children after Fontan palliation. It is characterized by the formation of branching bronchial casts that partially or completely block the airways. PB is associated with a high mortality risk reaching 33% (14–50%) in children with congenital heart disease (CHD). Various treatment strategies have been anecdotally reported but only few treatment options have been shown to be effective. We present a case of a girl with Fontan physiology and recurrence of respiratory distress 5 days after successful treatment of supposed pneumonia.

Case presentation: A 5-year-old-girl with heterotaxy syndrome and sinus inversus and asplenia, 15 months after Fontan palliation and 2 weeks after developing *Streptococcus pneumoniae* sepsis presented with cough and dyspnea without fever. She was initially diagnosed with left-sided pneumonia with pleural effusion and atelectasis of the left middle and lower lobes (Figure 1). Introduction of third-generation cephalosporin and clarithromycin resulted in complete resolution of radiological changes and recovery. Serological examination confirmed acute infection with *Chlamydophila pneumoniae*.

Five days after discharge, she was readmitted due to the recurrence of severe dyspnea with desaturation to 75%, with neither symptoms of infection nor fever. On readmission her vital signs were: tachypnea 70/min, HR 134/min, SpO2 75% on room air, RR 104/77 mmHg. Her physical examination revealed: cyanosis, dyspnea at rest, surgical scars, hypertelorism, dextrocardia, dullness to percussion and diminished breath sounds over the left lung, liver was palpable 2 cm below the left costal margin. Other systemic examination was unremarkable. Investigations revealed slightly elevated inflammatory markers and metabolic acidosis. Chest radiography depicted pulmonary opacities in the left middle lobe (Figure 2), and lung ultrasound (LUS) demonstrated atelectasis of the lower lobe of the left lung. Treatment with bronchodilators and mucolytics was started with initial improvement. However, on the following day, her symptoms worsened with hypoxia and severe dyspnea. Parents reported an episode of expectoration of branching bronchial cast during a previous hospitalization. Diagnosis of PB was established and treatment with inhaled alteplase was started. She received 12 mg initially, 10 mg after 1 h, and 5 mg every 2 hrs for 24 hrs. After 24 hours of treatment, she expectorated a bronchial cast (Figure 3) with subsequent dyspnea relief and normalization of oxygen saturation. Morphological examination of the cast revealed the presence of mucus, fibrin and lymphocytes. The symptoms recurred 12h after cessation of alteplase treatment. Reintroduction of alteplase and concurrent initiation of low fat diet and once-daily azithromycin at a dose of 5 mg/kg resulted in complete symptom relief. She was further referred to the Department of Pediatric Cardiology for clinical evaluation. Cardiac catheterization was inconclusive. At 5 months follow-up, she occasionally expectorates small casts without symptoms of dyspnea or desaturation. She awaits the results of lymphatic vessel imaging studies.

Discussion: PB is an uncommon pulmonary condition in children but a known complication of surgical treatment of CHD, Fontan palliation in particular. It is associated with the abnormalities of lymphatic vessels apparent after cardiac surgery, similar to those observed in protein-losing enteropathy. PB carries a high mortality and morbidity risk in patients with CHD. Atelectasis and dyspnea with low oxygen saturation due to mechanical occlusion of the bronchial tree are common presentations with potentially fatal outcome. Treatment strategies are reported in case reports and small case series, yet some effective therapies have been described. These include airway clearance, inhaled fibrinolitics, bronchoscopy, correction of abnormal lymph flow and procedures to optimize cardiac output with heart transplantation in severe cases. Other possible treatment options encompass inhaled hypertonic saline, inhaled corticosteroids and low-dose macrolides. However, no recommended regimen is available. After review of the literature, we decided to start inhaled alteplase and we followed the previously reported doses with initial improvement. However, 12 hrs after treatment cessation, we observed the recurrence of symptoms. Our patient required reintroduction of alteplase for an additional 48 hrs. Long-term low fat diet and low-dose azithromycin were also started decreasing symptoms to subclinical disease in 5 months follow-up. Since PB is believed to be a sign of failing Fontan physiology, a thorough cardiological examination is warranted. Abnormal thoracic lymphatics have been reported in PB patients and ablation of such vessels is an effective therapeutic option.

As an experiment, we incubated expectorated bronchial casts in heparin, alteplase, urokinase, erdostein, N-acetylcysteine and ambroxol (Figure 4). After 7 days of incubation, we observed complete dissolution of casts only in heparin solution, and its structural change in alteplase solution. Therefore, inhaled heparin could be a better treatment option for this patient.

Conclusion: PB is a potentially fatal condition. Severe dyspnea symptoms in children with Fontan physiology and no signs of infection are a typical clinical presentation. Among treatment options, we report
inhaled alteplase, low fat diet and low-dose azithromycin to be effective.

**#4 D1 - Pediatric Endobronchial Mucoepidermoid Carcinoma Completely Resected via Video-Assisted Thoracic Surgery Sleeve Resection: A Case Report.**

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Primary lung tumors are unheard of in the pediatric population, more so, tumors in the bronchial tree that may be equally enigmatic to diagnose, as with the case of our patient. Our patient is a 3-year-old male who was initially treated as asthma due to recurrent difficulty of breathing and cough. The persistence of symptoms prompted admission at a local hospital, and further evaluation with a chest radiograph and chest computed tomography scan (CT Scan) showing a possible obstruction at the right bronchus with atelectasis of the right lung. Bronchoscopy was performed upon transfer to our institution showing a polypoid mass at the right bronchus. He was eventually diagnosed by biopsy with endobronchial mucoepidermoid carcinoma (MC), a very rare lung tumor in the pediatric age group. Surgical removal via sleeve resection was performed, a first in our country for this age group.

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**C. ADVANCES IN CYSTIC FIBROSIS**

**#1 Benefits and Risks of Early Diagnosis in Cystic Fibrosis**

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Many aspects of disease in cystic fibrosis (CF) have their onset in early life [1]. Pulmonary inflammation, infection, nutritional impairment, growth deficiencies and structural lung damage manifest during infancy and can be present even in the absence of symptoms or signs. Early childhood represents a pivotal period amenable to intervention strategies that could delay or prevent the onset of lung damage and alter the longer term clinical trajectory for patients with CF. Indeed, over the past decades improved care of preschool children has resulted in improved outcomes, for example, significantly better forced expired volume in one second (FEV1), when first measured at school age. The majority of the secular improvement in lung function over this time is evident by school-age demonstrating the importance of early interventions and also their potential for later impact on health-related quality of life and even life expectancy. Recognition of this has resulted in the widespread introduction of screening programs for CF in newborns, in the hope that an earlier diagnosis provides an opportunity to introduce earlier monitoring and introduction of interventions, with at least 16 European countries having introduced such programs [2]

Benefits of an earlier diagnosis through newborn screening – does intervening early work?

The most significant, established benefit of an earlier diagnosis through newborn screening is the ability to improve nutritional outcomes [3] which is itself linked to improved lung function. Improvements in early life growth patterns can persist into adolescence at least and impact longer-term pulmonary outcomes in CF [4]. At the population level, individuals who were diagnosed early through newborn screening with CF appear to display improved nutrition and lung function outcomes [5, 6]. Indirect benefits include the avoidance of late, missed or problematic diagnoses following multiple doctor-shopping, as was common in the era prior to community screening. An earlier diagnosis also affords a better opportunity to inform future reproductive choices.

Another advantage of an earlier diagnosis is that it permits introduction of earlier surveillance and screening for disease [7]. Recent unpublished data (but that will be presented at this conference) suggest that early surveillance itself can lead to improved markers of lung disease that can be detected even during the preschool years.

Therefore, earlier diagnosis is associated with enhanced surveillance opportunities prior to established disease, including lung disease, and the opportunity to intervene with improved outcomes being evident. In the future, in addition to normalizing FEV1, our goal should be to
prevent bronchiectasis or to normalize more sensitive markers of lung damage such as lung clearance index which are both abnormal even when FEV1 remains within the normal range. Lung clearance index has the potential to serve as a surrogate to chest computed tomography (CT) as an indicator of underlying structural changes to the lung, including bronchiectasis [8]. Achieving these goals will not be possible without early diagnosis.

**Risks of earlier diagnosis**

An early diagnosis of CF does confer certain theoretical and real risks. These can be considered in terms of process measures, surveillance measures or treatment.

An early diagnosis usually results in frequent outpatient review. This is usually undertaken for education around the disease, close monitoring, especially of growth, and to facilitate early interventions. However, it is possible that attendance at clinics in the hospital results in exposure to CF and other hospital-acquired pathogens, including multi-resistant bacteria. Cross-infection practices need to be as stringent as possible to mitigate this risk. There may be specific risks associated with disease surveillance at this age, especially if complex investigations such as infant pulmonary function tests that require sedation, bronchoscopy with broncho-alveolar lavage and chest CT that require general anesthesia, or X-ray and CT examinations that expose the preschool child to radiation, are performed. All such investigations need to consider the risk-benefit ratio for this specific age group.

Similarly, the risk-benefit ratio of most interventions in healthy infants and young children with CF needs to be considered as it is very likely to be different to that in older patients. There is a risk of introducing treatments early that increase life-time exposure risk, such as use of aminoglycoside antibiotics, and an early diagnosis may lead to exposure to poorly evidenced practice, such as the use of prophylactic antibiotics. Efficacy, effectiveness and cost-effectiveness of interventions may also be very different in the infant. There may additionally be a risk to healthy feeding practices when the diagnosis of CF is made, such that in an era of greater life-expectancy, the side effects of a standard CF high-fat diet may have later repercussions for cardiovascular health [9].

Also extremely important in the context of the high prevalence of anxiety and depression that occurs in people with CF and their caregivers [10] is that diagnosis of CF in relatively well children may impact on the degree of watchfulness in parents compared with the past, with diminished ability to be reassured even when faced with a well child. It is unknown whether an earlier diagnosis impacts on bonding, nurturing and the development of neural pathways and brain maturation in the infant that could result from impaired or altered attachment. Certainly, the relationship between parents and the CF team is very different in the era of earlier diagnosis compared with that associated with clinical diagnoses, with the multi-disciplinary team now being responsible for breaking bad news rather than responding to parental desperation for help with an explanatory diagnosis. These factors likely result in a very different ongoing relationship with the specialist CF center.

**What do we need to know?**

Many of the risks associated with an earlier diagnosis of CF could be mitigated if we had a better way of predicting the clinical course of early lung disease. Several studies are ongoing to attempt to determine this. It would be extremely helpful to be able to predict longer term outcomes associated with earlier lung disease, for example, the decline in lung function that occurs in adolescence. It is important to develop clinical trial networks to study interventions specifically in preschool children. Such networks probably require global partnership and co-operation. Critically, we need to determine whether earlier diagnosis and intervention contributes to the substantial mental health issues borne by people with CF and their families. Such knowledge will enhance our ability to not only extend life but quality of life.

**References**


Heart rate variability was first explored as a tool to predict the risk of acute cardiovascular deterioration, and represents autonomic imbalance (1). However, with time, and more availability of equipment, heart rate variability analysis has been applied to other conditions, including asthma, chronic obstructive pulmonary disease (COPD), and Cystic Fibrosis (CF). First it must be realized that we use the term heart rate variability, but in fact measure the R-R interval (2). Second, the relation between heart rate and R-R interval is not linear. So at high heart rates, a small change in R-R is associated with a large change in heart rate, while at low heart rates, the same small change in R-R intervals is associated with only a small change in heart rate.

While the heart has its own intrinsic nervous system, and much has focused on the sinoatrial node, there are peripheral and central modulators, with both afferent and efferent pathways (3). Tracings can be done over long periods of time, as well as shorter epochs, typically 5 min in length. Variability will change depending on the situation in ambulatory patients, such that the beat-to-beat interval will shorten during stressful events or activities. It has thus been a research and monitoring tool in psychology. As the heart sits in the thoracic cage, it is subject to changes in thoracic pressures, blood volume, and other inputs. For the same tidal volume, slow breathing causes much more heart rate variability than rapid breathing (4).

What does the heart do without exogenous autonomic control, the so-called intrinsic heart rate? Blocking both sympathetic and parasympathetic signaling raises the heart rate, suggesting that there is a predominance of vagal tone (5). Secondly, looking at this intrinsic heart rate over an age spectrum, it decreases with increased age. Of interest, with aging, parasympathetic tone decreases, while sympathetic tone increases, perhaps to compensate for this decrease in intrinsic heart rate. The reasons for this decrease in intrinsic heart rate are not totally clear, although decreased diastolic depolarization of the sinus node with aging may be the explanation (6).

Extrinsic control by vagal and sympathetic discharge is not equal. In a canine study, vagal discharge impacted pulse interval one beat later, while sympathetic discharge impacted two beats later. With baroreceptor stimulation, the impact occurs sooner, with the impact of vagal stimulus being on the same beat, and sympathetic pulse impacting the next beat. Why does this occur? This is because of the effect and metabolism of the different neurotransmitters. Acetylcholine, released from parasympathetic nerves, can act directly on potassium channels causing rapid depolarization. Further, acetylcholine is rapidly metabolized in the extracellular space. In contrast, norepinephrine does not directly activate any channels, and is more slowly metabolized and reuptaken, so its effect takes longer to have an impact.

Most analyses of heart rate variability use linear aspects and relate to the R-R interval (2.3). There is the mean interval, its standard deviation, the mean standard deviation of 5 minutes epochs, and then a mean of differences in successive R-R intervals, squared (RMSSD), which is a short term measure of vagal tone.

There is also frequency analysis. Any complex signal is really a mix of simpler wave signals of different frequency and amplitude. The relative contribution of each simpler wave to the complex signal can then be quantified. For example, a complex signal can be made up of a base wave at a very low frequency, another wave of low frequency and lots of noise caused by a high frequency wave. Spectral analysis can give the overall variability, as well as the relative contributions of the different frequencies, typically the relative contribution of low and high frequency waves. The frequency domain can also be analyzed in a linear fashion. Typically, this is divided into 4 frequency domains, high, low, very-low, and ultra-low. The high frequency domain represents sinus arrhythmia, the low frequency oscillations in sympathetic tone, the very low frequency are slow oscillations generated by the heart with sympathetic input, and the ultra-low frequency due to circadian rhythm. Many of these heart rate variability indices increase during childhood (7).

Cystic Fibrosis (CF) has both upper and lower airways disease and inflammation, and patients take many medications that can affect autonomic tone. So before getting to CF, let's look at some of these potential influences from experience in other diseases to highlight some of the effects in more isolated conditions.

Air pollution exposure in healthy volunteers can be used as an inflammatory exposure. Healthy volunteers were exposed to 3 levels of air pollution and asked to walk around at a moderate pace (8). More exposure to air pollution resulted in a greater inflammatory response. Focusing on heart rate, all three levels of pollution exposure resulted in increases in heart rate and increases in the contribution of the low frequency domain over the high frequency domain, suggesting increased sympathetic tone, although mechanical effects of breathing can affect this. Looking at the effects of small particles, there was a decrease in RMSSD, suggesting decreased vagal tone, and an increase in low frequency and the low frequency to high frequency ratio, compatible with increased sympathetic tone. To summarize, exposure to air pollution can affect heart rate variability with changes suggesting decreased vagal tone and increased sympathetic tone.

Turning to asthma, which has both lower airways disease and inflammation, at rest supine, when there is poorer control (lower
FEV₁), there is a greater contribution of the low frequency domain and a lower contribution of the high frequency domain. In going from seated to supine, compared to controls, there is a greater contribution of the low frequency domain both seated and supine, and the change from seated to supine highlights the persistence of the low frequency domain.

As the heart sits in the thoracic cage and is subject to volume and pressure changes, especially when there is more mechanical impairment resulting in wider pleural pressure swings. In some studies, hyperinflation and air trapping was associated with greater contribution of low frequencies, suggesting increased sympathetic tone (9). In contrast, others found that with worse air trapping, the low frequency contribution decreased (10). They also found a modest increase in low frequency to high frequency ratio (LH/ HF) with elevations in C-Reactive Protein. When obstructive sleep apnea is added to COPD, the relative importance of the low frequency component becomes even more important (11).

Finally turning to CF, the first thing to note is that there are only limited studies, and at least in children with CF, many parameters do not have good reproducibility (12). In CF adults, although overall results did not differ from healthy controls, lung function was correlated with the relative contribution of low to high frequencies, reflecting a relative increased contribution of high frequencies with worse lung disease (13). This, unlike some of the COPD studies, suggested increased vagal tone. In contrast, a study in children found that the low frequency to high frequency ratio is elevated in CF patients, and this becomes more exaggerated after a 6-minute walk (14). It is unclear why this difference from CF adults was seen, as the FEV₁ was similar (69 and 71%).

In summary, heart rate variability can be measured and quantified. There are both linear and nonlinear methods of evaluation. While it has been taken as a measure of autonomic regulation, many factors pertinent to Cystic Fibrosis make the causality difficult to ascribe. These factors include upper airway obstruction, work of breathing and tidal volume, muscle mass affecting vascular bed, inflammation, diabetes, and medications.


#2 Can We Afford Novel Targeted Therapies?

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Patients with cystic fibrosis (CF) having poor resources experience deprivation-related health disparities. They are generally diagnosed at a later age, have worse nutritional status, and worse lung function than those from more affluent areas (1,2) and there is a lack of collective and individual resources necessary to optimize comprehensive CF care (3). Current CF care guidelines include treatments not available in resource-poor states. The high-cost, intensity of treatments and lack of knowledge preclude residents from developing countries from benefitting from enhanced CF care. Strategies that will impact on
longevity and quality of life for patients with CF living in resource-poor countries are: early diagnosis, treatment at a specialized CF center, nutritional optimization consistent with the nutritional resources of the region, focusing on airway clearance therapies, infection control, developing alternative lower-cost drug delivery systems, and improving adherence and compliance (4). Early diagnosis and treatment do provide significant long-term benefits for patients with CF (5). Increasing the awareness of CF as a possible diagnosis is important. But, early diagnosis can only realize its full benefit, if patients are then followed from diagnosis by a multi-disciplinary team in specialized CF centers (6).

At the CF center, another major challenge is providing the standards of CF care to the patients if they live long distances away from the center, when family resources are limited, and when the knowledge about CF of the personnel at the center and in their community is rather poor. But it is possible to enhance the care of children with CF even in battle-torn resource-poor regions through the implementation of the above strategies (4). Building the necessary capacity and expertise will require an effort made by the local community as well as the health care authorities.

In low-income countries, the state of the art document on CF (7) provides an excellent starting point. It provides a clear treatment guideline and emphasizes the importance of the basic treatment: mucolytic drugs, chest physiotherapy, prevention and treatment of lung infection; striving for an optimal nutritional status and continuous quality improvement as third pillar. Even without the costly new CFTR modulator drugs, a lot can be achieved and the current expected survival to age 50 years supports this (8). However, access to treatment in lower resources countries is an important part of the battle against CF. In resource-poor countries, costs of medications fall heavily upon the family and therefore cost and affordability are major hurdles.

The cost of some medicines must come down: medicines can only save lives if they are affordable for those who need them. The current competition in CFTR modulator development is therefore very welcome. Also, as the number of eligible patients in need of specific treatments rises, a positive effect on the cost is expected. To obtain drug access for patients, a combined action of the lay community providing the pressure and the medical community proving the rationale for the need of specific drug reimbursement will be important.

REFERENCES

D. ADVERSE ENVIRONMENTAL EXPOSURE AND CHILDHOOD LUNG HEALTH

#1 Outdoor Air Pollution and Children’s Health.

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Children are exposed to a mix of air pollutants. In urban areas, the pollutants linked with adverse effects are predominately generated by human activity and include particulate matter (PM) and oxides of nitrogen (NOx). Particulate matter is a complex mix of carbon, ammonium nitrate and ammonium sulphate, oxides and salts of many metals, and organic materials. However, PM from traffic-related air pollution (TRAP) predominately consists of particles of soot from incomplete combustion of fossil-fuels. Oxides of nitrogen, including nitrogen dioxide (NO2) are produced directly by combustion and by the oxidation of nitric oxide in the air via either a slow reaction with oxygen or a more rapid reaction with ozone. In some cities, ozone is another major pollutant. Ozone is formed by chemical reactions between other air pollutants, especially oxides of nitrogen with volatile organic compounds (VOCs) that are emitted from petrol car exhausts and directly from petrol. Recent evidence suggests a new source of outdoor VOCs –VOCs from cleaning products used indoors 1.

In urban areas, there is a high correlation between the concentrations of NOx and PM, especially for TRAP, and separating out independent effects is difficult in epidemiological studies. Therefore it is reasonable to assume that studies reporting associations with either pollutant reflect exposure to a complex mix of fossil-fuel derived emissions. An important source of outdoor air pollution in urban areas, especially in countries such as the UK and Germany, is diesel vehicles. Diesel exhaust comprises of gases, PM, VOCs and polycyclic aromatic hydrocarbons (PAHs). The smallest, and most inhalable diesel exhaust PM (PM less than 10 microns in aerodynamic diameter; PM10), consists of elemental carbon (soot or “black carbon”), with toxic compounds...
ABSTRACT

adsorbed onto its surface – including organic compounds, sulphate, nitrate and reactive transition metals. Diesel vehicles produce disproportionately more NO\textsubscript{2} than equivalent petrol or hybrid cars and vans, and have therefore been a focus of exposure-reduction policies. For example, on February 27th 2018, the German Federal Administrative Court ruled that the cities of Stuttgart and Düsseldorf (and setting a precedent for other cities) can legally ban more older, more polluting diesel cars from zones worst affected by pollution, despite opposition from both the government and the car industry. Despite opposition from both the government and the car industry, more polluting diesel cars from zones worst affected by pollution, (and setting a precedent for other cities) can legally ban more older, more polluting diesel cars from zones worst affected by pollution, despite opposition from both the government and the car industry

Long-term exposure of children to air pollution has adverse effects not only in childhood, but also across the lifecourse. From the very start of life, exposure of the mother to air pollution impairs fetal growth. For example, an analysis of pooled data from 14 population-based mother–child cohort studies from 12 European countries found an inverse association between head circumference at term and outdoor air pollution, in addition to increased prevalence of low birth weight at term. Reduced postnatal organ growth was found in a landmark study of over 11,000 schoolchildren from 16 communities in California, where clinically relevant suppression of lung function growth was lowest in children living in communities with the highest concentrations of PM\textsubscript{10}, dust, and NO\textsubscript{2}. In the same study, exposure to higher local concentrations of NO\textsubscript{2} was associated with new-onset asthma, with the risk of lifetime asthma higher in children living closer to a freeway. Indeed, a meta-analysis, which included 19 studies, concluded that increased exposure to either NO\textsubscript{2} or PM is associated with incident wheeze. An emerging area of concern is the link between air pollution and risk of pneumonia. For example, a metaanalysis analysis of 10 European birth cohorts, found associations between either PM or NO\textsubscript{2} and pneumonia in early childhood. For adults, it is very likely that exposures in childhood contribute to the associations between long-term exposure to air pollution and incident cardiovascular disease and lung cancer.

Given the robust evidence that air pollution has adverse effects children’s health, what should policy makers do? In 2016, the Royal College of Paediatrics and Child Health and the Royal College of Physicians published its report “Every Breath we take; the lifelong impact of air pollution” 7. Recommendations for policy makers in the report include: i) that governments must empower local authorities and incentivise industry to plan for the long term, ii) alternatives to cars fuelled by petrol and diesel must be actively promoted, along with active travel, iii) polluters must be required to take responsibility for harming health and political leaders must introduce tougher regulations, including reliable emissions testing for cars – and must enforce regulations vigorously, and iv) we must protect those most at risk – especially children. For health professionals, the report concludes that health professionals should be provided with the “tools to discuss air pollution with their patients”. To date, relevant guidelines (e.g. for asthma) do not provide these tools. A good start for those revising management guidelines is the advice developed by the British Lung Foundation (BLF) 8, which includes; i) reducing strenuous, outdoor exercise on high pollution days and exercising indoors in a well-ventilated area, and for asthmatics, to ensure a reliever inhaler is at hand, and ii) when travelling to school or work, to stay away from pollution hotspots. Parents may ask about giving their child a facemask on high pollution days – but the BLF guidance sensibly states that “at the moment there’s very little evidence to recommend the use of face masks, and that many people find wearing a mask very uncomfortable, and some people with a lung condition report finding breathing more difficult when there’s something covering their mouth”.

In conclusion, there is overwhelming evidence that air pollution harms children’s health, with implications across the whole lifecourse. Governments must therefore urgently reduce children’s exposure to TRAP. Removing the current toxic fleet of diesel vehicles is an important first step in this process.


#2 Adverse Environmental Exposure and Childhood Lung Health: Household Air Pollution and Lung Health

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There is increasing evidence suggesting that lung health trajectories are set in early life with the antenatal and early-life period as critical exposure time points.[1] Further, childhood respiratory diseases are a global health problem with lower respiratory tract infections (LRTI) remaining the leading cause of under-5 mortality in low- and middle-income countries.
Household air pollution (HAP) from inefficient combustion or the use of alternate fuels is a major global problem with 3 billion people relying on alternate fuels for cooking and heating, resulting in 4 million premature deaths associated with this.[2] Further, 40% of children are exposed to environmental tobacco smoke, often from within the home.[3]

In low- and middle-income countries (LMIC), types of alternate fuels used depend on availability and geographic distribution. Burning of alternative fuels (such as paraffin, wood, coal and other biomass substances) contributes to indoor air pollution, a recognized risk factor for respiratory disease.[4] This coupled with inadequate ventilation may result in very high exposure levels particularly to infants and children. However, HAP exposure may also play a significant role in lung health for children from high-income countries (HIC) with exposure from a multitude of sources including combustion, tobacco smoke, furnishings and cleaning products.[2, 5] With rapid urbanization and mushrooming of peri-urban communities, volatile organic compounds such as benzene and toluene and trace metals (vanadium) are increasingly recognized exposures impacting on lung health.[6]

Antenatal air pollution exposure impacts lung development[7] and has been linked to decreased lung function in infancy and childhood, increased respiratory symptoms, and the development of childhood asthma.[8] A large number of studies from both high-income and LMIC explore the associations between HAP and a number of childhood respiratory outcomes.[9, 10] An overall summary risk of HAP and childhood respiratory disease found an almost 2-fold increase.[11, 12] Further, postnatal air pollution exposure is associated with decreased lung function and impaired lung growth.[13, 14]

Addressing HAP exposures is vital in decreasing childhood lung disease and improving long-term lung health outcomes. To date, intervention studies have been largely inconclusive.[15, 16] and urgent and effective public health policies focusing on reducing HAP and tobacco smoke exposure are required.

References


Climate change is a real and undeniable occurrence, with changes in weather patterns, droughts, floods and extreme weather events becoming more frequent all over the world. In this presentation, I will focus on how climate change modifies environmental factors that impact on respiratory disease and “climate sensitive” respiratory conditions. The interactions between climate change and health outcomes are complex (1). Ambient air pollution, with increasing tropospheric particulate matter (PM), \( \text{SO}_2 \), \( \text{O}_3 \), and oxides of nitrogen (NO\(_x\)), contribute to greenhouse gases, a major contributor to climate change. Air pollution and climate change both contribute to ecosystem dysfunction and biodiversity loss. This, together with the adverse social impacts from climate change directly and from ecosystem dysfunction have adverse impacts on human health. Table 1 sets some of the ways in which climate change contributes to adverse health outcomes.

Higher ambient temperatures are likely to have adverse environmental consequences through heat waves (2) and the creation of urban heat islands. Higher temperatures increase the risk of physiological disturbances e.g., dehydration, electrolyte imbalance and heat stress, especially on vulnerable groups (3–5). Temperature rise is also predicted to contribute to deteriorating air quality, with an increase in particulate matter and surface level \( \text{O}_3 \) (6). Poor air quality has negative impacts on lung growth and development and on lung function. Higher levels of particulate matter are associated with lower lung function in children (7). Higher levels of ozone alter lung structure and growth in infant rhesus monkeys (8).

Climate sensitive respiratory diseases include: respiratory infections, asthma, cystic fibrosis and chronic obstructive pulmonary disease (COPD) (9). The impact of climate change on respiratory infections is complex and depends largely on the local environmental conditions. Pneumonia in the tropics occurs in the rainy season (10), which is anticipated to become more prolonged under climate change scenarios. However, respiratory syncytial virus seasons are becoming shorter in temperate climates (11). Poor air quality increases the risk of respiratory infections through a variety of mechanisms including increased ambient \( \text{O}_3 \) reducing vitamin D levels and increased PM increasing the risk of tuberculosis. Climate change impacts on COPD include increased mortality and increased acute pulmonary exacerbations.

In summary, climate change is real and will adversely affect human health; especially respiratory health. Pediatricians have a major role to play in educating policy makers, the general public and their patients about the dangers and the need for mitigation strategies.

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**Table 1: Consequences of climate change and adverse health outcomes**

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<th>Consequence of climate change</th>
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Allergic diseases cover a heterogeneous group of symptoms in various organs and systems, ranging from lower respiratory (wheezing, coughing, breathlessness), upper respiratory and ocular (hay fever and rhinitis), to skin conditions such as eczema. Different manifestations of allergic disease may co-exist in the same patient [1]. However, it is important to emphasize that in clinical situation, confirmation of IgE-mediated sensitization (e.g. by using skin prick tests and/or measurement of specific serum IgE) does not necessarily indicate that patient’s symptoms are caused by an immunologically-mediated allergic reaction [2]. Recent studies which used machine learning techniques to investigate patterns of skin test and IgE data collected on multiple time points throughout childhood in a population-based birth cohort have shown that “allergic sensitization” is heterogeneous, and that there are several distinct sub-groups of sensitization, which differ in their association with asthma presence, progression, severity and response to treatment [3,4]. The disaggregation of sensitization, and knowing which subtype a child belongs to, may help clinicians predict how asthma is likely to progress, and later-life asthma outcomes. However, while different sensitization subtypes can be uncovered using a large amount of data collected over long periods of time, this cannot be directly translated to a clinical practice, when the pediatrician sees a child at a single time point. We urgently need better diagnostic markers and algorithms to help practicing physicians differentiate between benign and clinically important allergic sensitization.

In the context of respiratory allergy, the interpretation of skin prick tests and blood tests which measure specific serum IgE remains arbitrary, since it traditionally relies on arbitrary cut-offs which have relatively poor ability to distinguish between asymptomatic sensitizations and clinically relevant allergy. Furthermore, age, sex or ethnicity of the patient is usually not taken into account. We have shown that both age and sex should be taken into account when interpreting the results of standard allergy tests, and that age- and sex-specific normative data are urgently needed [5]. Also, the diagnostic accuracy of these tests in asthma diagnosis can be improved by reporting the results in a quantitative manner (e.g. the titer of IgE, or the size of skin test wheal diameter).

There is increasing evidence that sensitization to some, but not all allergenic proteins from different sources (e.g. house dust mite or pollen) is important for the expression and severity of asthma. Therefore, measuring sensitization to these individual molecules (often referred to as allergen components) using component-resolved diagnostics (CRD) may be more informative than standard tests using whole allergen extracts. In two population-based birth cohorts from the UK and Sweden, we have recently shown IgE reactivity to a limited number of components in preschool identified children at high risk of asthma in adolescence [6]. Persistent asthma at age 16 years in Sweden was predicted by IgE reactivity in early life to four risk molecules (peanut Ara h 1, birch Bet v 1, cat Fel d 1, and grass Phl p 1), whilst in the UK similar association was observed for five allergenic components (dust mite Der p 1 and Der f 2, timothy grass Phl p 1), and each of these patterns was associated with different risk for having asthma [7]. We have also shown that different longitudinal trajectories of sensitization to allergenic molecules from timothy grass and house dust mite during childhood had different associations with asthma [8]. These data suggest that understanding the developmental pathways of IgE responses to multiple allergenic components may help development of diagnostic and prognostic algorithms for asthma. To address this, we applied novel machine learning techniques to CRD sensitization data throughout childhood to describe the architecture of the evolution of IgE responses to >100 allergen components from infancy to adolescence [9]. This analysis has shown that the timing of onset of
specific patterns of sensitization may a key indicator of the subsequent risk of asthma [9].

The above studies show that better resolution of longitudinal patterns of sensitization to multiple allergenic components may facilitate the development of diagnostic algorithms, which can be used for the prediction of current and future risk of asthma. However, most current guidelines do not recommend the assessment of allergic sensitization as an objective test for asthma diagnosis. For example, UK National Institute of Health and Care Excellence (NICE) guidance on the diagnosis of childhood asthma proposes a diagnostic algorithm which incorporates the sequential use of four measures of lung function and inflammation (spirometry, bronchodilator reversibility, fractional exhaled nitric oxide, and peak flow variability; http://www.nice.ac.uk/Guidelines/In-Development/). We have recently tested this algorithm, and found poor agreement between the algorithm and asthma diagnosis amongst children aged 13–16 years [10]. One important question going forward is how to best incorporate tests for the assessment of allergic sensitization into diagnostic algorithms for asthma, both in terms of confirming asthma diagnosis, and for the assessment of future risk (e.g. of asthma exacerbations, or disease persistence) amongst patients with established disease.

In conclusion, a series of recent studies have shown that it may be possible to develop individualized risk prediction algorithms for the diagnosis and prognosis of asthma, which should include novel methods for assessing IgE sensitization status, likely in conjunction with information on the patterns and severity of symptoms, and other objective tests (such as lung function and measurement of airway inflammation).

REFERENCES

#2 Management of Food Allergy, Cross Reactivity and Sensitization.

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The technique and standardization of extracts for the diagnosis of allergy have experienced an outstanding improvement, even though skin tests (ST) are still performed essentially following the principles formulated by Charles Blackley almost 150 years ago. This is so because ST basically identify sensitization against allergenic protein sources. After the discovery in 1967 of IgE as the immunological substrate responsible for allergic reactions, in vitro methods able to detect IgE antibodies in sera of allergic patients were developed (RAST, ELISA). Nevertheless these new methods still identified specific antibodies against allergenic sources.

However, crude biological extracts obtained from these allergenic sources are in fact a very heterogeneous mixture containing proteins, glycoproteins and polysaccharides, some of which have an allergenic power, and others not. Different in vitro methods (i.e. Immunoblotting) can be used to identify which of these proteins contained in an allergenic source are actually allergens, because they are able to attach specific IgE.

Furthermore, the use of the DNA technology has made it possible to sequence and to clone molecules with allergenic potential, which has in turn enabled the creation of an increasingly more complete base of allergens. The incorporation of these proteins to a series of diagnostic systems constitutes the so-called MOLECULAR or COMPONENT-RESOLVED diagnosis that, unlike traditional diagnostic methods, do not use proteic extracts from allergenic sources, but natural purified or recombinant allergens. This has led to a major advance in allergy diagnosis, since:
It provides a greater diagnostic precision. Indeed, this new diagnostic approach makes it possible:

a) To identify new allergens able to explain allergic reactions previously inexplicable.
b) To distinguish clinically relevant molecules from others that, even if able to attach IgE, have a marginal or even null significance.
c) To consistently explain cross-reactivity phenomena in both vegetal and animal proteins.
d) To explain some geographical differences observed in allergy patterns among patients sensitized to the same allergenic source.
e) To elucidate the differences in the clinical profiles depending on the patient’s age.

It makes it possible to perform more precise prognostic approaches, as well as to improve the safety of other commonly used diagnostic procedures, such as challenge tests. In this sense, the mere positivity as well as the intensity of that positivity against certain allergenic components can be useful to evaluate:

a) The chronology of the progress from sensitization to clinically patent allergy.
b) The possibility to overcome the allergic disease.
c) The risk of developing reaction during a challenge test.
d) The risk of reactions and the foreseeable intensity of those reactions in relation to the food cooking process.
e) The risk of more severe reactions.

In consequence, molecular diagnosis can be useful in taking a decision with regards to performing or not a challenge test, to decide whether that test should be performed with the food raw or cooked as well as the cooking method, in relation to establishing a prognosis about the probability to overcome the allergic disease and when that could happen, etc.

It permits a more accurate and precise therapeutic approach, both in relation to the recommendation of preventive measures, and in the prescription of drugs and Specific Immunotherapy (SIT). In this last case, not only in relation to whether SIT should be prescribed or not, but also in relation to its composition.

It makes it possible to establish a sound suspicion in relation to the primary sensitizing allergenic source in case of polysensitized patients. Among the proteins contained in an allergenic source, some are species-specific and others are homologous proteins present in several allergenic sources. Thus, sensitization to species-specific proteins would indicate a genuine sensitization to that allergenic source, whereas sensitization to cross-reactivity proteins would raise more doubts about what would be the primary sensitizing source.

The use of multiplex platforms can help to clarify some cases suspect of allergy in which it has not been possible to find the potentially responsible allergen (i.e. Idiopathic Anaphylaxis).

In summary, the traditional diagnosis by using ST, RAST or both offers quite limited information about the authentic nature of allergic diseases and their potential clinical, therapeutic and prognostic implications. The Component-Resolved Diagnosis entails an outstanding qualitative step that permits a great improvement in the diagnosis and management of allergic patients, since its concomitant use with clinical history and other in vivo and in vitro diagnostic methods significantly increases the diagnostic accuracy.

RECOMMENDED REFERENCES
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Topic Sessions - Part 3
A. SPANISH SESSION

#1 Is It Worth Knowing Which Virus Is Associated With a Lower Airway Respiratory Infection in Children? The Experience of Severo Ochoa Hospital.

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Respiratory viral infections, especially respiratory syncytial virus (RSV) and rhinovirus, are the major risk factors for the occurrence of episodes of wheezing in infants and young children.

Bronchiolitis is the most common acute respiratory infection of the lower respiratory tract in children under one year of age and accounts for 18% of all pediatric hospitalizations. RSV causes approximately 70–80% of all of them, followed by rhinovirus, adenovirus, metapneumovirus (HMPV) and bocavirus (HBoV).

In studies in which all patients with a history of bronchiolitis regardless of the causal virus have been analyzed globally, the prevalence of recurrent wheezing is 75% in the first two years of life. RSV was the first to be related to the development of asthma in children, although in recent years other viruses such as rhinovirus or the recently described HMPV and HBoV are also being evaluated. In fact, several recent studies have shown that the risk of presenting asthma at 6 and 11 years, among children hospitalized for bronchiolitis, is higher in children RSV-negative compared to RSV-positive. A cohort study with follow-up until 15–18 years has shown that the risk of developing asthma in adolescence is higher in children hospitalized for rhinovirus-associated bronchiolitis compared to that associated with RSV.
With regard to HMPV, to date only one study has evaluated the mid-term evolution of children admitted for bronchiolitis due to HMPV, finding a frequency of recurrent wheezing similar to that of children admitted for RSV bronchiolitis, in both cases being 5 times higher than the control group.

Since its description, numerous studies have investigated the prevalence of HBoV and its role in respiratory infections, but to date only one has evaluated its possible role in the development of asthma, noting that 50% of children admitted for bronchiolitis due to HBoV had asthma at 5–7 years.

The role of respiratory viruses as triggers of asthma attacks in adults and children has been known for more than three decades. In recent years, the use of PCR-based techniques has revealed that the proportion of asthma exacerbations associated with viruses is very high. In Spanish children hospitalized for an asthmatic exacerbation, at least one respiratory virus was identified in 71% of the included patients.

Although almost all respiratory viruses, including HMPV and HBoV, have been associated with asthma attacks, rhinovirus and RSV are the most frequently detected in infants and schoolchildren with asthma. The systematic study of the viral etiology of lower respiratory tract infections, especially bronchiolitis and recurrent wheezing, can make it possible to anticipate the short and medium / long term evolution of children.

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the normal progression of the disease despite adequate antibiotic or drainage treatment. This aspect is crucial for the design of studies on the treatment of children with PEE. If a clinical or research protocol leads to an increase in therapeutic measures in case of therapeutic failure, it is necessary that this failure is well defined and reliable. Otherwise, many patients with a slow progression (for example, with persistent fever after several days) will be assigned to the group of therapeutic failure, which will lead to an overvaluation of second-line treatments over the generally more conservative first-line treatments.

Need for clinical trials

The number of clinical trials conducted in children with PEE is surprisingly scarce and most have been aimed to comparing treatment with pleural tube and fibrinolytics versus videothoracoscopy. Although treatment with antibiotics, without a pleural tube, is a first option considered in many centers, there is no clinical trial that has compared conservative treatment (only with antibiotics and supporting measures) with treatments that include measures to evacuate the effusion (pleural drainage or surgery). This may be due to a prejudice against the efficacy of conservative treatment, which can be seen as inferior or dangerous. However, the evaluation of more conservative treatments and their comparison with invasive techniques, such as surgery, does develop in other diseases such as appendicitis. In the last 10 years, numerous clinical trials in adults and children have shown that treatment without surgery is an adequate therapeutic option in patients with acute uncomplicated appendicitis, something that would have been unthinkable 10–20 years ago.

Conclusions

Although a not too infrequent disease, the treatment of PEE in children continues to be controversial. The lack of clinical trials and the lack of definition of what is considered a therapeutic failure continue to allow excessive variability in clinical practice and favor the idea that more invasive treatments are more effective than the more conservative ones, without there being any adequate evidence of this. Well-designed clinical trials are needed to answer unresolved questions regarding this issue.

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#3 The Challenge of Diagnosing Tuberculosis and Nontuberculous Mycobacteria Pulmonary Disease in Children

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Tuberculosis

The World Health Organization estimates that 530,000 cases and 74,000 child deaths every year are attributable to tuberculosis (TB), but a recent modeling exercise estimated 239,000 deaths in children in 2015, most of them being under 5 years old and not receiving TB treatment (1).

The immunodiagnosis of TB relies on the detection of a cell-mediated immune response. The tuberculin skin test (TST) is the standard test, but can have low specificity in BCG-vaccinated children. Interferon gamma release assays (IGRAs) measure the concentration of interferon gamma in blood exposed to specific M. tuberculosis antigens, improving specificity. However, TST and IGRAs have significant limitations such as their inability to discriminate between latent TB infection and active TB and also, both are negatively affected by immune compromise and malnutrition. Furthermore, IGRAs have contradictory results in young children, are solely licensed for the diagnosis of latent TB infection (not active TB) and are not recommended in resource-limited, high-burden TB countries, where their sensitivity is lower than that of TST. The new Quantiferon TB Gold Plus test (Qiagen, Hilden, Germany) adds CD4-stimulating and CD8-stimulating antigens but has not yet been fully tested in children. The C-Tb is a new intradermal skin test using ESAT-6 and CFP-10 to induce IFN-gamma releasing CD4+ T cells. A recent study showed that C-Tb administration was safe and detected similar numbers of people with TB infection with very high concordance to QFT. Furthermore, the test showed good specificity and was not affected by BCG vaccination. However, children younger than 5 years were not included in the study and the test was positive in fewer patients with active tuberculosis than was QFT.

The confirmation of active TB through culture and drug susceptibility testing of Mycobacterium tuberculosis still remains the diagnostic gold standard. Samples in children include gastric aspirates, induced sputum and nasopharyngeal aspirates. However, mycobacterial growth requires 3 weeks and becomes positive in only 30% of children with probable TB. Moreover, smear microscopy that gives a presumptive rapid diagnosis of TB is rarely found in children. Bronchoalveolar lavage should be reserved for children with uncertain diagnosis or endobronchial TB as its bacteriological yield is lower than that of serial gastric aspirates. To overcome the difficulty of respiratory sampling in children, stool has been studied as an alternative sample but it has not shown better sensitivity.

Nucleic acid amplification tests (NAATs) and antigen detection are rapid tests that include real-time polymerase chain reaction and line probe assays. The limits of detection of PCR are approximately 100–150 CFU/mL versus 10–100 CFU/mL and 50–150 CFU/mL for liquid and solid media respectively and 1000–10,000 CFU/mL for microbiology. The PCR has similar sensitivity than culture in smear-positive samples but less than culture in smear-negative samples.

Recently developed NAATs can also simultaneously detect genes conferring drug resistance. The rapid Xpert MTB/RIF detects a series of mutations associated with rifampicin resistance (rpoB) of the Mycobacterium complex and the WHO recommends this test in children suspected of multidrug-resistant TB or HIV coinfection. The
new Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, USA) uses two amplification targets (IS6110 and IS1081) to reduce the limits of detection to 16 organisms per milliliters. One study showed that the Ultra detected most of the children with positive culture and also some with negative culture(2). Other tests such as the GenoType MTBDRplus® (Hain Lifescience, Holland) or the Genoscholar NTM + MDRTB® (Nipro Europe, Germany) are especially useful for simultaneously detecting isoniazid- and rifampin-resistance mutations.

Despite the use of all these techniques, 70% of the children with active TB will not have a positive microbiological confirmation and the diagnosis will be based on the history of exposure, the clinical features and the chest radiograph findings. Mediastinal lymphadenopathies are the hallmark of TB in children but poor interobserver agreement has been reported for radiologist and clinicians. A standardized approach to analyze chest X-ray could improve interobserver agreement in the interpretation(3). Also, CT, mediastinal ultrasound and MRI can be useful to detect lymphadenopathies and lung involvement in patients with difficult diagnosis or complications. However, there is no role for the use of these techniques in a tuberculin-positive child with no symptoms and a normal chest radiograph(4).

Biomarkers, including cytokine responses to different specific antigen stimulation, can provide information about disease status and risk for progression(5). More studies are required to evaluate the sensitivity and specificity of these biomarkers as well as their clinical implications.

Nontuberculous mycobacteria

There are more than 170 recognized species of nontuberculous mycobacteria (NTM) but the majority of disease in humans is caused by fewer than 20 of them. NTM are ubiquitous in the environment, and can be found in soil, tap water, fresh water, brackish water, salt water, foodstuffs, and a variety of animals. The mode of transmission in pulmonary infections is by inhalation of aerosolized NTM.

The estimated incidence of NTM disease in children is approximately 0.6 to 2.1 cases per 100,000 children per year. During the last decades, an increasing incidence of pulmonary NTM isolation has been reported. NTM have emerged due to the declining incidence of TB, aging population with chronic lung diseases, the improvement in diagnostic techniques and an increased awareness of NTM diseases by physicians. The majority of children with NTM pulmonary disease (NTM-PD) have underlying lung disease, such as cystic fibrosis, bronchopulmonary dysplasia or primary ciliary dyskinesia.

The prevalence of NTM varies in different countries. M. gordonae is frequently recovered from a clinical sample but it is mostly considered not to be clinically relevant. Mycobacterium avium complex (MAC) is the most frequently isolated NTM in pulmonary disease in European countries and also in CF patients in the United States. M. abscessus complex (MABSC) includes three subspecies with different clinical significance (massiliense, abscessus and bolletii) and is more commonly seen in young adults and children with more severe lung disease.

Many children with NTM-PD will have positive TST as PPD is a heterogeneous mixture of more than 200 mycobacterial peptides, some of which are expressed by NTM. Skin testing with mycobacterial sensitins derived from NTM (e.g. M. avium or M. kansasii) has been shown to be more sensitive than TST in NTM disease, but are currently available only for in vitro use and have limited ability to discriminate between different mycobacterial infections. IGRAS are supposed to be specific for M. tuberculosis but ESAT-6 and CFP-10 are also expressed by various NTM species, including M. kansasii, M. marinum, and M. szulgai. "False-positive" IGRA results have been reported in patients infected with these NTM species and also in patients with NTM species without this RD-1 region.

Clinical symptoms may be indistinguishable from TB or other respiratory diseases. They typically present with fever, weight loss, fatigue, asthenia or anorexia, cough, sputum production, hemoptysis or dyspnea. Also, a hypersensitivity pneumonitis syndrome due to mycobacteria may occur in patients who are exposed to MAC antigens. In a CF patient, NTM should be suspected when there are constitutional or respiratory symptoms, unexpected decline in lung function, or progressive radiographic disease, that do not respond to usual therapy.

A chest radiograph may not be adequate for evaluating a patient with suspected NTM infection. High-resolution computed tomography is more sensitive to detect the parenchymal lung damage, including bronchiectasis, infiltrates, multiple nodules, multifocal bronchial disease, and cavities.

Sputum, induced sputum, bronchial washings, bronchoalveolar lavage or transbronchial biopsy samples can be used to evaluate individuals suspected to have NTM-PD. Laboratory processing of samples should ideally be performed within 24 hours of collection or refrigerated if delays longer than 24 hours. Oropharyngeal swabs fail to detect NTM infection and are not recommended. Also, there is no role for the culture of gastric aspirates, fecal specimens or urine to detect NTM infection in HIV-negative patients.

Most NTM grow under the same culture conditions as M. tuberculosis. Respiratory tract samples should be cultured (following decontamination) on solid and liquid media for 8 to 12 weeks. Some NTM species such as M. genavense or M. haemophilum only grow in culture after prolonged incubation times or after the addition of special growth factors. Microscopy, preferably carried out using auramine-phenol, allows the direct evaluation of bacterial burden but cannot distinguish NTM from M. tuberculosis.

Direct molecular detection can detect NTM in respiratory specimens but are more expensive and less sensitive than conventional culture and their role in routine clinical practice remains to be determined. Available methods include the line probe assay GenoType® CM (Hain Lifescience, pers. commun.), the CapitalBio Mycobacteria Real-Time PCR Detection Kit (CapitalBio Corporation, Beijing, China) and the REBA Myco ID (YD Diagnostics, Yongin, South Korea). A useful application of direct molecular detection is to rapidly differentiate M. tuberculosis complex from NTM in smear-positive samples.

New commercially available spectral reference libraries have been issued for the differentiation of NTM using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry.
Abstract


Computed tomography should be performed in children with tuberculosis in whom the diagnosis is suspected but in whom the disease is not apparent. The radiographic signs, including TB, plus compatible clinical symptoms and exclusion of other diseases with similar symptoms and radiological changes are unspecific, and clinical deterioration could occur due to the natural progression of the disease or other concomitant respiratory infections. Probably, patients with multiple positive cultures and/or positive AFB smears are more likely to have NTM disease but a lower threshold to treat may be appropriate for more virulent species, such as MABSC(10).

The American and British Thoracic Societies proposed a simplified criteria for the establishment of the diagnosis of NTM disease(8,9): [1] compatible correlates in a radiograph or CT scan of the thorax, including bronchiectasis, infiltrates, multiple nodules, multifocal bronchial disease, and cavities, plus [2] compatible clinical symptoms and exclusion of other diseases with similar symptoms and radiological signs, including TB, plus [3] at least 2 sputum samples which are positive on culture from 2 separate expectorated samplings or 1 positive culture from at least 1 bronchial wash or lavage (both of which are only relevant for patients with nodular bronchiectatic disease, who do not expectorate sputum) or isolation of mycobacteria from a sterile site, including lung tissue obtained by transbronchial or open lung biopsy.

These criteria are difficult to apply in CF patients because radiological changes are unspecific, and clinical deterioration could occur due to the natural progression of the disease or other concomitant respiratory infections. Probably, patients with multiple positive cultures and/or positive AFB smears are more likely to have NTM disease but a lower threshold to treat may be appropriate for more virulent species, such as MABSC(10).


4 Severe Asthma in Costa Rica

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Asthma is the most common chronic disease in childhood and its prevalence has been increasing worldwide in the last years. It is a complex disease that involves genetic and environmental factors, and has a variable expression among individuals. Severe asthma, defined as asthma that requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller drug to be controlled, or that remains uncontrolled despite this medication is even more challenging, with an estimated global prevalence of 5–10%. However, data of the true prevalence of severe asthma are scarce, particularly in developing countries.

The ISAAC (International Study of Asthma and Allergies in Childhood) study managed to record data on prevalence of asthma and allergies in children around the world and found a wide variation with reports ranging from 1.6% to 36.8% (1). These findings suggested that environmental factors and lifestyle changes could be involved. Latin American countries that participated (including Costa Rica) were found to have a high prevalence of asthma in childhood (>15%). The region is very heterogeneous in matters of ethnicity, culture, education, climate, health access and socioeconomic conditions, all of which make asthma an important health burden in these countries, with greater morbidity and mortality (2).
Costa Rica is located in a tropical region, it has various micro-climates through its territory and it hosts around 5% of the world’s biodiversity. These features result in a highly humid environment with a broad spectrum of allergens. A research study collected house dust samples from different homes in Costa Rica and discovered high concentrations of mite and guanine allergens in beds and bedroom floors, especially in more humid areas and in urban settings (3).

Asthma in Costa Rica has been studied in the last decades, with initial analyses determining a prevalence of 23.4% that increased to 27% according to the latest ISAAC report (4); to date, asthma prevalence in Costa Rica is one of the highest around the world. Several reasons for this statistic have been proposed: allergen sensitization, genetics, infectious causes, and vitamin D levels and lifestyle changes, among others.

The relationship between total serum IgE level, skin test reactivity to aeroallergens, asthma, allergic rhinitis and eczema was examined in a group of Costa Rican school children (5); high levels of total serum IgE were found and they established a strong association between serum total IgE levels and asthma and between the number of positive skin tests to allergens and allergic rhinitis. The results were similar to those found in countries with a “Western” lifestyle. Another study demonstrated asthmatic children were more sensitized to mites, cockroach, cat, and molds (Alternaria and Cladosporium) than nonasthmatic children. Other investigations have also established factors such as paternal asthma, exposure to mold and positive IgE response to dust mite as determinants for airway hyperresponsiveness in children with asthma in Costa Rica. Similarly, studies on helminth infection and asthma have been performed; Costa Rica has a low prevalence of Ascaris lumbricoides infection, but a cross-sectional study found a strong association between sensitization to Ascaris lumbricoides and increased asthma severity and mortality in children.

Vitamin D has been a common research topic in the last decade. Costa Rica was one of the first countries to address the relationship between vitamin D levels and asthma; the study demonstrated vitamin D deficiency in a group of children with asthma and an association between lower levels of vitamin D and increased asthma severity (6).

Costa Rican society’s lifestyle has changed in the last years, adopting many habits from more developed countries. This has resulted in more sedentary children, high sugar and fat diets and more chronic diseases. It is well known that obesity is a risk factor for severe asthma and this is becoming a health issue in our population. Epidemiological studies have reported an overweight and obesity prevalence of 34.5% and 26.2% respectively among schoolchildren, especially in children aged 7–9, boys, children from urban areas, and from mid-high socioeconomic status (7).

In Costa Rica, asthma represents a major health problem; poor asthma control is frequent in our population due to environmental factors, lack of patient education, low adherence to controller medication and limited access to health services. This leads to increased hospital admissions, more school absences and lower quality of life.

Severe asthma accounts for a small part of all children with asthma, however, this condition comprises difficulties in diagnosis, treatment and further monitoring that increase healthcare costs. When assessing severe asthma, the first step should be confirming the diagnosis (9). At primary levels, general practitioners and pediatricians may face difficulties with this task since symptoms can be under-recognized and professionals may not have clear concepts on what severe asthma is and how to treat it. Furthermore, when ruling out differential diagnosis, complementary tests are not always available in primary care centers (spirometry, specialized blood analysis, bronchoscopy, sweat test, CT scan). Referral to a specialist is often delayed because of misdiagnosis and patients are frequently under treated.

Once diagnosis has been reassured, treating comorbidities, avoidance of risk factors and adequate treatment are key elements in severe asthma management (8). As mentioned before, Costa Rica’s climate and abundant flora and fauna results in an allergen-rich environment, thus much of the patient’s education should focus on recognizing and avoiding potential triggers. Our center has developed a Home Visit Program, where a multidisciplinary team (nurses, respiratory therapist, pharmacist and social worker) visits patients homes and schools weekly. Their role in evaluating the environment where severe asthma patients live has been vital to identify risk factors that otherwise would have been missed. This has also allowed the development of educational strategies in order to improve adherence and an appropriate use of controller therapies.

Due to severe asthma heterogeneity, multiple clinical phenotypes have been described. Novel asthma therapies aim to develop phenotype-specific interventions that will grant patients a better disease control. Biologics such as omalizumab and mepolizumab have shown good results, and genetic analysis is being used to target specific mechanisms in asthma pathogenesis. This individualized precision medicine signifies a financial concern to public health authorities in developing countries, as resources are limited in the region and these new therapies may not be widely available. Treatment for severe asthma represents a high economic burden for Costa Rica’s public health system. Patients may require two or more drugs to achieve controlled asthma status and medication options are limited. A subgroup will not respond to traditional interventions and will require more complex treatment regimens. Omalizumab was one of the first “add –on” therapies used in children with severe asthma, and it implies a very high cost to our institution. Currently 6 patients are being treated with Omalizumab in our center with good results.

Further follow-up for severe asthma patients involves a multidisciplinary team; pulmonologists, allergists, dietitians, nurses, social workers, pharmacists and respiratory therapists work together to support these patients. Patient access to these services may be challenged by geographic, social and economic factors, so assuring a continuous surveillance in this group is sometimes difficult, making severe asthma even more complicated to treat.
Since the development of worldwide guidelines on the diagnosis and management of asthma, key goals in asthma management have been established: i) achieving and maintaining asthma control; ii) decreasing hospitalization; iii) decrease mortality. Trends in hospitalization and mortality due to asthma were analyzed during a 15-year period, along with the results of a national asthma education program for health professionals and the free usage of inhaled corticosteroids in primary care settings (9). The outcome was an important reduction in asthma hospitalizations both in children and adults (53%) and reduced asthma mortality.

Costa Rica is a Latin American country with multifactorial high asthma prevalence, with studies reporting multiple allergen sensitizations in children in our population. Challenges remain in improving awareness on severe asthma management among health professionals in order to achieve an adequate diagnosis and treatment. Educational strategies should focus on avoidance of risk factors and promotion of treatment adherence. Socioeconomic limitations in our region are still a barrier to overcome when treating asthma patients. Further asthma research in developing countries is needed to obtain a better knowledge of our population.


clinicians and the families. Tomassoni identified several indications for exercise testing:

- Evaluating symptoms associated with exercise
- Evaluation for exercise-induced asthma
- Assessment of aerobic capacity, either by maximal or submaximal protocols
- Assessment of muscular endurance or strength
- Documenting the course of progressive diseases
- Evaluating the effects of therapy and rehabilitation programs

Exercise is also an effective diagnostic tool for evaluating the symptomatic child. The exercise challenge test improves diagnostic results and also provides information that is helpful in developing PA programs or in prescribing specific, individualized, exercise protocols.

The importance of physical activity and exercise has been more widely described in a few respiratory conditions such as asthma and cystic fibrosis, although we can also find information regarding its benefits in patients with bronchopulmonary dysplasia, cerebral palsy and others.

**Asthma**

Asthma is one of the most common respiratory disorders in childhood. Considerable attention has been given to the relationship of asthma and obesity. The question remains whether children with asthma are more likely to be obese or if obese children are at greater risk of becoming asthmatic.

One possible benefit of routine PA or exercise is that increased cardiorespiratory fitness may reduce the occurrence of effort-induced bronchoconstriction/effort-induced asthma by decreasing the ventilatory requirement of a given work rate.

Children affected by chronic asthma or bronchoconstriction and who are involved in PA, frequently will avoid exertion that requires higher ventilation. If the individual learns to induce a state of refractoriness through warm-up activities, he/she would be able to manage the breathing difficulty associated with exertion and the related anxiety.

Specific recommendations for PA and exercise in children with asthma may include:

- Sports and other activities can be allowed if symptoms are well controlled. Patients with severe symptoms would need to alter training or competition.
- Scuba diving is not recommended if children are symptomatic or have abnormal pulmonary function.
- Optimal long-term control of asthma may be achieved by use of medication and routine control

**Cystic fibrosis**

Many patients with mild cystic fibrosis (CF) have adequate exercise tolerance, but as the disease progresses, exercise tolerance likewise decreases. Aerobic fitness has been shown to be a key predictor of disease prognosis and mortality in patients with CF, independent of factors such as age, sex, lung function and nutritional status.

For children and adolescents with CF, the associations between health, activity, and fitness are important to understand in order to establish how these variables impact on the disease processes. For the CF child, it is important to be as active as possible from the beginning of their lives because when the disease progresses and pulmonary function severely deteriorates, the disease will itself contribute to a decrease in PA. This pattern creates a cycle of ensuing hypoactivity leading to deterioration in physical condition that causes further hypoactivity.

Although the use of exercise will not alter the pathophysiological course of CF, it will bring significant benefits to the patient. There is some evidence to suggest that both aerobic and strength training programs can have a positive impact on patient’s health. However, whilst the potential benefits of habitual PA and exercise are known, the lack of guidelines and recommendations are holding back many clinicians to allow their young patients and families to enjoy these benefits.

Determining the effects of exercise training post lung transplantation would also be an important area of future study.

Healthcare providers need to be better educated in PA promotion and exercise training prescriptions, and implementing both in clinical practice. Researchers and clinicians must develop plans that will allow monitoring the combined effect of pharmacological treatment, exercise, psychological and nutritional support, and should be able to be precise about the magnitude of the training response.

**References:**

Lung transplant Children Cystic fibrosis Pulmonary hypertension Diffuse lung diseases retransplantation

Lung transplantation has become established as a therapeutic option in selected children with severe lung disease in whom other therapeutic options have failed, resulting in good quality of life and prolonged survival\(^1\)\(^2\).

Although pediatric transplant results have improved considerably in the last two decades due to advances in the transplant technique, organ preservation, peri-operative management, immunosuppression, and the prophylaxis and treatment of infectious complications, chronic graft dysfunction limit long-term survival\(^1\)\(^3\).

Pediatric transplantation has numerous unique features in relation to transplantation in adults; specific characteristics of children at different stages of development (from infants to adolescents), different indications for different age groups, the effects of immunosuppressant treatments, special susceptibility to infections related to an immature immune system, and particular problems in the availability of suitable donors\(^1\)\(^2\).

According to the data of the International Society for Heart & Lung Transplantation (ISHLT), which represents approximately 75% of worldwide transplant activity\(^4\)\(^5\), 57,934 Lung and heart-lung transplants were performed between 1986 and 2015, 2288 of which were pediatric (3.9%). The highest percentage of transplants took place in the adolescent group (11–17 years), representing 72.7% of pediatric transplants, followed by the 6–10 y group (15.5%), 1–5 y (7.2%) and < 1 y (4.6%)\(^5\).

The number of pediatric lung transplants per year has increased only moderately in the last decade: year 2000: 73, year 2013: 137, year 2015: 96. This is in contrast to the growth observed in adult patients over the last two decades due to advances in the transplant technique, organ preservation, peri-operative management, immunosuppression, and the prophylaxis and treatment of infectious complications, chronic graft dysfunction limit long-term survival\(^1\)\(^3\).

The low frequency of transplants in children is related to 3 factors\(^2\):

- The low prevalence of severe lung disease in children.
- Advances in the medical care of patients with cystic fibrosis (the primary indication in pediatric patients) have considerably improved its course and delayed the age at which lung transplantation may be required.
- The limited availability of young donors. Some young patients with severe lung disease are too sick to survive the waiting list.

Improvement in ECMO support and paracorporeal lung assist devices may help to bridge these critically ill patients to lung transplantation, especially with the new techniques that allow the patients to be “awake” on ECMO. This prevents physical deconditioning as children have the possibility to get mobilized and perform physiotherapy\(^1\)\(^3\).

**Indications**

The general indication for lung transplantation is progressive respiratory failure with a short life expectancy, less than 1–2 years, and very poor quality of life\(^1\)\(^2\).

Cystic fibrosis (CF) is the most common indication in children. In the ISHLT registry, it represents 57.6% of the lung transplants (66.7% for children 11–17 y old and 50% for children 6–10 y old). The other major groups of indications are diffuse parenchymal lung diseases (including obliterative bronchiolitis (16.3%)), pulmonary vascular diseases (mainly pulmonary hypertension (14.3%)) and retransplants (6.4%). Non-CF bronchiectasis (1.5%), and severe bronchopulmonary dysplasia (0.9%) are rarer indications\(^5\).

Before including a child in the waiting list, the child and family require to be appropriately informed and educated. They both should consent to the planned transplant operation and to the close post-operative long-term follow-up needed\(^3\).

**When Should a Child Be Referred for Lung Transplantation?**

The decision to place a child on the waiting list for a lung transplant is not easy, as it is very difficult to predict survival. It is very important to make this decision properly, in order to provide a survival benefit.

Patient with CF should be referred for evaluation for lung transplant if on maximal medical therapy, including a trial of the new CF therapies, when having a forced expiratory volume in one second (FEV\(_1\)) <30% predicted or a rapidly fallen FEV\(_1\), a 6-minute walk distance < 400 m, pulmonary hypertension, clinical decline characterized by increasing frequency of exacerbations associated with any of the following: acute respiratory failure requiring non-invasive ventilation (NIV), increasing antibiotic resistance and poor clinical recovery from exacerbations, worsening nutritional status despite...
supplementation, pneumothorax, life-threatening hemoptysis despite bronchial embolization.

Listing of patients with CF for lung transplant is generally recommended in case of chronic respiratory failure with hypoxia alone or hypercapnia, long-term NIV, rapid pulmonary function decline, pulmonary hypertension, frequent hospitalizations and/or WHO functional class IV.

In children with diffuse parenchymal lung diseases, the most important thing is to assess the presence of moderate or severe functional impairment, need for mechanical ventilation or very high oxygen supplementation, lack of response to treatment, and taking into account the natural course of the disease. With some diseases, such as surfactant protein B deficiency or neonatal presentation of ABCA3 deficiency, the child will rarely survive without a transplant, while others may have a variable response to treatment, such as surfactant protein C deficiency or ABCA3 deficiency presenting later in life.

Patients with post infectious obliterative bronchiolitis with major hypoxemia or requiring invasive mechanical ventilation who do not improve with medical treatment should also be considered for transplantation, taking into account the possibility of improvement over the first years after the initial insult.

The prognosis in pulmonary hypertension has improved considerably with the new treatments available, so the following criteria are now recommended: children in functional class IV: place on the transplant list and begin medical treatment; if they improve, remove them from the waiting list. Children in functional class III: administer medical treatment; if they improve, remove them from the waiting list. Children with bilateral pulmonary vein stenosis or alveolar capillary dysplasia would have to be included on the transplant list at an early stage, as they do not respond to other treatments.

The nature of these indications means that lung transplantation in mechanically ventilated children is indicated more often than in adults. Infants on mechanical ventilation or children on long-term mechanical ventilation may be considered candidates for lung transplant. It has been shown that mechanically ventilated infants who have received transplants have the same survival post-transplant as non-ventilated older children, and better than ventilated older children. Invasive mechanical ventilation in children with cystic fibrosis is a risk factor for higher post-transplant morbidity and mortality, unlike non-invasive ventilation.

Contraindications

There are several situations in which lung transplantation may not be advised, some absolute and others relative, while some are specific to each center.

In patients with cystic fibrosis, *Burkholderia cepacia* genomovar-3, *Mycobacterium abscessus* and multi-resistant fungal infections (*Scedosporium prolificans*) constitute a contraindication in some centers.

Patients with cyanotic heart diseases in whom previous thoracotomies have been performed for palliative purposes have a very high risk of bleeding from chest wall collateral vessels, and should be assessed individually.

Prognosis and Survival

Lung transplant recipients experience a major improvement in quality of life, and 88% of children do not have any limitations in their activity 3 years after the transplant.

Overall survival in children after lung transplantation is similar to that reported in adults, with a median survival of 5.4 vs. 5.9 years, respectively. For those who survived the first year after transplant, the median survival is 8.8 years. The long term survival (≥ 15 y) is about 30%.

Adolescent lung transplant recipients have poorer overall survival when compared with younger children and adults, with those 15 to 19 years old having the highest risk of death. They have reduced 1-year survival (82%) compared with those 10 to 14 years old (88%), and reduced 3-year survival (59%) compared with those 10 to 14 (73%) and 20 to 24 years old. This survival disparity among age groups likely reflects the difficult period of adolescence and its biological and social transitions, which may influence both immunological function and adherence.

In cases in which the transplant fails, the only alternative is retransplantation, which may be limited by donor availability. The survival after retransplantation may be similar to that of the primary transplant if performed after the first year of transplant in unventilated cases, but it is poorer if performed within the first year of transplant or in ventilated patients. Over the last two decades, only 100 pediatric lung re-transplants have been reported to the ISHLT registry. Ideally, pediatric candidates for lung re-transplantation should have no second organ failure.

The advances made in recent years in surgical techniques and immunosuppression mean that lung transplant in children is a reality. Efforts are needed to increase the number of donors available, and to improve our understanding of the underlying mechanisms of chronic lung allograft dysfunction and develop therapies to prevent or treat it.

References


B. BIRTH COHORTS IN DIVERSE ENVIRONMENTS & CHILDHOOD LUNG HEALTH

#1 The Drakenstein Child Health Birth Cohort Study

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The Drakenstein Child Health Birth Cohort Study is a unique, multidisciplinary, South African birth cohort, to investigate the impact of antenatal and early life exposures on child health.(1,2) A core focus of the study is on the incidence, risk factors and etiology of lower respiratory tract infection (LRTI) and the long term impact on child lung health.(3) One of the key outcomes is the spectrum and factors associated with development of chronic lung disease. 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.(1)

The study is situated in a poor, peri-urban community in Paarl in the Drakenstein region of South Africa, 60 km outside Cape Town. Pregnant women were enrolled in the second trimester at 2 public health antenatal clinics – Newman (serving a mixed ancestry population) and Mbekweni (serving a Black African population). Women were followed through pregnancy and child birth; mother-child pairs are followed until children are at least 5 years old. All births occurred at a central public facility, Paarl hospital. Biomedical, environmental, psychosocial, and demographic risk factors are longitudinally measured. Environmental exposures (carbon monoxide, particulate matter, dust microbiome, SO2/NO2 and volatile organic compounds) were measured using monitors placed at home visits antenatally and at 4–6 months of the child’s life.(4); 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 Paarl Hospital and at clinics, which provide a strong primary health care program including a strong HIV prevention and treatment program and immunization including 13-valent pneumococcal conjugate vaccine given at 6, 14 weeks and 9 months. An intensive cohort of infants was followed 2 weekly for the first year of life, which included 2 weekly nasopharyngeal (NP) swabs, to determine colonization and microbiome patterns and association with LRTI. For the other children, NP swabs were done 6 monthly.

Active surveillance for LRTI is done for hospitalized and ambulatory episodes, and all cases have a NP swab and induced sputum taken. The etiology of LRTI is investigated using a 33 multiplex PCR done on these specimens at each episode. A case control analysis is performed, matching cases with NP swabs collected from age-matched children without LRTI. In addition, PCR is done on NP samples that have been longitudinally collected to investigate the nasopharyngeal microbiome preceding LRTI.

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 unsedated children during quiet sleep at 6 weeks, annually and during LRTI episodes.(5) There were 1143 live births (4 sets of twins and 1 triplet) amongst 1137 women enrolled; all children have completed 2 years of follow-up, with high cohort retention and very low mortality (< 1%). The population is poor (with the Mbekweni population relatively poorer than that from Newman), mostly single mothers and 20% of mothers were HIV-infected. Rates of tobacco smoke exposure were very high, with 27% of pregnant women active smokers.(6) At birth, 56% of neonates had cotinine levels indicative of exposure, with 19% had levels of an active smoker.(6) Most infants were born full term, but 17% were premature; the median birth weight was 3 kg (7). Most (92%) of the children were breastfed but the median duration of exclusive breastfeeding (1 month) was very short.

Despite high immunization coverage for the EPI schedule, including 13-valent pneumococcal conjugate vaccine, the incidence of LRTI was high [0.27 episodes per child year in infancy; e/cyl]. 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 LRTI; bocavirus, parainfluenza virus, adenovirus or CMV were less strongly associated. 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. catarrhalis or S. aureus as well as several organism interactions up to 3 months prior to LRTI.

A total of 490 children (46%) had at least one episode of wheezing in the first three years of life, with the highest prevalence in the first year; wheezing was strongly associated with LRTI. The prevalence of recurrent wheezing over this period was approximately 8%.

Determinants of lung function at 6 weeks of age included infant size, sex, HIV exposure, benzene exposure or maternal smoking in pregnancy or maternal alcohol use (8). Lung function was tracked through the first 2 years of life. LRTI occurring early in childhood impaired lung function at 1 and at 2 years of age.(9) Severe LRTI requiring hospitalization or recurrent LRTI were associated with further reductions in lung function.

This study provides an innovative, longitudinal assessment of a range of clinical, molecular, environmental and socioeconomic variables impacting on child lung health and the evolution of chronic disease in a low- and middle-income country setting. The study identifies new areas for potential interventions to prevent early life LRTI, impairment in lung function and evolution of chronic respiratory disease.

References

#2 Birth Cohorts in Diverse Environments and Children’s Lung Health - Inner City Cohorts

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The problem of inner city asthma as a major public health issue emerged in the United States in the late 1980s. There was increasing recognition of a rural-urban difference in asthma prevalence and there was a well-documented rise in asthma prevalence that had been observed in many industrialized countries. The increasing prevalence of asthma was also seen in inner city settings but the rise was faster and associated with increased severity of asthma in these compared with other locations1. The reasons for these observed geographical disparities were likely to be complex and multifactorial. The demographics of inner city living vary by country and with time but, at least in the US, inner city populations had marked differences in composition and lifestyle compared with suburban and rural populations. People living in the inner cities are disproportionately more likely to be of black or Hispanic race, to be single carer families and to be living in financial hardship; in the NCICAS survey of inner city children with asthma2, 61% were from families with a reported household income of <$15,000 per annum. Although ethnicity is associated with asthma, it appears to have a greater impact on morbidity than prevalence and hence may reflect inner-city disadvantage. Families in inner-city areas are more likely to live in overcrowded and sub-standard housing, to have disrupted lifestyles that impact in health seeking behaviors, poorer access to healthcare facilities, and to be non-adherent to treatment regimens. Each of these may each impact asthma morbidity and mortality. Although much of the research on lung health in inner city populations has focused on asthma, deprived inner city populations have higher rates of preterm and low birthweight for gestation births3, both of which are associated with long-term decrements of lung function. In addition, some exposures that are prevalent in inner city environments, including indoor and outdoor pollutants, may be associated with adverse effects on lung development and subsequent lung function4.

The differences in reported asthma in inner city populations compared with other settings may give clues about the pathogenetic mechanisms and it likely that these have their origins in early life, including prenatal life. Birth cohorts, particularly when recruited during pregnancy,
provide an opportunity to prospectively collect information on a range of early life exposures and to investigate their associations with subsequent health outcomes. They are well suited to common outcomes such as asthma and are less prone to recall bias than case-control studies but retain the disadvantages of all observational studies; that of measured and unmeasured confounding. Despite such caveats, studies of geographical dispersion of exposures associated with differential rates of disease outcomes have been instrumental in identifying some important pathways in asthma4. Variables that have been put forward as possible explanatory factors in differential rates of asthma in inner-city children include maternal and familial distress, exposure to pollutants in both the indoor and outdoor environment and including tobacco smoke, allergen exposure, nutrition, and microbial agents. A series of research networks was established in the US to examine the problem of inner-city asthma5. From these, the importance of allergen exposure and sensitization was highlighted; in particular, the high prevalence of cockroach allergen in the environment and cockroach sensitization in children were noted6. These were related to asthma symptoms and morbidity, rather than prevalence, and intervention studies tailored to individual children were successful in reducing environmental allergen load and asthma control7. The Columbia Center for Child Environmental Health (CCCEH) is a birth cohort study of African American and Dominican children living in inner-city New York. This group has largely focused on the long-term health effects of urban chemical pollutants. They have reported observational associations between exposure to phthalates8, polycyclic aromatic hydrocarbons (PAH)9 and bisphenol A10 and asthma or wheezing outcomes in children and between childhood residential exposure to particulates (PM2.5) and black carbon and new onset wheezing11. Some of these exposures also showed effects associated with atopic sensitization, including to cockroach, which exemplifies the complex relationships between inner-city exposures and respiratory outcomes.

To address some of these complexities, the Urban Environment and Childhood Asthma (URECA) multicenter, birth cohort study was designed to measure a comprehensive range of exposures covering allergens, pollution, infections, microbial exposures, stress and diet with a particular focus on immune development in the genesis of asthma12. This study reported that cumulative allergen exposure in early life was associated with sensitization but first year exposure to cockroach, mouse and cat allergens was negatively associated with recurrent wheezing. They also found differences in associations between specific microbial taxa in house dust samples and risk of recurrent wheezing at age 3 years; in particular Firmicutes and Bacteroidetes were negatively associated with atopy and wheezing, suggesting an early life protective effect of high levels of exposure to certain allergens and bacteria13. This complex interaction between allergen sensitization and microbial exposure in early life accords with other emerging evidence about the early life events associated with the development of asthma and allergy in children and further understanding of these processes may lead to development of preventative strategies.

References

#3 Birth Cohorts in Diverse Environments: Urban and Rural Cohorts

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Longitudinal birth cohorts have been used to help understand how diseases develop. They have been used to understand risk factors and causes of respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD) (1,2). A significant advantage of a well-designed longitudinal birth cohort is that subjects can be followed until disease outcome, allowing investigators to look back in time to determine how the disease was produced. As shown in the figure, this can be extremely useful in understanding early origins of disease.

In this example, the early origins of COPD are uncovered by looking back to early data collections occurring in early adulthood, early childhood and during fetal development. Such a study requires lots of time, lots of money and the foresight to understand enough about the likely disease pathogenesis to have collected the right samples and measured the right data!

Epidemiological studies can be used to inform cohort study design. Many epidemiological studies have pointed to lower prevalence of asthma and allergic outcomes in children living on farms or in rural environments (3). Since the early observations, the number of rural cohorts or cohorts that include both urban and rural components has expended, with cohorts in many areas of the world established, including Australia, Central America, Germany, India, Scotland, Scandinavia, and the USA (4–13). Studies such as these have certainly provided many clues to the factors increasing and / or decreasing the risk of asthma and allergic outcomes in children. They have also highlighted the complexities of genes by environment interactions, where the one exposure can increase or decrease an individual child’s asthma risk based on their genotype. The next generation of cohort studies are likely to examine exposures and risk not considered until recent years, such as the influence of the maternal microbiome during pregnancy on offspring outcome (13) and the impact of chemical exposures in both rural and urban settings (7).

References
C. COMPLEX PATIENTS AND RESPIRATORY MORBIDITY

#1 Respiratory Consequences of Neuromuscular Disease

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Examples of Chronic Neuromuscular Diseases That Can Affect Respiratory System in Children (adapted from Brendit et al1)

Causes of respiratory morbidity in neuromuscular disease

A. Dysphagia2 and aspiration into airway

1. Neurogenic dysphagia
   Oral phase: impaired oral reflexes, weak suck, immature biting or chewing, poor food bolus propulsion
   Triggering of swallow reflex: delayed triggering, poor suck and swallow coordination, absent swallow reflex
   Pharyngeal phase: Laryngeal penetration, aspiration, choking, pharyngeal residue, nasopharyngeal reflux

2. Esophageal dysphagia
   Esophagitis
   Reflux-induced and eosinophilic (EoE)
   Esophageal surgery
   esophageal atresia/TEF, status postsurgical anti-reflux treatment (Nissan fundoplication and other)
   Achalasia

3. Aspiration into lower airway due to anatomical lesions
   Laryngeal cleft
   Tracheoesophageal fistula

B. Muscle weakness

1. Upper airway muscles
   Pharyngeal collapse is frequently found in children with neurological impairment and poorly recognized by practitioners. It occurs during sleep and awake hours and is characterized by inspiratory collapse of pharyngeal walls. Treatment of pharyngeal collapse is challenging and is mostly limited to non-invasive ventilation.

   Glossoptosis is very common in children with neuromuscular disease and is related to poor muscle tone of lower pharyngeal muscles. The base of the tongue presses on epiglottis creating upper airway obstruction and noise. Treatment of glossoptosis is challenging and mostly limited to non-invasive ventilation. Surgical mandibular advancement may be attempted on selected patients3.

   Laryngomalacia is also a very common condition in children with neuromuscular disorders. It may occur in children of any age and is also related to muscle dystonia. Surgical laryngoplasty/supraglottoplasty could be attempted. However, laryngomalacia in this category of patients is commonly associated with pharyngeal collapse and glossoptosis. In the latter situation, surgical treatment is not effective.

   NOTE: severe upper airway obstruction in children with neuromuscular disease may become an indication for tracheostomy

2. Expiratory muscles: weak cough
   Weak cough results in impaired clearance of lower airway secretions, which leads to bacterial superinfection

3. Inspiratory muscles: respiratory insufficiency
   Weakness of muscles of inspiration results in small lung volumes, frequent atelectasis of lower lobes and in respiratory failure

   Regular pulmonary function assessment4 is recommended in children with neuromuscular disease. Multiple parameters were suggested, however, most practitioners agree on the following values, which suggest evolving respiratory failure and need for cough assistance ventilator support5,6
   - Peak cough flow rate less than 160 L
   - VC less than 770 ml
   - Awake PaCO2 more than 50 mm Hg

   NOTE: in many children with neuromuscular disease, pulmonary function assessment with traditional methods (spirometry, lung volumes measurement, etc.) is extremely difficult or impossible. In these cases, polysomnography and end tidal CO2 measurements become useful practical tools

C. Suppurative lung disease and bronchiectasis

Piccione et al.7 studied 100 consecutive patients referred for evaluation to the Aerodigestive Center at Cincinnati Children’s

<table>
<thead>
<tr>
<th>Cerebral cortex</th>
<th>Brainstem and basal ganglia</th>
<th>Spinal Cord</th>
<th>Motor nerves</th>
<th>Neuromuscular junction</th>
<th>Myopathies</th>
</tr>
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<tbody>
<tr>
<td>Stroke</td>
<td>Neoplasm</td>
<td>Trauma</td>
<td>Spinal muscular atrophy</td>
<td>Myastenia gravis</td>
<td>Muscular dystrophies</td>
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<tr>
<td>Neoplasm</td>
<td>Central alveolar hypoventilation</td>
<td>Syringomyelia</td>
<td>Charcot Marie Tooth disease</td>
<td>Systemic Corticosteroid use</td>
<td>Glycogen storage disease</td>
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<tr>
<td>Degenerative disease</td>
<td>Progressive bulbar palsy</td>
<td>Neoplasm</td>
<td>Nemaline body myopathy</td>
<td>Mitochondrial myopathy</td>
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<td>Seizure disorder</td>
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Hospital. Clinical evaluation, flexible bronchoscopy, HRCT of the chest and swallowing study were performed. From 30 neurologically impaired children, 93% had bronchiectasis.

Prevalence of bronchiectasis was similar in children before and after 2 years. Interestingly, bronchiectasis improved and even resolved in several cases with aggressive management. Extremely high prevalence of bronchiectasis in children with neuromuscular disease needs to be acknowledged. The pathogenesis of bronchiectasis in this category of patients is multifactor and is illustrated in the figure below:

NOTE: early and rapid development of bronchiectasis in children with neuromuscular disease and aspiration into airway needs to be acknowledged by the practitioners.

D. Other important respiratory co-morbidities

Vocal cords unilateral and bilateral paresis and paralysis

Tracheomalacia

Iatrogenic intubation and tracheostomy related laryngeal and tracheal stenosis

Chest deformities

Bronchial distortion and stenosis related to chest deformities

Gastroesophageal reflux and reflux-induced esophagitis

Tracheostomy complications

Assessment of children with neuromuscular disease and respiratory problems

Procedure | Purpose
---|---
Sleep fiberoptic laryngoscopy | Assessment for upper airway obstruction and vocal cords motility
Rigid microlaryngoscopy | Thorough assessment of posterior glottis and intra-arytenoid space. Rule out laryngeal cleft as a cause of aspiration into airway
Flexible bronchoscopy with BAL | Assessment of lower airway inflammation and infection
Rigid bronchoscopy | Thorough assessment of posterior tracheal wall to rule out H-type tracheoesophageal fistula
Esophagogastroduodenoscopy (EGD) | Assessment of esophageal anatomy and presence of inflammation

Aerodigestive approach to the assessment

Clustering of multiple procedures with utilization of single anesthesia

Multispecialty team: ENT, Pulmonology, GI, Speech

Coordination of services

“Triple endoscopy”, single anesthesia concept

Sleep laryngoscopy and flexible bronchoscopy with BAL

Rigid laryngoscopy and rigid bronchoscopy

Esophagogastroduodenoscopy with biopsies plus esophageal pH-metry/impedance probe placement if needed

NOTE: Aerodigestive medicine has been rapidly evolving. The Aerodigestive Foundation was started in 2017 and Consensus Statement on structure and function of aerodigestive programs was recently published.

Main concepts of treatment of respiratory problems in children with neuromuscular diseases

Aspiration precautions

The crucial role of avoidance of aspiration in management of respiratory complications cannot be overestimated. Careful assessment of swallowing, management of dysphagia, assessment for gastroesophageal reflux and secondary aspiration, and timely decision on initiation of G-tube nutrition are crucial parts of management.

Management of upper airway obstruction

Non-invasive and invasive ventilation

Non-invasive ventilation has been used with great success in this category of patients. Tracheostomy and invasive ventilation play an important role in their management.

NOTE: The choice of ventilation possesses extremely difficult medical and ethical problems in many cases, which cannot be properly addressed in the format of this presentation.

Treatment of bronchiectasis in children with neuromuscular diseases

Liberal use of antibiotics for acute exacerbation of lower airway disease is essential. Prophylactic use of antibiotics in children with suppurative lung disease and bronchiectasis is strongly encouraged. Azithromycin prophylaxis was found to be effective in prevention of non-cystic fibrosis bronchiectasis and has been successfully used in children with neuromuscular disease by practitioners.
Cough assistance
Use of cough assistance and lung recruitment is essential. Mechanical insufflator-exsufflator use became a standard of care for children with respiratory manifestation of neuromuscular weakness. 

Chest PT
It has to be used aggressively for improvement of clearance of lower airway secretions, which is severely impaired due to multiple factors, which include weak cough, shallow breathing with tendency towards small lung volumes and atelectasis, and presence of tracheal and bronchial stenosis and distortion due to chest wall deformities. Fitzgerald et al. showed significant reduction of hospitalizations with use of high frequency airway compressions (VEST physical therapy) in children with neuromuscular disease.

Other considerations
Multiple supportive services have to be available for successful management of respiratory problems in children with neuromuscular disorders. They include Nutrition, Social Services, Pediatric Psychology, Family Support, etc.

In conclusion, respiratory morbidity in children with neuromuscular disease is multifactorial in nature. Detection and treatment of aspiration into the airway is the cornerstone of its management. The practitioners need to acknowledge rapid development of bronchiectasis in this category of patients and importance of management of suppurative lung disease. Finally, multidisciplinary team assessment and management are essential for successful care for patients with respiratory consequences of neuromuscular diseases.

References

#2 Gastroesophageal Disorders in Development of Pulmonary Diseases
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Introduction
Normal gastroesophageal function is a complex mechanism depending on effective esophageal motility, on timely relaxation and contractility of the lower esophageal sphincter (LES), on the average intraluminal pressure of the stomach, on the efficacy of the contractility in emptying of the stomach, and on the ease of gastric outflow [1]. Gastroesophageal reflux (GER) is a physiological process occurring with different frequency and characteristics in healthy infants, children and adults, most episodes being brief and asymptomatic. In contrast, GER disease (GERD) develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms, involving the upper portion of the gastrointestinal tract and/or the respiratory system [2]. The so-called “anti-reflux barrier”, that limits reflux of gastric contents into the esophagus, is made up of LES, of the crural diaphragm, of the angle of His and of mechanisms keeping the thorax-abdomen pressure gradient within normal values. Furthermore, esophageal peristalsis helps to clear the refluxate and to reduce exposure to the noxious components of gastric contents [1,2]. As we will see, esophageal abnormalities, related to congenital or acquired structural dysfunction, or associated with other pathological conditions, are among the main factors favoring GERD and its manifestations [2].

Gastroesophageal disorders and gastroesophageal reflux diseases
The pathophysiology of GERD is multifactorial and involves: a) transient LES relaxations as well as other LES pressure abnormalities, such as hypotensive LES; b) impairment of the esophagogastric junction (EGJ), such as in the presence of hiatal hernia; c) ineffective esophageal acid and bolus clearance; d) anatomic malformations, such as pyloric stenosis and malrotation or esophageal atresia and short esophagus; e) delayed gastric emptying; f) excessive gastric acid secretion; g) impaired defensive factors of the esophageal
mucosa [1–3]. Physiologically, LES relaxes in response to swallowing and esophageal peristalsis, to allow saliva, liquids and solid foods to pass into the stomach. Transient LES relaxations are induced by vagally-mediated reflexes, stimulated by the activation of mechanoreceptors in the esophagus and in the stomach, like in the presence of gastric distention [1,3]. Defective LES motility, lower basal LES tone and an increased frequency and/or duration of transient LES relaxations can be further facilitated during post-viral gastritis or by delayed gastric emptying due to overfeeding or by increased intra-abdominal pressure in overweight subjects or in pregnant women [2,4]. Impaired esophageal clearance can be caused by ineffective peristaltic waves that are either not transmitted or of low amplitude [4]. Low basal LES pressure and ineffective esophageal motility are characteristic features of patients with progressive systemic sclerosis, who are frequently affected by GER and by its respiratory complications [5]. Unclear is the protective role of the upper esophageal sphincter (UES), that physiologically functions as a barrier against entry of air into the esophagus and against regurgitation of materials coming from below [1–3]. This sphincter does not seem to offer a real protection against stomach content regurgitation during GER episodes. Complex disorders of the foregut motility are often present in patients with neurological disorders, where autonomic neuropathies may delay esophagogastric transit and gastric emptying [1–3]. In neurologically impaired patients, overfeeding with nasogastric or gastrostomy tubes may also lead to gastric distension and frequent GER events with aspiration [2,3], whilst in patients with diabetes, high prevalence of gastrointestinal motility disorders may occur because of autonomic neuropathies at the esophagus levels [6]. Also chronic upper airway obstruction may favor GER: indeed, increasing the thoraco-abdominal pressure gradient during inspiration, this condition may overcome the anti-reflux barrier mechanisms [1–3]. Finally, GER is enhanced or favored by certain foods, including alcohol, chocolate, mint, caffeinated beverages, fatty and/or spicy foods, and orange juice, among others, and by various medications, including drugs used to treat asthma [1,2]. Albuterol and xanthines may decrease LES pressure, albuterol decreases esophageal contraction, while xanthines increase gastric acid secretion and prednisone increases esophageal acid content [7].

**GER and Pulmonary Diseases**

In children, the classical respiratory manifestations of GERD include apnea, apparent life-threatening events, persistent and/or nocturnal cough, wheezy bronchitis, recurrent aspiration pneumonia and difficult-to-treat asthma and, more generally, bronchial hyperresponsiveness [1]. GER may alter airway reactivity through a variety of mechanisms that include direct injury to the respiratory structures induced by microaspiration of the gastric content, but also axonal and vagally-mediated reflexes [1]. The end result is a neutrophilic inflammatory reaction, induced by pro-inflammatory cytokines and chemokines released by the damaged bronchial epithelial cells and promoted by tachykinins (substance P and neurokinin-A) generated by nitric oxide-containing neurons [1]. The severity of the GER-associated respiratory disorder is related not only to the frequency and duration of the reflux events, but also to ability of the patient to avoid or limit aspiration and to the characteristics of the GER constituents. The refluxate is composed by gastric acid and pepsin and, frequently, by less acidic contents, such as foods, beverages and duodenal secretions [1]. With the advent of pH/MII monitoring, it has been shown that weakly acidic refluxes are frequent in the pediatric population and that they can induce respiratory symptoms, similar to those induced by acid refluxes [8]. A recent prospective study has demonstrated that children with GER and respiratory symptoms have a higher number of weakly acidic refluxes than children with GER and gastro-intestinal symptoms [9]. These findings may at least partially explain the often observed ineffectiveness of acid-suppressive treatments in this patient population, also when proton pump inhibitors (PPI) are prescribed. Acid suppression can only change acid into weakly or to weakly acidic or non-acid refluxes, not the frequency of reflux events that, if aspirated, may still produce airway injury and inflammation [10].

**References**


Lower respiratory tract infection is one of the most common causes of morbidity and mortality worldwide (1). Advances in the use of vaccination, rapid point-of-care diagnosis, and appropriate use of antibiotics all contribute to the improvement of care of children with lower respiratory infections. With the widespread use of conjugated pneumococcal vaccine in children, the prevalence of invasive pneumococcal infections has decreased dramatically especially in young children (2–5). However, complicated pneumonia associated with parapneumonic effusion and empyema has been documented to be increasingly common especially in countries where PCV-7 or PCV-10 has been widely used. This is partly related to the serotype replacement after introduction of PCV-7 and PCV-10 in the past decade (6). The major problems in the management of childhood respiratory tract infections have been the inappropriate use of antibiotics, performance of useless investigations, and overuse of antibiotics. Advances in the development of multiplex PCR greatly enhanced our ability to diagnose viral respiratory tract infections and may help to reduce unnecessary use of antibiotics (7). In the meantime, antibiotic resistance is becoming more prevalent leading to excessive use of potent antibiotics. There has been an excessive use of measurement of acute phase reactants for helping to differentiate viral from bacterial pneumonia. Despite having been used for many decades, penicillin remains the most effective antibiotic in the treatment of streptococcal pneumonia. Severe complications of pneumococcal infections including hemolytic uremic syndrome associated with certain serotypes such as type 3 and 19A are frequently encountered. In the meantime, resistance to macrolides is increasingly common among strains of mycoplasma isolated in Asia. In many regions in Asia, macrolide resistant rates have reached almost 100% (8). One may argue whether patients with a mild case of pneumonia due to mycoplasma need treatment or not. It is time to rethink our diagnostic approach and treatment options for children with community-acquired pneumonia and complicated pneumonia. Milder cases of mycoplasma pneumonia may not even need antibiotic treatment as many of them will resolve on their own.

References:

#2 Pulmonary Tuberculosis (PTB) and Lower Respiratory Tract Infection in Children

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Tuberculosis is a leading cause of childhood morbidity and mortality, estimated to cause approximately 1 million new cases and 250,000 deaths per year. Almost 80% of TB-associated deaths occur before five years of age and many are never diagnosed. Pulmonary tuberculosis (PTB) is the commonest form of childhood TB globally. Pulmonary TB has been regarded as a chronic disease, associated with persistent symptoms. Symptoms of chronic cough, loss of weight or failure to thrive in the context of an epidemiological suspicion for TB such as a household contact or a positive tuberculin skin test in a child who comes from a TB endemic area have been key features of the diagnosis of pediatric PTB. However, increasing evidence links M. tuberculosis with acute lower respiratory tract infection (LRTI). Studies from TB endemic areas in...
Africa have reported culture-confirmed TB in approximately 8% of children presenting with acute LRTI. As the sensitivity of culture for diagnosis of PTB is sub-optimal, it is likely that the true number of children with M. tuberculosis in the context of LRTI is much higher. A systematic review of hospital-based studies of children under 5 years of age with a severe LRTI found high rates of PTB ranging from 1–23% (with rates of 5–8% for culture-confirmed tuberculosis). The median duration of cough in children with culture-confirmed TB was approximately 4 days in children hospitalized with culture-confirmed disease in South Africa. However there is no clear evidence that pneumococcal conjugate vaccination in infants has reduced subsequent hospitalization for pulmonary TB.

HIV-infected children are at higher risk for developing PTB compared to HIV-negative children, but the risk of PTB is substantially reduced by the use of antiretroviral therapy and preventive therapy. PTB may be especially important to consider in HIV-infected children presenting with acute LRTI in TB endemic areas, especially if they are not on antiretroviral therapy or have significant immunosuppression. High rates of tuberculin conversion (11.8 conversion per 100 child-years; 11.8% annual risk of infection) and tuberculosis disease (2.9 pediatric cases per 100 child-years) were found in the Drakenstein Child Health study, amongst the highest reported estimates of pediatric tuberculosis globally. In this cohort, tuberculosis disease and the occurrence of LRTI or recurrent LRTI were strongly associated and both were highly endemic in this cohort. These two conditions may be risk factors for each other or there may be common risk factors for both. In contrast use of INH prophylaxis amongst children with a positive tuberculin skin test was highly protective for development of disease.

The challenges of accurately diagnosing childhood TB and of obtaining microbiological confirmation in children may lead to underestimation of the burden of TB, particularly when associated with LRTI. Programs for LRTI and tuberculosis should be integrated. Children living in TB endemic areas should be routinely, regularly tested for TB infection and prevention programs strengthened. Screening for TB disease should be done when a child presents with LRTI. Further study of the mechanisms of interaction of LRTI and TB in children are needed.

References

#3 New Interventions for RSV LRTI – Where Are We Going?

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Asthma is the most common chronic disease among children, affecting an estimated 235 million people worldwide. The diagnosis of asthma as a chronic condition is typically made when children reach school age and the prevalence in this age group ranges from 6–20% in Europe and approximately 10% in the United States. While asthma occurs in all countries, over 80% of asthma-related mortality occurs in low- and low-middle-income countries. Moreover, since asthma typically begins earlier in life compared to other chronic diseases, this condition imposes a higher lifetime burden. Therefore, interventions to prevent or reduce the development of asthma could produce substantial public health benefit.

The link between early RSV disease and subsequent wheezing illnesses in young children has been demonstrated in many observational case-control and prospective cohort studies. The association between significant RSV illness in infancy and early childhood wheezing has been well demonstrated. However, the link between early severe RSV illness and later asthma in older children is less consistent, with some studies supporting an association, while others do not (reviewed recently) strengthening the current understanding that the etiology of asthma is multifactorial.

The majority of studies examining the association of early RSV illness with subsequent wheezing conditions have been observational and, therefore, do not offer strong evidence of a causative relationship. The
strongest indication that RSV causes later wheezing comes from follow-up studies of prospective interventional trials of RSV mAb (palivizumab) in premature infants (such as this recent one, in Japan6). By preventing early severe RSV illness within the context of a randomized design, these evaluations presumably are not subject to the same degree of confounding as natural history studies can deliver.7 The effect of randomization, however, can be somewhat diluted in such follow-up studies, and the use of a high-risk population still exposes them to potential bias.

The demonstration that provision of passive immunity against severe RSV can reduce later wheezing illnesses suggests that a similar effect could be achieved through maternal immunization, which acts through a similar mechanism. The advancement of maternal RSV vaccine candidates to clinical testing, therefore, provides a unique opportunity to examine the relationship between early RSV and later wheeze outcomes such as asthma, since the ongoing large-scale efficacy trials are being conducted in healthy populations and will include randomization.8 A reduction in asthma among children in the years following their participation in these trials could provide strong evidence for a causative role of RSV in asthma (or at least in a significant fraction of it), and would indicate an additional benefit of maternal immunization, increasing the intervention’s incremental cost effectiveness and impact.

A number of candidate vaccines for maternal or infant immunization and passive protection strategies against RSV have been clinically evaluated, and so far no serious adverse events were detected. So far, ongoing clinical trials have not shown information on long-term effects, especially among children who present recurrent wheezing and asthma. Prospective studies in late preterm babies demonstrated a protective role for palivizumab against development of recurrent wheezing during infancy until 5 years old, but Mochizuki et al. did not find a reduction in atopic asthma after 59 months of age.6

There are no good data in literature about the link between RSV preventive strategies and other asthmatic phenotypes. Additionally, a phase 3 randomized trial of motavizumab, which enrolled healthy Native American, late preterm infants (36 w), did not show a beneficial effect on rates of recurrent wheezing at 1–3 years of age.9 A new evaluation of these children, now 8–14 years old, is currently under way and has the potential to better define long term benefits.

In yet another palivizumab vs. placebo randomized controlled trial, Blanken et al. were able to show a significant protection of recurrent wheeze in the intervention group during the first year of life, among children born preterm.7 Contrarily, this effect did not persist, and after a six-year follow-up period, children who received palivizumab or placebo had the same frequency of parentally-reported current asthma, and there was no significant difference in lung function.10

To date, the true burden of early life severe viral infections on recurrent wheeze and asthma is yet unanswered. The multiple current and future intervention trials offer us a unique opportunity to better understand if these early life viral events do play a significant role in the pathway leading to chronic respiratory symptoms. Due to the complex phenotypes of the asthma syndrome, it is essential that these longitudinal follow-ups amass the best possible data in these populations (including biological and physiological markers) that will allow us to identify possible mechanistic explanations for these associations.

References

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ABSTRACT

ISAM Joint Session

#1 Asthma Medication Delivery: Mists and Myths

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Introduction

Inhaled drugs are the mainstay of asthma treatment at all ages. These
drugs are inhaled as aerosols enabling delivery of a higher drug dose to
the target area with considerably fewer systemic side effects than with
systemic administration. Aerosols are either solutions containing
medication, or suspensions of solid particles in a gas, generated from
devices such as pressurized metered dose inhalers (pMDI), dry powder
inhalers (DPI) or nebulizer systems. Improving drug deposition to the
lungs by better adherence and better use of aerosol devices may
improve asthma control. In this review we discuss commonly held, but
incorrect beliefs or myths about aerosol therapy.

Despite strong evidence, practices persist that are ineffective,
time consuming, and expensive. I have identified many of these
common myths and practices around pediatric aerosol therapy and
present the evidence and facts. Then again, perhaps I am
perpetuating newer myths. Only time and research will tell. Lacks
in knowledge include where inhalant drugs are deposited in
children with their smaller and partly obstructed airways. They
would probably benefit from high resistance inhalers that will lead
to a low inspiratory flow, but this has to be demonstrated. Future
research on asthma medication delivery should focus on ways to
increase adherence as the most effective means to optimize
asthma control rather than developing another ICS.

A brief quiz about common aerosol therapy myths – Test your
knowledge:

Deposition

the target area for ICS is all 23 airway generations
  ○ true/false
the target area for inhaled bronchodilators is all 23 airway generations
  ○ true/false
the same target area can be reached with a larger particle size, using a
slower inspiratory flow
  ○ true/false

the area of particle deposition is the same in health and disease
  ○ true/false

targeting inhaled drug treatments to distal airways results in a
homogeneous lung drug concentration
  ○ true/false

Particles

HFA aerosols always have smaller particles than CFC aerosols
  ○ True/false
HFA aerosols with ethanol as co-solvent have a lower plume
velocity
  ○ True/false

For effective powder dispersal, a high flow within the dry powder
inhaler is needed
  True/false

Higher inhalation flows through the inhaler lead to increased impaction
in upper airways
  ○ True/false

Extra-fine particle size ICS are superior to normal particle size ICS in
gaining asthma control
  ○ True/false

Patients

Nominal drug doses for inhalation generally remain the same with
increasing age
  ○ True/false

Crying leads to decreased drug delivery for reasons including high
inspiratory flows and poor mask seal
  ○ True/false

For easily distressed infants, administration during sleep is an
alternative
  ○ True/false

The optimal inhalation maneuver from valved holding chambers is
5–10 tidal breaths
  ○ True/false

Adherence can be improved by a patient-centered care approach
including shared decision-making
  ○ True/false

Drugs

Rather than giving back-to-back nebulization of different medications,
drugs should be combined in a single treatment
  ○ True/false
When a patient is being given many different medications by aerosol, the order of medication delivery is critically important
- True/false

Ciclesonide, beclomethasone, and flunisolide HFA pMDIs emit ultrafine particles (MMAD about 2 \( \mu m \))
- True/false

Albuterol/salbutamol is more effective when used as larger particles (MMAD about 5–6 \( \mu m \)) and inhaled very slowly
- True/false

For intubated children in the ICU, it is important to administer albuterol/salbutamol both by pMDI to increase proximal airway dose and by IV infusion so that drug will reach obstructed airways.
- True/false

Devices

All aerosol devices (nebulizers, pMDI, DPI) can be equally effective when used correctly
- True/false

In children, using a holding chamber with a mask is equally effective as using one with a mouthpiece
- True/false

It’s been shown that large plastic (polyethylene) drink bottles can be used as a makeshift holding chamber in an emergency
- True/false

It is important to inhale very quickly from all DPIs in order to disperse the drug
- True/false

In children under 6 years of age with asthma who are treated in the ED, using a pMDI and holding chamber may decrease time in the ED and the admission rate to hospital
- True/false

### #2 Basics of Aerosol Science – Scientific Principles, Devices and Inhalation Techniques Suitable for Children

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**Introduction**

Despite recent interest in the development of biologic therapies designed to target specific molecular pathways leading to a number of respiratory diseases, the delivery of aerosolized medications via oral inhalation is still, globally, the most common method of treatment of respiratory disease. Inhalation therapy has many advantages, allowing quicker onset of action in the target organ, the lungs, while reducing both the administered dose required for therapeutic effect, and systemic drug exposure. The scientific principles enabling us to maximize aerosol deposition in the lungs apply to all devices, and to patients in all age groups. However, effective and reproducible delivery of aerosols to children introduces additional difficulties and limitations. Many of these issues can be addressed with the appropriate choice of device and formulation for the patient’s age and condition, and then through education and training of both parents and children in the optimal use of the chosen form of therapy.

**Scientific principles**

Drugs formulated for aerosol delivery may be in solid (powder) or liquid (aqueous or suspension) forms. The drug particles will often contain additive compounds or carriers, generally required to optimize delivery. Some form of gaseous phase must be generated in order to disperse the solid or liquid drug into aerosol particles. The ‘gas’ may be generated in different ways: within the aerosol device (as in pressurized metered dose inhalers or pMDIs); from an external source (such as the driving gas flow required for jet nebulizer use) or by the patient’s own inspiratory effort (as is the case for most dry powder inhalers or DPIs).

For effective delivery and deposition within the lungs, aerosol particles must first bypass the upper airways (head and neck) during inhalation, i.e., inertial impaction of larger drug particles in the oropharynx should be minimized. In simplistic terms, the particle size and velocity of emission from the aerosol device combined with the patient’s inhalation flow are usually the most important factors determining the proportion of drug that will deposit in the lungs and therefore have a therapeutic effect.

Having entered the conducting airways, gravitational sedimentation becomes more important. Factors such as particle velocity, size and density, hygroscopic growth, and residence time in the lungs will determine deposition rates. For smaller particles, factors such as diffusion due to kinetic movement and electrostatic charge will determine whether the particles will deposit in the airways or be exhaled.

In addition to the physical principles described above, patient-related factors such as airway size and diameter, disease severity, inspiratory rate and volume, physical and cognitive ability to use the inhalation device as recommended, access to education and training in the use of the prescribed device will all have a marked effect on the efficiency of aerosol deposition. When reviewing these factors, it becomes clear why optimization of aerosol drug delivery to children can present something of a challenge.

**Devices for children of different ages**

The choice of an appropriate aerosol device for children is highly dependent on the age, dexterity and cognitive ability of the child. The (in)ability to quickly generate a high inspiratory flow, or to coordinate inhaler actuation with the start of inhalation eliminates the use of most DPIs or pMDIs used without accessory devices such as valved holding chambers (VHCs) in young children. The age limits for recommendations on the use of the various types of inhalation devices generated considerable discussion when developing the ERS/ISAM task force consensus statement. The published recommendations represent a
compromise between international experts\(^2\), and should only be taken as a guide.

Devices which allow inhalation of drug via tidal breathing such as nebulizers and pMDIs used with VHCs can be used by patients of all ages. It is important to note here that a \textit{valved} holding chamber is essential for children requiring multiple tidal breaths to clear the holding chamber of drug. Infants and pre-schoolers will also require the use of a facemask rather than a mouthpiece. The availability of the more portable vibrating mesh nebulizers has made nebulization much more convenient for patients these days. Nebulization also allows the delivery of a much wider range of therapeutic agents, whereas pMDIs and DPIs are limited to the more widely used and commercially viable drugs to justify the long and costly development, testing and regulatory approval process required. Nebulizers still have the disadvantage of requiring careful cleaning and maintenance, such as servicing and calibration of the pumps for jet nebulizers and regular replacement of the meshes for the mesh nebulizers.

The age at which a mouthpiece should be introduced in place of a facemask is another area of controversy. In general, the recommendation would be to start using a mouthpiece as early as possible, as soon as a child can be trained to consistently tidally breathe through the mouth rather than the nose (around 3 years of age). While there are now a number of very well designed, non-static facemasks available, they still introduce an additional area of potential variability in inhaler use that can impact the efficiency of drug delivery. For most commonly available aerosol formulations, nasal inhalation should be discouraged as significant impaction of drug will occur in the nasopharynx, reducing the amount of drug available for deposition in the lungs. This recommendation is also dependent on the context of the requirement for aerosol therapy. Facemasks are often preferred for hospitalized patients, or by parents of children requiring multiple and frequent inhalation treatments since facemask can be strapped on and the patient left to complete the treatment unsupervised.

Devices that require the patient to reproducibly and consistently perform a single maximal inhalation maneuver such as DPIs and pMDIs used without VHCs or breath-actuated pMDIs should not be used for children under 5–6 years of age, and children over this age should be trained and observed when using these devices before prescribing to confirm their ability to perform the required inhalation technique correctly. The use of a VHC is still strongly recommended with pMDIs for patients of all ages, if they are willing to use them. Additionally, if there are concerns regarding local or systemic effects from the prescribed drugs, oropharyngeal or swallowed drug exposure is minimized with the use of a VHC.

\textbf{Appropriate inhalation techniques}

As mentioned above, devices requiring only tidal breathing can be used universally, across all age groups. However, training in the use of a slow single maximal inhalation when using a pMDI (either with or without a VHC) has the dual advantage of optimizing lung deposition and reducing the time needed to deliver aerosol therapy.

Breath-actuated pMDIs would seem ideal for patients who are unable to coordinate actuation with inhalation, however they do require training in a specific inhalation maneuver and young children may not have the lung capacity to inhale long enough to trigger the actuation, then continue inhaling long enough to draw sufficient drug into the lungs. The optimal technique is similar to that required for a pMDI alone, once the dose actuation has been triggered near the start of inhalation.

DPIs also require a maximal inhalation, but it needs to be a hard and fast inhalation, especially when using the Turbuhaler. In addition, the maximum inspiratory flow needs to be reached as quickly as possible, early in the inhalation maneuver. Otherwise, the drug dose is cleared from the device at the lower inspiratory flow, before the patient reaches peak inspiratory flow. Because of the marked differences in optimal flow rate between pMDIs and DPIs, it is strongly recommended that, as much as possible, the same device type is selected for patients requiring multiple drug administrations via inhalation.

\textbf{Conclusion}

Parental training and motivation is another complication that should be considered, especially in younger children. Unlike adults or adolescents who would generally be solely responsible for the use or misuse of their aerosol therapy, in younger patient age groups, both the parent and the child need to be taken into consideration when selecting the inhalation therapy to be used, as well as observing the use of the device when training.

The age of 6 years seems to be the ‘magic’ figure in most guideline or consensus documents in terms of the lower age limit at which the more complex devices or inhalation maneuvers can be prescribed. However, the age recommendations in the use of the various aforementioned devices and inhalation techniques are only guidelines. An assessment of the ability of the child is needed to ensure that he or she will be able to use the relevant treatment in a consistent and reproducible manner, i.e., not only when being observed in a clinic or hospital setting.

Adolescents present a completely different set of issues to deal with. Anatomically, and cognitively, they would be very similar to adults and hence able to effectively utilize the full range of aerosol devices now available. However, issues such as adherence and deliberate misuse of their prescribed therapies may come into play here, and will be addressed in the final topic in this symposium.

\textbf{References}

Many patients that may benefit from aerosolized medication delivery require acute or long-term respiratory support. This can complicate delivery of inhaled medications as most aerosol devices are not designed for use in conjunction with respiratory support devices and vice versa. Three of the most common complications are alterations of the delivered concentration of drug to the airways, altered deposition of the drug within the airways, and interference of the drug or drug delivery system with the respiratory support device. This session aims to provide a concise review of appropriate devices, techniques, and considerations for the delivery of aerosol medications to patients requiring respiratory support.

Respiratory care support devices can be categorized as non-invasive oxygen delivery devices, non-invasive pressure delivery devices, and invasive ventilatory support devices. Non-invasive oxygen delivery devices typically do not interfere with aerosolized medication delivery, with the exception of a non-rebreather mask. Non-invasive pressure delivery devices, such as continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP) require integration of the aerosol delivery device to the CPAP or BiPAP circuit. This allows the bias flow of the CPAP or BiPAP to dilute and alter the deposition of the aerosolized medication. Invasive ventilator support devices, such as conventional and oscillatory mechanical ventilators, can affect aerosol delivery in the same way that CPAP and BiPAP do; moreover, in ventilator systems that have a dual-limb circuit, which is common, the aerosolized medication can negatively affect the function of the ventilator. Optimal aerosol device selection and delivery techniques can aid clinicians in overcoming these issues.

References

#4 Inhaled Therapy: A Commercial Success but a Therapeutic Embarrassment. Are We Seeing the First Signs of Change? « plus ça change, plus c’est la même chose »

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If major car crashes continually occur at the same road junction, it may be that the fault lies not primarily with the individual drivers involved but with the design and designer of the junction.

The Blunders of our Governments; King A, Crewe I

Why use inhaled therapy for pulmonary disease?

When considering the role of aerosol therapy, it is important to understand the reasons for utilizing this route since the hurdles to be overcome are considerable if effective delivery of medication to the lungs is to be achieved.

- For most β-agonists, their onset is much more rapid when inhaled than when taken orally (5-10 mins vs. 3 hrs for short acting β-agonists)
- For many drugs such as corticosteroids, β-agonists and aminoglycosides, their therapeutic index can be considerably improved, significantly reducing the risk of clinically important systemic side effects for comparable efficacy when compared with oral therapy
- A relatively large dose can be delivered to the epithelial surface such as when using antibiotics for the treatment of biofilm endobronchial infections
- Drugs which have very low oral bioavailability can be used such as DNase and, historically, sodium cromoglycate

What are the challenges?

- The airways have evolved to exclude foreign material from the lungs – a CF patient can take many enzyme replacement capsules in one swallow but getting a few dozen micrograms of drug to the lungs through the inhaled route is a significant challenge
- The improved therapeutic index is only relative, as demonstrated by the epidemics of death in young persons reported in the UK and NZ associated with the use of relatively non-selective β-agonists and reports of death due to adrenal suppression in children using relatively high doses of inhaled steroids (ICS).
- Drug is most effectively delivered to healthy lungs. With deteriorating lung function, delivery becomes increasingly
patchy and centrally distributed with many peripheral areas receiving little or no drug

- Poor regimen compliance (sometimes referred to as adherence) can have a significant impact on outcomes. For example, an asthmatic patient seemingly needs to take in excess of 80% of the recommended doses of inhaled corticosteroids (ICS) for the medication to have a significant impact on the levels of morbidity and frequency of significant exacerbation [1]

- Poor device compliance (not using a device effectively) adds an added layer of complexity when using current delivery systems. Lack of competence or patient contrivance (knowing how to use a device effectively but contriving to use it ineffectively) can result in total failure to achieve the therapeutic objective [2,3]. A patient who takes a tablet before a meal rather than after a meal may reduce the efficacy of that medication. In contrast, a patient can adhere to a suggested regimen (i.e. 2 puffs twice a day) but receive no benefit for their efforts if their inhaler technique is sub-optimal either because they cannot use it or contrive to use it in an ineffective manner (such as having a perfect technique with a pMDI and spacer in the clinic but choosing not to use the spacer when at home).

The great challenge therefore (assuming one has the correct diagnosis) is to ensure that a patient is supplied with a device that he or she can and will use correctly.

A resounding commercial success but therapeutic embarrassment

In many if not most developed countries, portable inhalers, particularly those delivering combination ‘preventer’ therapy, are high on the list of drugs ordered by national expenditure. The pharmaceutical companies are doing just fine thank you and see little reason to change other than potentially tweak their molecules to try and gain a competitive advantage. In contrast, there are endless studies from many countries demonstrating high levels of morbidity among asthmatics despite very effective therapy. In a country such as Australia where ICS/LABAs are widely prescribed and where these products figure near the top of the list of health care system expenditure, mortality rates remain among the highest in the world and morbidity ‘remains unacceptably high’ [4]. Prescribing data from such studies indicate low levels of regimen adherence.

In essence, large swathes of patients are not taking their medication or failing to use their inhalers effectively and doctors and other health care professionals are failing to act on the impact of this problem on patients’ quality of life.

What underlies the therapeutic under-achievement of inhaled therapy?

- Patients are expected to utilize devices that use technology that was developed in the mid C20th and which fail all current usability standards such that they would never be approved by regulatory bodies such as the FDA if they were brought to the market today

- The regulator bodies such as the FDA have in effect fossilized the field by
  - ensuring that any ‘generic’ inhaler should be as bad as its comparator device
  - failing to insist that devices given to patients meet their own ‘usability’ standards [5]

The FDA insists on product withdrawal or remediation in numerous cases where harm is being or potentially being caused by a particular product – sadly their inhaled therapy division appears to be the one exception, being apparently prepared to ignore on-going harm resulting from the continued marketing of devices that most patients cannot and/or will not use.

To be effective, the patient is required to use the device with a delivery system that can deliver droplets or particulates of a size that might penetrate through the upper airway and deposit effectively in the lower airway and use the device regularly. With current portable devices such as pMDIs (pressurized metered dose inhalers) and dry powder inhalers, the patient must use a specific technique to maximize the chance of drug delivery – sadly, optimal techniques for these two classes of drug are diametrically opposed with patients ideally inhaling slowly when using a pMDI (with or without a spacer) and holding their breath, while for the dry powder inhalers (DPIs), they are required to breathe in as rapidly as possible as the patient is required to provide the energy necessary for aerosolizing the drug. For the pMDI, the required energy is provided by boiling of the propellant as they are released from the metering valve.

There is overwhelming evidence that most health care professionals (including many respiratory physicians) and pharmacists do not understand the basic principles underlying inhalation therapy and cannot teach patients to use these devices effectively. Consequently, the constant stream of papers that have appeared since the 1960’s illustrate that it is only the minority of patients who have an optimal technique and that lack of competence is associated with unnecessary morbidity [6,7]. The range of novel ‘techniques’ that are described probably illustrates the endless ingenuity of Man to misuse a device better than any other area. Even when patients are competent to use the devices, they frequently contrive to use them ineffectively (such as inhaling rapidly from a pMDI or not using a spacer), ignoring the instruction they have received.

The above highlights the added challenge faced when using the aforementioned inhalation therapy and simply trying to ensure that patients take their medication regularly which is a major challenge in the management of any chronic condition. It would appear that for patients requiring inhaled corticosteroids (ICS) with or without add-on therapy for troublesome asthma, they need to take their medication at least 80% of the time due to the slow onset and rapid off-set of ICS [1].
While clear and effective education can significantly improve competence and reduce contrivance, it appears to have little effect on regimen compliance in most cases. Recent data suggest effective feedback of an individual’s regimen compliance can have a major impact not only on the frequency with which a medication is taken but, more importantly, it can also significantly improve therapeutic outcomes [8].

Progress in inhaler technology since the 1950’s?

As noted above, those working in respiratory medicine seem to miss ‘the elephant in the room’ which is that, unlike almost all other areas of medicine, or indeed any sphere of endeavor, inhaler technology has in essence not progressed beyond the mid 1950s by which time DPIs, pMDIs and jet nebulizers were all in-service [9]. If we consider the management of diabetes, another chronic childhood disease, in the 1950s insulin was administered in glass syringes with metal needles that needed to be sterilized; outside of medicine, portable music involved carrying a record player and the records to a site with a plug to power the record player. For the diabetics, disposable syringes and needles came next followed by insulin pens and then pumps. Now patients are being given implantable automated delivery systems that both act as sensor and delivery, thus largely taking the bother and the need for frequent and continuous patient self-management out of the equation. Similarly, accessing music on the go is just another task devolved to the mobile phone. The failure to develop devices that minimize the opportunities for patients to not take their medication effectually (through not using their device or failing to use it correctly) leads to high levels of unnecessary morbidity, contributes to preventable deaths and is a major factor in the problems experienced by patients being considered for invasive and expensive therapies such as thermoplasty and monoclonal agents [10], the latter representing very expensive solutions for preventable patient behavior. The big risk to patients of being given effective devices that address the known usability and human factor issues is they will be at risk of side effects from the excessive doses of steroids prescribed in response to ongoing morbidity by physicians who fail to deal with the underlying non-compliance.

Where to from here?

How do we progress beyond the current embarrassing under-achievement given that inhalation therapy has conspicuously failed to deliver the benefits that it should? The blocks to progress have been primarily the regulatory authorities who fail to understand the impact of their failure to insist that devices meet usability standards appropriate to the C21st. However physicians are probably equally culpable in that they have failed to advocate for their patients, in large part due to a lack of awareness that things could be better.

Dataloggers that can provide the patients as well as their physician, nurse or pharmacist information regarding their use of their regular medication are starting to appear with the aim of improving regimen adherence. Recent studies have clearly shown improved adherence although only one, to date, has clearly shown improvements in clinically important outcomes such that there is still a lack of clarity of how they should be used in clinical practice. Their real benefit is likely to be observed in those with more troublesome asthma who are experiencing ongoing morbidity and hence are bothering their physician. This area is likely to progress rapidly in the coming years through pharma companies trying to obtain a commercial advantage or nullifying a competitor’s potential advantage.

More education regarding inhalers – the mantra of those trying to preserve the status quo – is an old and completely worn out record that needs to be discarded. Well-designed devices should be intuitive to use effectively, difficult to use ineffectively and promote adherence through the ability to feedback patterns of adherence.

However, improved usability (making it very difficult for patients to misuse their inhaler) is only going to come when regulators are pressured by clinicians and patient groups into recognizing their responsibility in the huge levels of unnecessary morbidity existing among asthmatic subjects.

I would suggest this is one of the great health promotion challenges that professional bodies such as the Thoracic and Respiratory societies should be taking up as a priority. Failing this, a class action taken by patients and relatives citing the FDA’s failure to protect them from unnecessary morbidity and mortality may do the trick.

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Young Investigator's Oral Communications

A109 – Phenotype and Endotype Clusters in Very Severe Asthmatic Preschool Children: The P'tistathme Cohort

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Background: Consistent epidemiological data indicate that the outcome of asthma in adults may be determined in early childhood. This may be due to primary airway remodeling AR an abnormal repair process that contributes to the development of poorly reversible airway narrowing.

Hypothesis: Performing bronchial biopsies in severe preschool wheezing may help the clinician clarify etiological factors and mechanisms involved in AR.

Objectives: 1) to determine the incidence and characteristics of AR in a select group of very severe recurrent preschool wheezers, and 2) to define the clinical determinants of such remodeling and to identify clusters of patients based on phenotypes and endotypes.

Methods: A prospective epidemiological cohort study conducted in 2 University Hospitals (Bordeaux & Toulouse, France). Severe preschool wheezers aged 1 year to <6 years were included in the study. Medical history, asthma control evaluation, clinical examination, lung function testing, allergy prick tests, chest X-ray and blood sampling were noted/ performed. BAL and bronchial biopsy specimens were obtained by fiberoptic bronchoscopy and AR was assessed by morphological (immunochemistry) analysis.

Results: We included 67 preschool children (54 with severe wheezing, 11 controls from a tissue bank) with a median age of 3 years. All patients demonstrated AR which occurred at an early age (1 year). The rank order of frequency of AR according to individual components was as follows: epithelial alteration (100%) > RBM thickening (98%) > increased BSM surface area (52%) > mucus gland hyperplasia (21%). Three clusters could be identified. The main classifying factor was cigarette smoke exposure during pregnancy and in its absence, gender (male or female sex). Cluster 1 was characterized by male sex, early onset respiratory disease and asthma, MTW, impaired humoral immunity, increased BALF PMN, and a trend towards greater total bacterial load. Cluster 2 was characterized by female sex, late onset respiratory disease, and a trend towards allergic sensitization, greater viral carriage and increased BSM surface area. Cluster 3 was characterized by male sex, lower BW, in utero and post-natal cigarette smoke exposure, impaired humoral immunity, more viral carriage, greater epithelial shedding, and a trend towards increased BSM surface area.

Conclusion: Very severe preschool wheezing pheno-endotype is heterogeneous and can be attributed to 3 classes. This may pave the way for larger (therapeutic) studies.

E103 – Gas Exchange Abnormalities in Prematurely Born Infants Developing Pulmonary Interstitial Emphysema

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Background: Despite advances in neonatal respiratory support, pulmonary interstitial emphysema (PIE) still occurs and can lead to fatal respiratory failure. We hypothesized that infants with severe PIE, compared to those same infants before the development of the condition, would have poorer oxygenation and ventilation efficiency despite increased tidal volume requirements due to an increase in dead space ventilation. Furthermore, we hypothesized that composite gas exchange indices would predict death or bronchopulmonary dysplasia (BPD) development.

Aims: To determine how oxygenation, ventilation efficiency and tidal volume requirements change with the development of PIE and whether composite gas exchange indices would predict death or bronchopulmonary dysplasia (BPD).

Study Design: Retrospective cohort study.

Subjects: All infants who developed PIE from 2010 to 2016 at King’s College Hospital NHS Foundation Trust, London, UK.

Outcome Measures: The oxygenation index (OI), ventilation efficiency index (VEI), ventilation to perfusion ratio (VA/Q) and inspiratory tidal volume (VT) were calculated at two time endpoints: before radiological evidence of PIE (pre-PIE) and at the worst radiographical appearance of PIE (PIE-worst).

Results: Thirty infants were included in the study with a median (IQR) gestational age of 24.6 (24.3–26.7) weeks. Age at pre-PIE was 11 (6–19) days and age at PIE-worst was 23 (13–42) days (Table 1). Compared to pre-PIE, at PIE-worst OI [4.8 (3.1–6.1) vs. 14.5 (10.7–19.2) respectively, p < 0.001] and VT [6.8 (5.5–6.8) vs. 9.9 (7.2–13.1) ml/kg, p = 0.007] were significantly higher and VEI [0.16 (0.13–0.19) vs. 0.01 (0.01–0.11) respectively, p < 0.001].
respectively, p < 0.001] and VA/Q [0.26 (0.20–0.37) vs. 0.15 (0.11–0.40), p = 0.033] were significantly lower. An OI exceeding 11.4 at PIE-worst predicted death or BPD with 80% sensitivity and 100% specificity. Table 1 Comparison of gas exchange indices corresponding to the last chest radiograph without PIE (Pre-PIE) and to the chest radiograph with the worst PIE (PIE-worst)

<table>
<thead>
<tr>
<th></th>
<th>Pre-PIE</th>
<th>PIE-Worst</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>62.2 (49.8-72.5)</td>
<td>41.4 (34.7-49.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FIO2</td>
<td>0.44 (0.34-0.51)</td>
<td>0.75 (0.57-0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (cm H2O)</td>
<td>9 (9-10)</td>
<td>11 (10-13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIP (cm H2O)</td>
<td>19 (18-22)</td>
<td>24 (21-26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEEP (cm H2O)</td>
<td>5 (5-5)</td>
<td>5 (5-6)</td>
<td>0.125</td>
</tr>
<tr>
<td>RR (per minute)</td>
<td>50 (45-60)</td>
<td>60 (52-60)</td>
<td>0.011</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>46 (41-53)</td>
<td>54 (50-74)</td>
<td>0.001</td>
</tr>
<tr>
<td>OI</td>
<td>4.8 (3.1-6.1)</td>
<td>14.5 (10.7-19.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VEI</td>
<td>0.16 (0.13-0.19)</td>
<td>0.01 (0.01-0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PA-aO2 (mmHg)</td>
<td>184 (115-236)</td>
<td>396 (271-526)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>42 (38-45)</td>
<td>43 (41-46)</td>
<td>0.091</td>
</tr>
<tr>
<td>VT (ml/kg) (N = 12)</td>
<td>6.4 (5.5-6.8)</td>
<td>9.9 (7.2-13.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>VA/Q</td>
<td>0.26 (0.20-0.37)</td>
<td>0.15 (0.11-0.40)</td>
<td>0.033</td>
</tr>
<tr>
<td>Shunt (%)</td>
<td>13 (9-19)</td>
<td>19 (12-23)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Median and IQR values are presented
*Mann-Whitney U rank sum test


Figure 1 The chest radiograph on day two of life of an infant born at 25 weeks of gestation with a birth weight of 850 grams, before the development of PIE (a), and the chest radiograph of the same infant on day seven after birth corresponding to the worst radiographic appearance of PIE (b).

Conclusions: Development of PIE is associated with poorer oxygenation and ventilation efficiency despite increased tidal volumes. Composite oxygenation indices predicted death or BPD in PIE.

E180 – Abnormal Childhood Lung Function in Former Preterm Infants: Who Is at Risk?

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Rationale: In the US, 12% of babies are born preterm at < 37 weeks gestation and are at risk for respiratory disease, specifically bronchopulmonary dysplasia (BPD). BPD, the most common complication of extreme prematurity, affects over 10,000 premature infants every year. How advances in neonatal management may impact lung function later in life remains to be characterized. We hypothesize that gestational age, birth weight, and neonatal disease severity will be predictors of long-term lung function in a cohort of former preterm infants with respiratory disease.

Methods: Former preterm infants < 37 weeks gestation seen in the pulmonary clinic at Boston Children’s Hospital since 2008, and enrolled in a patient registry, were included. Baseline NICU history, respiratory symptom & environmental questionnaires, and longitudinal spirometry were examined. Predictors of childhood lung function including gestational age, birth weight, and respiratory support at 36 weeks corrected gestational age (CGA) were assessed using linear mixed models.

Results: Among 916 former preterm infants enrolled in the patient registry, 157 had spirometric testing available. These 157 subjects were born from 1999–2013, with gestational ages of 23 + 3/7–36 + 1/7weeks (mean 27 + 1/7weeks), and birth weights of 455-2870g (mean 915g). Moderate to severe BPD was present in 84%. Maternal smoking during pregnancy was reported in 2%, household smoke exposure in 5%, and no subjects were smokers at the time of spirometric testing. There were 483 spirometric measurements.
ABSTRACT

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In this cohort of former preterm infants with respiratory disease, 42% of spirometry sessions demonstrate abnormal childhood lung function with FEV1 less than 80% predicted, suggesting obstruction. This analysis supports the use of BPD severity in the NICU as a predictor of risk for long-term lung function abnormalities, with the recognition that this risk is complex and BPD severity alone is an incomplete predictor. Going forward, this longitudinal cohort can provide important information about predictors of childhood respiratory disease in former preterm infants with respiratory disease.

Conclusions: In this cohort of former preterm infants with respiratory disease, 42% of spirometry sessions demonstrate abnormal childhood lung function with FEV1 less than 80% predicted, suggesting obstruction. This analysis supports the use of BPD severity in the NICU as a predictor of risk for long-term lung function abnormalities, with the recognition that this risk is complex and BPD severity alone is an incomplete predictor. Going forward, this longitudinal cohort can provide important information about predictors of childhood respiratory disease in former preterm infants with respiratory disease.

Funding: Supported by National Institutes of Health (NIH) grants K23HL136851-01 (LPH), K12HL120004 (EK Silverman/ST Weiss), R01HL130512 (CPH), R01HL125583 (CPH), R01 HL113264-03 (EK Silverman/MH Cho), and K23AI106945 (JMG).


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Purpose: to compare two structured report (STR) models for chest Computed Tomography (CT) in patients with Cystic Fibrosis (CF) to the CF-CT scoring system.

Methods and Materials: a radiologist and a pulmonologist from 17 international CF centers were recruited to test two STR models (STR1, STR2). Each radiologist reported 20 CF-CT scans using STR1, STR2 and Free Text Reporting (FTR). Ten CT scans were repeated twice to assess intra-observer variability. Pulmonologists compared the information obtained from FTR, STR1 and STR2. Both the radiologist and the pulmonologist provided feedback with a questionnaire. STR scores were correlated with the reference CF-CT score. Descriptive statistics was used to determine mean reporting time and STR evaluation scores. Paired Chi-square test was used to determine significant missing information between FTR and STRs. Intra-observer variability was assessed with Intra-class Correlation Coefficient (ICC) and Bland-Altman plots. Mixed-models analysis was used to assess the effect of the covariates (STR model, CF center, gender, experience on CF imaging, familiarity with CF scoring systems, use of any CF scoring system, use of STR for CF imaging) on the three STR score outcomes (total score, bronchiectasis score, and air trapping score). The Akaike information criterion (AIC) was used to test which STR model best predicted the CF-CT score.

Results: STR was barely used by radiologists (18%) and pulmonologists (13%), although 94% of radiologists and 73% pulmonologists were in favor of using STR in the clinic. Comparing FTR and STRs, site of the worst bronchiectasis (p < 0.001), bronchiectasis extension (p < 0.001), air trapping extension (p < 0.001) and its pattern (p = 0.001) were significantly missing in FTR. Radiologists preferred STR2 because simpler and faster to complete, while pulmonologists preferred STR1 because more complete and clear. Mean reporting time for STR1 was 8 min ± 3.5 SD, for STR2 6 min ± 3 SD. Good correlation was found between STRs and CF-CT score (STR1: r = 0.71, P < 0.001, STR2: r = 0.7; P < 0.001). Intra-observer agreement was excellent (ICC range 0.939–0.988) both for STR1 and STR2.

Conclusion: the use of STR can simplify radiologist and pulmonologist workflow. Since both STR models are characterized by a strong positive correlation with the CF-CT score, STR can provide semi-quantitative data to monitor CF pulmonary disease directly from the radiology reports.

I89 – Differences in Inflammatory Gene Expression and Asthma Risk in Urban and Rural Children.

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Background: Children who grow up in rural areas are much less likely than urban children to develop allergic diseases such as asthma, but underlying immunological mechanisms are inconclusive.

Objective: To characterize the innate immune profiles of children living in rural China and to determine the possible mechanisms of the protection against asthma.

Methods: In our initial screening of 17,587 preschool children aged 5–8 years from Hong Kong (urban, n = 3435) and the County of Conghua (rural southern China, n = 14,152), asthma and allergies were 2–3 times more prevalent in urban Hong Kong. We then proceeded to perform a case-control study recruiting asthmatic and non-asthmatic children from both Hong Kong (47 controls vs. 32 cases) and Conghua (47 controls vs. 19 cases). Blood samples were collected to examine mRNA expression of 8 innate immunity genes involved in inflammatory signaling pathways using quantitative real-time PCR. Peripheral blood mononuclear cells (PBMC) were assessed before and after lipopolysaccharide (LPS) stimulation.

Results: At baseline, all inflammatory genes we measured were expressed at significantly higher transcription levels in Hong Kong controls as compared with Conghua counterparts, such as A20 (difference between means: −1.04, 95% CI: −1.39 to −0.69, p < 0.0001, ΔCt), MALTL1 (−1.62, −2.14 to −1.09, p < 0.0001, ΔCt) and TRAF6 (−1.28, −2.16 to −0.41, p < 0.001, ΔCt). Upon LPS stimulation in vitro, both urban and rural controls were able to upregulate the expression of innate immunity genes, but the upregulation was substantially stronger in children from the urban areas, especially for TRAF6 (P < 0.05, fold-change). However, there were no significant differences between Conghua and Hong Kong cases either with or without stimulation.

Conclusions: Living in rural environment will lead to downregulation of inflammatory gene expression, which may be an important mechanism explaining the rural protection against asthma and allergies.

Keywords: childhood asthma, rural environment, gene expression, innate immune response

Abbreviations: CI, confidence interval; CT, cycle threshold; LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cell; MLTL1, mucosa-associated lymphoid tissue lymphoma protein 1; N, number of subjects; TRAF6, tumor necrosis factor receptor associated factor 6.

L25 – Long-Term Intermittent or Sustained Hypoxia Divergent Effects on Inter-Scapular Brown Adipose Tissue.

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Background: Brown adipose tissue (BAT) is unique in its ability to convert chemical energy directly into heat upon sympathetic stimulation, thus increasing caloric consumption and promoting metabolic health. On the other hand, white adipose tissue (WAT) stores energy as lipids and releases fatty acids. Increases in the amount of WAT and reduction in BAT depots have been associated with the metabolic syndrome and obesity. Conversely, sympathetic stimuli, such as cold exposures or β-adrenergic agonists increase the amount of BAT. In addition to classical BAT tissues, brown adipocytes can develop within WAT upon sympathetic stimulation, so-called “beige” fat. Both brown and beige adipocytes have become appealing targets to increase energy expenditure and combat obesity.

We have previously shown that long-term intermittent hypoxia (IH), such as occurring in patients with obstructive sleep apnea, promotes inflammation of the visceral WAT (vWAT) with concomitant insulin resistance and vascular rarefaction. In contrast, long-term sustained hypoxia (SH) is not associated with such changes. In the current study, we aimed to examine the effect of these two hypoxic profile modalities on inter-scapular BAT (iBAT).

Methods: 8-week old male C57BL/6J mice (n = 10–12/group) were exposed to IH (FIO2 6.1% alternating 21% every 90s, mean FIO2 ~8% for 12-hr/day during the light period) or to room air (RA) for 20 weeks and were maintained on a regular low-fat chow, while another group of mice was exposed to SH (FIO2 8%) or RA (n = 6/group). Following exposures, iBAT was examined for gene expression, protein levels, and morphology in pathways previously implicated in the thermogenic activity of BAT.

Results: Both IH and SH resulted in decreased body weight (BW): RA>SH>RA, p < 0.001. Compared to RA, SH resulted in significant increases in the amount of iBAT/BW, while IH-exposed animals had significantly reduced iBAT/BW. Morphologically, iBAT had larger adipocytes with more lipid content in both IH and SH conditions. SH resulted in ~4-fold increase in the expression of ASC-1, a white adipose tissue marker, with concomitant increase in the brown and beige markers (~P2RX5 ~50% reduction and PAT2 ~25% reduction, respectively). IH did not induce any noticeable changes in the expression of those genes within the iBAT. Similarly to our previous report on vWAT, only IH was associated with vascular rarefaction, as evidenced by CD31 staining (a marker of newly formed vessels), while SH caused increased iBAT vascularity. Accordingly, VEGF expression in iBAT was reduced only in the IH group. Expression of genes involved in BAT thermogenesis was altered as well: PRDM16 expression, a gene regulating whitening of the adipose tissue for energy preservation under fasting conditions, was decreased. Similarly, uncoupling protein 1 (UCP1) levels were markedly decreased under SH, and less so under IH.

Conclusion: IH and SH induce divergent responses in the iBAT depot, indicating preferential whitening of iBAT under SH conditions. This change is accompanied by reduced expression of markers of mitochondrial respiration and increased vascularity, potentially indicating an adaptive mechanism similar to long-term fasting for energy preservation under hypoxic stress. In contrast, IH animals do not mount these adaptive responses, resulting in loss of iBAT tissue. Of note, whitening of iBAT under SH is not accompanied by systemic insulin resistance, but IH reduces insulin sensitivity. Thus, the present study provides initial insights into unique mechanisms leading to
"beneficial" whitening of brown adipose tissue, such as seen in SH, which are absent in IH.

References


M37 – Comparison of the Efficacy of Nebulized Lignocaine and Instillation Through a Bronchoscope; As a Topical Anesthetic Agent in Flexible Bronchoscopy – A RCT

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Introduction: Adequate sedation or anesthesia is a must in pediatric flexible bronchoscopy to achieve a comfortable procedure for both patient and bronchoscopist. Hence, most of the pediatric flexible bronchoscopies are performed under general anesthesia (GA). However, in the developing countries, the availability of theater and anesthesia facilities is severely limited in comparison to the large number of children who require bronchoscopies. Therefore, most of the pediatric flexible bronchoscopies are performed under conscious sedation in the developing world.

Introduction of a bronchoscope through the airway would be an unpleasant and painful experience for a child. In addition, it could arouse a sedated child and induce protective airway reflexes such as cough. Hence, provision of an adequate topical anesthesia is a must for a successful bronchoscopy performed under conscious sedation. Lignocaine spray and gel are used prior to the introduction of a bronchoscope in adults. However, these methods are practically difficult in children due to lack of cooperation. Thus, direct administration of lignocaine via the working channel of a bronchoscope in “spray as you go” fashion is the most commonly practiced procedure in children. However, application of a liquid into an unanesthetized airway in a sedated child has a potential to induce intense cough, aspirations and arousal by itself.

Nevertheless, a nebulized route might avoid these drawbacks and may allow an even distribution of local anesthetic agent over the airway epithelium. Nebulization is being used to administer a wide range of medications in children and is usually tolerated very well. Despite its off-label use, the safety of nebulized lignocaine as a topical anesthetic agent has been proven in many adult and pediatric studies. In addition, some adult studies have shown the effectiveness of nebulized lignocaine over direct administration through a bronchoscope. However, no pediatric study was found which directly compared the effectiveness of these two methods of lignocaine administration as a topical anesthetic agent for flexible bronchoscopy in children, which were performed under conscious sedation.

Objective: To compare the efficacy and safety of nebulized lignocaine and locally instilled lignocaine directly through a bronchoscope in “spray as you go” fashion, as a topical anesthetic agent in pediatric flexible bronchoscopy performed under conscious sedation.

Method: Study design: A parallel-group randomized controlled trial with 1:1 allocation ratio was conducted at the All India Institute of Medical Sciences, New Delhi, India. Nebulized lignocaine and locally instilled lignocaine through the working channel of a bronchoscope were used in the two arms. This was an open-labeled trial although assessment was performed blindly (use of placebos and double dummy technique to facilitate blindness was not considered in this study since local instillation of 0.9% NaCl alone into the larynx as a placebo in the nebulization arm had a potential to induce intense cough while nebulization of 0.9% NaCl alone as a placebo in the local instillation arm had a potential to induce bronchospasms in a sedated child). Consecutive patients aged 1 month to 16 years who were scheduled for routine flexible bronchoscopies under conscious sedation were included.

Ethics clearance and trial registration: Ethics clearance was obtained from the Institute Ethics Committee and this trial was prospectively registered at the Clinical Trial Registry of India (number CTRI/2016/09/007327). The full protocol is available at http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid = 15469.

Randomization and allocation concealment: Computer-generated variable block randomization sequence was used to allocate participants. Sequentially numbered, sealed and opaque envelopes were used to maintain allocation concealment. Each patient received a serial number according to the order of enrolment. Sealed envelopes were kept in a locker at the bronchoscopy suite and were opened by the
Fifty-two patients were enrolled (26 for each study arm) after assessing 79 for eligibility from November 1st 2016 to April 21st 2017. The median ages of the participants of the nebulized lignocaine group (study arm A) was 42 (IQR: 7.5, 87) months (boys 61.5%) and of the participants of the locally instilled lignocaine through a bronchoscope group (study arm B) was 51 (IQR: 14, 122) months (boys 65.4%). There were no significant differences in baseline demographics and indications for bronchoscopy in both groups. All bronchoscopies were performed transnasally while patients were in supine position by two well experienced investigators of this study.

All enrolled children except one child in study arm A (underwent rigid bronchoscopy under GA) received the allocated intervention. No follow-up data were required and hence, no dropouts in this trial.

The median frequencies of cough during the entire procedure were 5.4 (IQR: 4.3, 12.5)/min and 9.4 (IQR: 4.5, 15.0)/min in arms A and B, respectively (P = 0.23). Median cough frequencies from insertion of the bronchoscope through a nostril to passing through vocal codes (nasal and laryngeal passage) were 4.15 (IQR: 2.3, 3.7)/min and 8.45 (IQR: 2.8, 11.5)/min in arms A and B, respectively (P = 0.0085). The mean severities of the cough (assessed using a 100 mm VAS) were 46 ± 11.2 and 41 ± 13.6 in study arms A and B, respectively (P = 0.26).

The mean maximum pulse rates per minute during the procedure in arms A and B were 147 ± 19.4 and 148 ± 34.4 respectively (P = 0.92) and mean percentage changes in pulse rate during the procedure were 27 ± 15.1 and 36 ± 15.2 in study arms A and B, respectively (P = 0.035). The mean minimum oxygen saturations during the procedure were 90% ± 4.3 in arm A and 88% ± 17.5 in arm B (P = 0.16) while, the mean percentage drops in oxygen saturation from the pre-procedure value were 7.9% ± 3.9 and 9.1% ± 4.6 in arms A and B, respectively (P = 0.31).

The bronchoscopist’s mean scores for relative easiness of the procedure (using a 100 mm VAS) were 62.5 ± 12.5 and 68.1 ± 17.3 for study arms A and B, respectively (P = 0.24). Similarly, the bronchoscopy nurse rated mean easiness as 69.2 ± 13.7 for arm A and 63.8 ± 16.5 for arm B (P = 0.19). The mean pain rating by children over 5y in arm A was 6.2 ± 1.2, while the same rating for arm B was 7.1 ± 1.0 (P = 0.93).

The mean additional lignocaine doses given at the larynx were 0.35 ± 0.17 mg/kg in arm A and 0.31 ± 0.12 mg/kg in arm B (P = 0.81). All participants of arm A required 1 mg/kg additional lignocaine at carina (mean = 1, SD = 0), whereas the equivalent mean of arm B was 0.31 ± 0.46 (P < 0.001). The mean total additional lignocaine required during the procedure was 1.35 ± 0.47 and 0.61 ± 0.68 mg/kg for arms A and B, respectively (P = <0.001). However, cumulative mean lignocaine dose was below 6 mg/kg in both study arms (arm A: 5.3 ± 0.47, arm B: 4.31 ± 1.41).

No participant in either study arm developed untoward reaction for lignocaine during or post procedure. Total mean duration of a bronchoscopy in arm A was 210.4 ± 98.1 s and arm B was 221.4 ± 113.2 s (P = 0.71).

**Results:** Fifty-two patients were enrolled (26 for each study arm) after assessing 79 for eligibility from November 1st 2016 to April 21st 2017. All enrolled children except one child in study arm A (underwent rigid bronchoscopy under GA) received the allocated intervention. No follow-up data were required and hence, no dropouts in this trial.

The median frequencies of cough during the entire procedure were 5.4 (IQR: 4.3, 12.5)/min and 9.4 (IQR: 4.5, 15.0)/min in arms A and B, respectively (P = 0.23). Median cough frequencies from insertion of the bronchoscope through a nostril to passing through vocal codes (nasal and laryngeal passage) were 4.15 (IQR: 2.3, 3.7)/min and 8.45 (IQR: 2.8, 11.5)/min in arms A and B, respectively (P = 0.0085). The mean severities of the cough (assessed using a 100 mm VAS) were 46 ± 11.2 and 41 ± 13.6 in study arms A and B, respectively (P = 0.26).

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No participant in either study arm developed untoward reaction for lignocaine during or post procedure. Total mean duration of a bronchoscopy in arm A was 210.4 ± 98.1 s and arm B was 221.4 ± 113.2 s (P = 0.71).

**Interpretation and Conclusion:**

Participants who received nebulized lignocaine developed significantly less cough from insertion of the bronchoscope through a nostril to passage through vocal codes. In addition, pulse rate was more stable during the procedure in the nebulized arm. There was no significant difference in safety parameters, participants’ perception of pain and bronchoscopist’s and bronchoscopy nurse’s assessment of the easiness in both arms. However, all of these parameters showed a more favorable trend towards the nebulized group. Although the total lignocaine dose was higher in the nebulized group, it still remained within the accepted range and obvious wastage during nebulization would be the reason. We did not have facilities to assess lignocaine serum levels. Safety of lignocaine as a nebulized medication was also shown because no participant developed an adverse reaction.

Therefore, nebulized lignocaine is more effective than routine local instillation as a topical anesthetic agent in pediatric flexible bronchoscopy performed under conscious sedation. Its overall safety and ability to reduce cough before entering through the vocal codes would be useful since manipulation of a flexible bronchoscope through...
the nasal passage and larynx would be an unpleasant experience for a sedated child. Additional doses of local instillation could be used (within the accepted range) during bronchoscope insertion, if required.

Finally, the use of nebulized lignocaine immediately before a flexible bronchoscopy is suggested as an effective alternative to routine local instillation for centers which do flexible bronchoscopies under conscious sedation in children.


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Objective: Tracheostomy is a frequent procedure, usually performed for assuring an airway access and bringing comfort to patients on mechanical ventilation with airway obstruction or neurological problems. Our objective was to describe the clinical and epidemiological characteristics of patients with tracheostomy at the National Children’s Hospital “Dr. Carlos Sáenz Herrera” in Costa Rica from January 2008 to December 2015.

Methods: We performed an 8-year retrospective study of patients who attended the Tracheostomy Clinic at the National Children’s Hospital “Dr. Carlos Saenz Herrera” from 2008 to 2015. We identified 384 patients, reviewed 249 records although for this report, we analyzed 179 patients who met the inclusion criteria. Recorded information included demographic data and clinical information. The database was created with Epidata Software V2.2 and data analysis was performed with the STATA program, version 14.

Results: A total of 179 patients were included, 61.4% (110/179) were males, 67% (67/100) were born at term (>37 weeks of gestational age), 26.7% (35/131) had low birth weight, 32% (41/128) required intubation at birth and 25.8% (33/129) suffered fetal distress. Congenital abnormalities of the upper airway were reported in 27.6% (47/170) of the patients, with cleft lip and palate being the most frequent (8/47, 17.0%), followed by Pierre-Robin Sequence (6/47, 12.7%) and Apert Syndrome in 2/47 (4.2%). Prolonged intubation was the most frequent indication for a tracheostomy (46.7%), followed by cerebral palsy (30.4%), laryngomalacia (28%), subglottic stenosis (15.2%), cranial malformations (7.6%), neuromuscular disease (6.4%), airway obstruction by a tumor (5.2%) while the least frequent indications were vocal cord paralysis and vascular tumors (1.7%). No cases of laryngeal papillomatosis requiring tracheostomy were reported.

Malnutrition was observed in 35.6% (61/171) of the patients. Feeding disorders were reported in 56.8% (95/167) of the patients, 44.9% were fed by gastrostomy, 40.7% were fed by mouth, 10.1% used a nasogastric tube and 4.1% used any combination of the latter.

Socio-economic risk factors were identified in 23% (35/151) of the cases. Of these patients, 48.6% (17/35) lived in overcrowded environments and 14.3% (5/35) were exposed to passive smoking. The main caregiver was the mother in 94% (141/150) of the patients and 82% had a second caregiver as well.

Long term post-tracheostomy complications were present in 85% (140/164) of patients, with tracheitis being the most common (54.2%), followed by stomal granulomas (12.1%), need for mechanical ventilation (9.1%), accidental decannulation (5.4%), and intra-tracheal granulomas (5.4%). Other complications such as cardiorespiratory arrest (5%), bleeding (4%), obstruction of the cannula (0.6%) were less common.

Decannulation was successful in 47% (76/162) of the patients and was achieved on the first attempt in 90% (69/76) of cases. Failed decannulation occurred only in 9.2% of the patients. Surgery was needed previous to decannulation in 16.1% (11/68) of the patients.

The average time for a positive bronchoalveolar lavage culture after the tracheostomy was 175 days (range 1–2057 days). Cultures were negative in 33% (54/164) of the patients, and in the positive samples, the more frequently isolated bacteria were: Pseudomonas aeruginosa (31.7%), methicillin-resistant S. aureus (MSSA) (9.7%), Klebsiella (3.6%), S. pneumoniae (1.8%) and methicillin-resistant S. aureus (MRSA) (1.8%). Most bacterial species found were highly sensitive (91.1%) and multi-resistant bacteria were only isolated in 5.5% of the samples. Prophylactic antibiotics were given to 27.7% (43/155) of the patients and the most common medications prescribed were trimethoprim-sulfamethoxazole (74.4%), amoxicillin (18.6%) and ciprofloxacin (7%).

Reported mortality in this group of patients was 15% (24/158), however none of the causes of death were related to complications from the tracheostomy.

Conclusions: Tracheostomy is a common procedure among the pediatric population. In our study, most patients were males and nutritional and social problems were identified in a considerable portion of the group. Prolonged ventilation was the most common indication for tracheostomy in our cohort. There was a high prevalence of complications; tracheitis was the most frequent complication and Pseudomonas aeruginosa was the main bacterial agent found. Decannulation was achieved in almost half of the patients. The data found in this study will allow our center to improve in attending the nutritional and social needs of our patients, making efforts to reduce prolonged ventilation and educating caregivers in order to avoid other complications.

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ABSTRACT

Posters

1. BRONCHIAL ASTHMA AND OTHER CHRONIC OBSTRUCTIVE PULMONARY DISEASES

A3—Impact of Allergic Factors with House Dust Mite and Environments on Childhood Asthma Control.

Dung NT.1,2
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Background: Indoor pollution with allergens including house dust mite influence asthma control levels.

Objective: To determine the rate of allergy to house dust allergens and its impact associated with indoor pollution on asthma control levels.

Methods: Study questionnaires, total IgE tests and skin tests for allergic house dust were collected in 129 children with asthma enrolled from January to March 2014. Diagnosis and assessment of asthma control level of the child was determined according to GINA 2012 criteria.

Results: There were 93 (72.1%) children with a positive skin test for at least one indoor respiratory allergen while the remaining 36 (27.9%) children were negative for the skin test. In the positive group, up to 89.9% were positive for 2 or more allergens. Of these, the positive proportion with Dermatophagoides pteronyssinus (29%) and Dermatophagoides farinae (22.9%) were highest, followed by house dust allergens (Blomia) with 22.9%, cockroaches (9.7%), hairy dog (8.6%). The lowest rate was 6.9% accounting for cat fur. The rate of positive allergen test in children over 5 years of age was higher (75.4%) than children under 5 years (46.7%) [OR = 3.51 (1.04 to 12.0); P = 0.019].

Similarly, the rate of positive allergen test in children with total IgE $\geq$ 100 IU/ml was higher (77.3%) than children with total IgE $< 100$IU/ml (56; 2%) [OR = 2.65 (1.14 to 6.71); P = 0.021]. There were 77 (82.8%) children with positive allergen test who had uncontrolled or partly controlled asthma, higher than the group of children with negative allergen test (15; 41.7%) [OR = 4.15 (1.74–9.98); P = 0.000]. Similarly, there were 52 (65.0%) children with positive test for two or more allergens who had uncontrolled or partly controlled asthma, higher than the group of children with positive test for only one allergen (3; 23.1%) [OR = 6.19(1.40–31.1); P = 0.010]

Conclusion: The rate of children with asthma has a high positive skin prick test with respiratory allergens such as house dust mite. Irregular bed hygiene less than once per month, charcoal fumes, smoke pollution and dog or cat ownership were found associated with an increased risk of uncontrolled or partly controlled asthma.

A7—Profiles and Characteristics of Bronchial Responsiveness in the Korean 7-Year-old General Population.

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Background/Aim: Bronchial hyperresponsiveness is the intermediate phenotype of asthma. Bronchial responsiveness does not exist so dichotomous has to be expressed "hyper-" or not, rather it exists as a spectrum. We aimed to evaluate the distribution profiles of bronchial responsiveness in the Korean 7-year-old general population and their relationship with clinical allergy.

Methods: The 7-year-old birth cohort participants were invited to visit 16 regional study hospitals. We performed a skin prick test, a standard spirometry and the bronchial provocation test as well as a detailed history and physical examination. The subjects' bronchial responsiveness was categorized into one of the five ordered groups as well as
log-transformed into the response dose ratio (RDR), a continuous marker of airway responsiveness. The distribution frequency, prevalence of recent wheezing, baseline lung functions, and the prevalence of atopic sensitization across all five groups as well as RDR association with clinical allergies were assessed.

Results: Among the 1577 birth-cohort participants, 642 children visited the study hospitals and 559 subjects reliably completed the bronchial provocation test. Ten percent (56/559) of the total population showed a provocative concentration of inhaled methacholine causing a 20% fall in forced expiratory volume in 1 second (PC20FEV1) < 4 mg/mL (Group 1) while 15.7% presented a PC20FEV1 between 4 and 16 mg/mL (Group 2). A total of 14.7% showed a PC20FEV1 ≥ 16 mg/mL but at the same time their PC15FEV1 < 16 mg/mL (Group 3), and the 18.4% displayed their PC15FEV1 ≥ 16 mg/mL with their PC10FEV1 < 16 mg/mL as well (Group 4). Finally, the other 41.1% presented a PC10FEV1 ≥ 16 mg/mL (Group 5). As the group sample increased, the proportion of subjects that had wheezy episodes during the last year decreased (P for trend < 0.001), whereas the mean baseline FEV1 percentage-predicted increased (P < 0.001). On the other hand, the RDR presented a significant elongation in current asthmatics than the others (P = 0.022). There also was a trend toward a increase in RDRs across the control, allergic rhinitis only, asthma only, other hand, the RDR presented a significant elongation in current asthmatics than the others (P = 0.022). There also was a trend toward a increase in RDRs across the control, allergic rhinitis only, asthma only, and the combined allergic rhinitis and asthma groups (P = 0.001).

Conclusion: The 7-year-old general population had a wide spectrum of bronchial responsiveness. Bronchial responsiveness at this age is associated with clinical allergies, namely negatively with baseline lung function and positively with atopic sensitization.

Keywords: Asthma, Bronchial responsiveness, Child, General population, Response dose ratio

A38 – The Clinical Implications of Bilevel Positive Airway Pressure Ventilation for Children with Severe Asthma Exacerbations in Intensive Care Unit.

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Background:
Increasing studies had demonstrated that early initiation of non-invasive ventilation, including the use of Bilevel Positive Airway Pressure (BiPAP), is safe and well-tolerated in the management of children having acute respiratory distress syndrome. Despite the proven efficacy in some pilot studies, the strategy of using BiPAP in asthma patients with severe dyspnea has not yet been well-adapted, and is thus termed “experimental approach” in guidelines. We conducted a retrospective study of children who were admitted to the pediatric intensive care unit (PICU) under the diagnosis of severe asthma exacerbation or status asthmaticus and were treated with or without BiPAP. The purpose of the study was to assess the treatment efficacy and tolerability of BiPAP.

Methods:
We conducted a retrospective study on asthma patients who were admitted to PICU between January 2015 and February 2017. Patients with other significant comorbidities or with certain identified respiratory pathogens were excluded. For patients with multiple admissions, each admission was recorded separately. The medical records were reviewed for the following characteristics: age at presentation, clinical symptoms, heart rate (HR), respiratory rate (RR), oxygen demand, partial pressure of carbon dioxide in serum (pCO2), oxygen saturation (SpO2), clinical laboratory data and chest X-ray images. These admission data were grouped according to BiPAP use (Yes/No). Clinical parameters were documented at selected time intervals (before intervention, after intervention: 0–2 hours, 2–4 hours, 4–8 hours, 10–14 hours, 16–20 hours and 24 hours). Time zero was defined as the initiation of BiPAP ventilation for the BiPAP-using group and any method of ventilation or oxygenation support at PICU for the non-BiPAP group. Mann-Whitney U test was used to analyze the serial data. Amongst the BiPAP(+) group, pCO2 and SpO2 were analyzed before and after the intervention using a paired T-test.

Results:
Data of 27 PICU admissions were obtained, four of whom were excluded for the reasons described above. Data of 23 admissions in 15 different patients were analyzed (19 with BiPAP and 4 without BiPAP). The mean age at admission was 49.21 ± 33.82 months. Respiratory rate (RR) was significantly different before treatment between the 2 groups (p = 0.005) and 0–2 hours after treatment (p = 0.047), with the BiPAP group having a higher respiratory rate. The RR improved significantly in the ensuing time intervals in the BiPAP group. For the heart rate (HR) analysis, there was no significant difference between groups for any time intervals. RR, HR and CO2 level all showed a decline in trend after treatment in both groups. In the BiPAP group, the decrease in pCO2 level did not show statistical significance, while SpO2 level improved significantly after the use of BiPAP. In our study, none received invasive mechanical ventilation support during PICU stay.

Conclusions:
In this study, we found that there was a significant improvement in respiratory rate in patients with BiPAP support. BiPAP was also well-tolerated compared with other means of non-invasive ventilation or oxygen support (nebulizer, mask). These improving trends were also reflected in RR, HR and CO2 similarly in both groups. In conclusion, BiPAP ventilation is safe and efficient in the relief of respiratory symptoms in children with severe asthma attack.

A47 – Children with Severe Acute Asthma Admitted to Dutch PICUs: A Changing Landscape

According to a nationwide database for pediatric intensive care unit (PICU) admissions, the number of children requiring intensive care admission for severe acute asthma (SAA) has increased between 2003 and 2013. SAA has the potential to progress to respiratory failure and can be fatal. SAA requiring admission at the PICU represents a major cost burden. Additionally, PICU admission itself is associated with greater psychological morbidity in children and their parents, when compared with admissions in general pediatric wards.

Objectives: The aim of this study was to identify factors explaining the increase in PICU admissions in The Netherlands.

Methods: We performed a multicenter retrospective cohort study across all tertiary care PICUs in The Netherlands in which we retrospectively analyzed the number and characteristics of children hospitalized for SAA in the PICU during an 11-year period in the Netherlands. Inclusion criteria were all children aged 2–18 years, hospitalized for SAA in PICUs in The Netherlands between 2003 and 2013. Children younger than 2 years were not included because of the uncertainty of the diagnosis. The SAA diagnosis had to be confirmed before PICU discharge. All admissions and re-admissions were included in the study. Data included demography, SAA treatment at the referring hospital and PICU, and mortality.

Results: In the 11-year study period, 590 children were admitted to a PICU, with a total of 660 admissions. During PICU admission, 83% of patients in our study received intravenous (IV) salbutamol. Dutch asthma guidelines require PICU admission in case IV salbutamol is given. Of these patients, 33% received a salbutamol infusion rate of 0.5 mcg/kg/min or less, and 58% received a higher infusion rate of 1.0 mcg/kg/min. Forty-two percent of all admitted children were 2–4 years old. Forty-four children were admitted for SAA in 2003, and this number remained relatively stable until 2010. Since 2010, the annual number of patients admitted to the PICU gradually increased to 138 in 2013. The age distribution and severity of SAA, based on the first blood gas and length of stay at the PICU, remained unchanged. The number of children with asthma did not triple since 2010. Over the years, the proportion of steroid-naïve patients admitted to the PICU increased gradually, although fewer children necessitated invasive ventilation. High-flow nasal cannulae (“Optiflow”) were introduced in 2010, and their use increased significantly in the following years. Seven patients (1%) needed extracorporeal membrane oxygenation (ECMO). In-hospital mortality was n = 4 (0.6%).

Conclusions: During the last decade, we observed a threefold increase in children with SAA admitted to PICUs in the Netherlands, while the age distribution and severity of illness remained similar. In our new 2006 national guidelines, PICU admission is mandatory with the use of IV salbutamol. We speculate that the observations are explained by implementation of the national SAA guideline, and by increasing undertreatment with inhaled steroids.

Reflections and concrete proposals for action: Priority should be given to adequate diagnosis and treatment of children with asthma to prevent PICU admissions, as they carry a high cost, and are associated with the risk of posttraumatic stress disorder. Prospective studies into the risk factors for children with SAA which require salbutamol IV are needed. The safety of salbutamol IV should be further studied, and the need for PICU admission reconsidered.

A50 – Assessment of Quality of Life in Children Suffering from Asthma.

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Asthma is the most common chronic inflammatory disease of the respiratory tract in children. Quality of life of children suffering from asthma is a subjective experience of satisfaction or dissatisfaction with their own lives. The main aims of our study were to verify the connections between symptoms of asthma lung functions and quality of life; influence of comorbidity and asthma on quality of life; to identify and quantify psychosocial areas that children perceive as handicapped due to illness and to verify the degree of similarity in the perception of quality of life between parents and children with asthma. Also, the aim of the study was to translate, adopt and validate on Serbian language Juniper questionnaires, namely (PAQLQ) Pediatric Asthma Quality of Life Questionnaire with standardized operations, a variant with the examiner and questionnaire regarding the quality of life of caregivers of children with asthma – (PACQLQ) Pediatric Asthma Caregiver Quality of Life Questionnaire. Using questionnaires, we wanted to verify the quality of life of the children with asthma and their parents. Results were analyzed in accordance with the severity and length of the disease, as well as with other parameters (degree of disease according to GINA, spirometry, comorbidity, etc.).

The study included 100 children from 6–16 years old with intermittent and persistent mild and moderate asthma. During the study, patients were also classified according to Asthma control score. Diagnosis of asthma was established using well known guidelines for the diagnosis and management of asthma. After registration, a detailed medical history was taken and physical examination was performed for all patients, as well as pulmonary function measurements. Upon arrival and during control examinations (week 1, 5 and 9), asthma control scores were obtained and interviews with children with asthma and their parents were organized. The PAQLQ includes 23 questions divided into three areas: limitation of activities (n-5), symptoms (n-10) and emotional functioning (n-8). The PACQLQ contains 13 questions divided into two main areas: restrictions in the performance of activities-A (5) and emotional function-E. For each question in both questionnaires, there were 7 possible answers, with grade 7 meaning...
without any symptoms and complaints and grade 1 meaning prominent symptoms.

There was a significant correlation between stage of asthma, symptoms, lung function and quality of life of children involved in the study. The clinical picture significantly affected the quality of life of children such that children with poorer control of the disease had a poorer quality of life. Also, improving disease control and asthma control score led to improved quality of life particularly in the areas of symptoms (F = 16,312, a p < 0.001) and emotional functions (F = 41.934, a p < 0.001). Comorbidity of asthma and other allergic diseases were very much present. Children with isolated asthma had a better quality of life then children with asthma and allergic rhinitis (5.76 vs. 6.24, p < 0.05). Parents and children had the same perception of the disease (coefficient correlation, r = 0.387 p < 0.001; r = 0.232 p = 0.031; r = 0.567 p < 0.001) while only parents assessed personal quality of life significantly worse than their children (t = 9.783 p < 0.001; t = 8.265 p < 0.001; t = 7.371 p < 0.001). Children involved in the study had the most complaints in the area of symptoms. Cough and limiting of physical activities were the elements most often cited. Emotional disturbances were less pronounced and sense of rejection did not significantly perturb patients involved in our study. Questionnaires for assessing the quality of life in children with asthma, translated into Serbian, showed good discriminative capability, a high reliability and specificity, with a Cronbach's alpha of 0.78 and, as such, may be recommended to assess the quality of life in routine medical practice and clinical trials.

As with all instruments currently available for use in children, further research is encouraged to verify the validity and usefulness of used questionnaires as a comprehensive health outcome measure in children. Results obtained in this study will promote the introduction of tools for measuring quality of life as an important parameter in estimating the stage of the disease and acceptance of asthma symptoms by patients.

### A66 – Efficacy of Tiotropium Add-on Therapy in Children and Adolescents Who Experienced Episodes of Asthma Worsening during Four Phase III Studies

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**Background:** Asthma is a leading cause of childhood morbidity, with episodes of disease worsening and exacerbation leading to hospitalization and impacting quality of life. Tiotropium add-on therapy has demonstrated improvements in peak and trough forced expiratory volume in 1 second (FEV1) in adolescents and children with symptomatic asthma despite inhaled corticosteroid (ICS) treatment ± other controllers. However, it is not clear what impact episodes of asthma worsening during treatment may have on these improvements. Here, we describe lung function outcomes of pediatric patients who experienced episodes of asthma worsening compared with those who did not during 4 Phase III trials in children and adolescents.

**Methods:** Post hoc analyses involved 4 Phase III, randomized, double-blind, placebo-controlled, parallel-group trials covering patients aged 6–11 years (CanoTinA-/VivaTinA-asthma® [NCT01634139/NCT 01634152]; moderate and severe asthma, respectively) and 12–17 years (RubaTinA-/PensieTinA-asthma® [NCT01257230/NCT012 77523]; moderate and severe asthma, respectively). Patients received once-daily tiotropium (2.5 μg or 5 μg) or placebo, delivered as 2 puffs via the Respimat® inhaler, as add-on to ICS ± other controllers.

The primary endpoint for all studies was peak FEV1 change from baseline (response) within 3 hours post-dose (FEV1(0–3h)) at Week 12 or 24 for severe and moderate asthma, respectively. Secondary endpoints included trough FEV1 response (key in PensieTinA-asthma®; CanoTinA-asthma® and VivaTinA-asthma®) measured at the end of the dosing interval, 10 minutes before the next dose of trial medication at Week 12 or 24 for severe and moderate asthma, respectively. Peak FEV1(0–3h) and trough FEV1 responses for patients who experienced episodes of asthma worsening during the trials were compared with those from patients who did not experience asthma worsening during the trials. Asthma worsening was defined as an episode of progressive increase in 1 or more asthma symptoms (as compared with usual day-to-day asthma symptoms) for 2 or more consecutive days. A decrease in the patient's best morning PEF of 30% or more from the patient's mean morning PEF for at least 2 consecutive days was also included in the definition. Analyses used a restricted maximum likelihood-based mixed-effects model with repeated measures.

**Results:** Baseline demographics and disease characteristics were generally balanced between those who experienced episodes of asthma worsening during the screening and treatment periods of the studies and those who did not, within specified age and asthma severity groups. Across the 4 studies there were improvements from baseline in peak FEV1(0–3h) and trough FEV1 responses in the placebo arms, and these improvements were generally lower in those patients who experienced episodes of asthma worsening or not during the CanoTinA-asthma® and VivaTinA-asthma® studies. The responses were slightly more variable in the VivaTinA-asthma® study, particularly in the asthma worsening subgroups, possibly due to their low number of patients (Figures 1 and 2).

Overall in adolescents, placebo-adjusted improvements in lung function were observed with tiotropium for patients in both the
Rubatina-asthma® and PensiTina-asthma® studies regardless of whether they experienced episodes of asthma worsening or not, with the exception of the 2.5 μg dose group in the Rubatina-asthma® study (Figures 1 and 2).

Conclusion: Once-daily tiotropium as an add-on to ICS maintenance therapy ± other controllers generally improved lung function in patients aged 6–17 years with moderate or severe asthma irrespective of whether they experienced episodes of asthma worsening during the trials. These data support the demonstrated broad efficacy of tiotropium in this age group and indicate that improvements in lung function are largely consistent even if some patients experience episodes of disease worsening.

Figure 1. Peak FEV1(0–3h) response in children and adolescents with and without episodes of asthma worsening during Phase III clinical trials

Figure 2. Trough FEV1 response in children and adolescents with and without episodes of asthma worsening during Phase III clinical trials

A67 – FEV1 Improvements with Tiotropium & Long-Acting Beta2-Agonists Added to Inhaled Corticosteroid Therapy Are Similar in Pediatric Patients with Asthma.

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1Department of Pediatric Pulmonology and Allergy, University Hospital Carl Gustav Carus, Technical University of Dresden – Dresden, Germany; 2Allergy and Asthma Care of Long Island – Rockville Centre, USA; 3Pediatric Pulmonology, Children’s Healthcare of Atlanta – Atlanta, USA; 4Department of Pediatrics, Children’s Hospital of Colorado and the University of Colorado School of Medicine, The Breathing Institute – Aurora, USA; 5TA Respiratory Diseases, Boehringer Ingelheim Pharma GmbH & Co. KG – Ingelheim am Rhein; 6Klinik für Kinder und Jugendmedizin, Evangelisches Klinikum Bethel, Bielefeld – Allergy Center of the Ruhr University, Bochum, Germany

Background: In this systematic literature review in pediatric patients with asthma, we compare the improvement in forced expiratory
volume in 1 second (FEV1) with tiotropium Respimat® added to inhaled corticosteroids (ICS) with the improvement in FEV1 reported for long-acting β2-agonists (LABAs) added to ICS.

**Methods:** The endpoints selected for the comparison were peak and trough FEV1 responses (i.e., change from baseline) in liters. A systematic literature search was performed to identify relevant publications that report on randomized, controlled trials where a LABA was added to ICS for at least 4 weeks in adolescents and children. The results were compared with results from the 2 Phase III trials of tiotropium Respimat® added to ICS in pediatric patients with asthma (RubaTinA-asthma® and CanoTinA-asthma®).

**Results:** The systematic literature search of trials investigating LABAs added to ICS in pediatric patients identified 9 relevant publications, 7 of which were included in a Cochrane meta-analysis. Details of these trials, and the trials with tiotropium Respimat® in pediatric patients with asthma, are provided in Table 1. In the LABA studies, mean ICS dose at baseline ranged from 200–500 μg/day budesonide or equivalent and 160–250 μg/day fluticasone propionate. In the tiotropium studies, mean ICS dose at baseline ranged from 300–600 μg/day budesonide or equivalent. The LABA studies included in the Cochrane meta-analysis present a combination of peak and trough FEV1 measurements, and some articles do not specify at what time point the measurement was taken. For LABA added to ICS versus ICS, the Cochrane meta-analysis of 7 studies found an adjusted mean FEV1 improvement of 0.08 L (95% confidence interval 0.06, 0.10 L) (Figure 1). The 2 newer studies found an increase in FEV1 between 0.04 L and 0.12 L with formoterol added to budesonide versus budesonide, and no benefit in FEV1 with vilanterol added to fluticasone propionate versus fluticasone propionate. If the 2 outliers (the vilanterol study that found no improvement and a very small [n = 21] salmeterol study) are excluded, all individual studies investigating LABA as add-on to ICS generally showed treatment differences between 0.04 L and 0.13 L. The magnitude of FEV1 improvements with once-daily tiotropium added to ICS was similar with twice-daily LABAs added to ICS: tiotropium 5 μg versus placebo showed improvements of 0.134 L to 0.174 L in peak FEV1 response, and improvements of 0.084 L to 0.118 L in trough FEV1 response (Figure 2). Comparing the once-daily LABA vilanterol with once-daily tiotropium 5 μg shows greater lung function responses with tiotropium 5 μg. The results with tiotropium 2.5 μg were broadly similar to tiotropium 5 μg.

**Conclusion:** The results of our systematic literature review suggest that tiotropium add-on therapy provides meaningful lung function improvements as an alternative to LABA, or may be considered as add-on to ICS + LABA, in adolescents and children with asthma.

Table 1. Details of the trials included in the analysis.

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Included in Cochrane analysis</th>
<th>Design</th>
<th>Patient age</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol added to budesonide versus budesonide</td>
<td>SD-039-0719 NCT00646529 Berger 2010</td>
<td>Yes</td>
<td>26-week, randomized, open-label, parallel-group, multicenter trial</td>
<td>6–11 years</td>
</tr>
<tr>
<td>Formoterol added to budesonide versus budesonide</td>
<td>SD-039-0725 NCT00646321 Eid 2010</td>
<td>Yes</td>
<td>12-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>6–15 years</td>
</tr>
<tr>
<td>Formoterol added to budesonide versus budesonide</td>
<td>Study 0688 Pohunek 2006</td>
<td>Yes</td>
<td>12-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>4–11 years</td>
</tr>
<tr>
<td>Salmeterol added to fluticasone propionate versus fluticasone propionate</td>
<td>SD 039 0714 ATTAIN CSR</td>
<td>Yes</td>
<td>12-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>11–17 years</td>
</tr>
<tr>
<td>Salmeterol added to fluticasone propionate versus fluticasone propionate</td>
<td>CHASE 3 NCT02091986 Pearlman 2017</td>
<td>No</td>
<td>12-week, randomized, double-blind, parallel group, multicenter trial</td>
<td>6–11 years</td>
</tr>
<tr>
<td>Salmeterol added to ICS versus ICS</td>
<td>SAS30031 Malone 2005</td>
<td>Yes</td>
<td>12-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>4–11 years</td>
</tr>
<tr>
<td>Salmeterol added to ICS versus ICS</td>
<td>SALMP/AH91/ D89 Russell 1995</td>
<td>Yes</td>
<td>12-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>4–16 years</td>
</tr>
<tr>
<td>Salmeterol added to ICS versus ICS</td>
<td>N/A Langton Hewer 1995</td>
<td>Yes</td>
<td>8-week, randomized, double-blind, parallel-group, single-center trial</td>
<td>12–17 years</td>
</tr>
<tr>
<td>Vila terol added to fluticasone propionate versus fluticasone propionate</td>
<td>NCT01573767 Oliver 2016</td>
<td>No</td>
<td>4-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>5–11 years</td>
</tr>
<tr>
<td>Tiotropium studies</td>
<td>Tiotropium added to ICS versus ICS</td>
<td>RubaTinA-asthma® Hamelmann 2016</td>
<td>No</td>
<td>48-week, randomized, double-blind, parallel-group, multicenter trial</td>
</tr>
<tr>
<td>Tiotropium studies</td>
<td>CanoTinA-asthma® Schmidt 2016 (ERS-26th Annual Congress)</td>
<td>No</td>
<td>48-week, randomized, double-blind, parallel-group, multicenter trial</td>
<td>6–11 years</td>
</tr>
</tbody>
</table>
CSR, clinical study report; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β2-agonists; N/A, not applicable; PEF, peak expiratory flow.

Figure 1. Treatment difference in FEV1 response with LABA compared with placebo added to ICS.

<table>
<thead>
<tr>
<th>Treatment difference, L (95% CI)</th>
<th>LABA + ICS, n</th>
<th>ICS, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chana 2015 0.08 (0.06 to 0.10)</td>
<td>1188</td>
<td>754</td>
</tr>
<tr>
<td>Formoterol added to budesonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger 2010 0.08 (0.02 to 0.14)</td>
<td>123</td>
<td>63</td>
</tr>
<tr>
<td>Erid 2010a 0.08 (0.02 to 0.12)</td>
<td>154</td>
<td>85</td>
</tr>
<tr>
<td>Erid 2010b 0.08 (0.03 to 0.13)</td>
<td>168</td>
<td>84</td>
</tr>
<tr>
<td>Polam 2006a 0.07 (0.01 to 0.13)</td>
<td>213</td>
<td>106</td>
</tr>
<tr>
<td>Polam 2006b 0.07 (0.01 to 0.13)</td>
<td>201</td>
<td>107</td>
</tr>
<tr>
<td>SD 059 0714 0.13 (0.04 to 0.22)</td>
<td>133</td>
<td>131</td>
</tr>
<tr>
<td>Pearlman 2017a 0.12 (0.03 to 0.20)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Pearlman 2017b 0.09 (0.06 to 0.16)</td>
<td>93</td>
<td>90</td>
</tr>
<tr>
<td>Pearlman 2017c 0.09 (0.02 to 0.18)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Pearlman 2017d 0.09 (0.04 to 0.12)</td>
<td>93</td>
<td>90</td>
</tr>
</tbody>
</table>

Points represent mean treatment difference versus placebo; bars represent 95% CIs. Treatment difference >0 favors LABA added to ICS over ICS alone.

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist.

Figure 2. Treatment difference in peak (A) and trough (B) FEV1 response between tiotropium Respimat® and placebo added to ICS.

1Not included in the Cochrane meta-analysis.
Points represent mean treatment difference versus placebo; bars represent 95% CIs.

Treatment difference >0 favors tiotropium over placebo.
Cl, confidence interval.

A68 – Safety and Efficacy of Tiotropium in 1–5-year-old Children with Persistent Asthmatic Symptoms.


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Background: There has been little investigation on the safety and efficacy of new potential asthma medications in very young children (≤5 years). We evaluated the safety and efficacy of once-daily tiotropium Respimat® (TioR) as add-on to inhaled corticosteroids (ICS) with or without further maintenance therapy in patients aged 1–5 years with persistent asthmatic symptoms.

Methods: In this Phase II/III, randomized, double-blind, placebo (PBO)-controlled, parallel-group trial (NinoTinA-asthma®, NCT01634113), patients aged 1–5 years with persistent asthmatic symptoms received tiotropium 2.5 μg (TioR 2.5) or 5 μg (TioR 5) or PBO as 2 puffs once daily for 12 weeks via the Respimat® inhaler, as add-on to usual maintenance therapy of ICS with or without other controller medication. The primary objective was to determine the safety of TioR by comparing adverse events (AEs) with TioR versus PBO. The primary efficacy endpoint was change in the weekly mean combined daytime asthma symptom score from baseline at Week 12 (response). The co-primary endpoint in 5-year-olds was peak forced expiratory volume in 1 second within 3 hours post-dose (peak FEV1(0–3h)) at Week 12; however, due to insufficient patient numbers, no treatment comparisons were performed. Exploratory analyses found significant reductions in the risk of AEs related to asthma exacerbations (broad) or worsening following TioR treatment (HR for TioR 2.5: 0.46 [95% confidence interval (CI) 0.22, 0.98], p = 0.044; TioR 5: 0.42 [95% CI 0.19, 0.94], p = 0.035), as well as the risk of asthma exacerbation (broad) with pneumonia or asthma worsening (TioR 2.5: 0.47 [95% CI 0.23, 0.98], p = 0.043; TioR 5: 0.40 [95% CI 0.18, 0.88], p = 0.022; Figure). At baseline, all patients used short-acting β2-adrenoceptor agonists; after 12 weeks of treatment, less than half of the patients used any rescue medication. Use of rescue medication at Week 12 (percentage of days per week) was comparable between groups (median of 0); however, there were differences in the upper quartile values between treatment groups (TioR 2.5: 42.9%; TioR 5: 28.6%; PBO: 50.0%), indicating that 25% of PBO-treated patients used rescue medication every second day, while 25% of the TioR 5-treated patients used rescue medication only every third day.

Conclusion: Our results suggest that tiotropium add-on therapy has a similar safety profile to PBO in preschool children with persistent asthmatic symptoms. Treatment with TioR resulted in some non-significant improvements in efficacy endpoints, including less frequent use of rescue medication, compared with PBO. Importantly, we observed a significant reduction in the number of children who reported AEs related to asthma exacerbation or worsening in the TioR groups compared with PBO, pointing towards an increased disease control. Additional well-powered trials are needed to confirm our findings.

Table. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tiotropium Respimat® 2.5 μg* (n = 36)</th>
<th>Tiotropium Respimat® 5 μg* (n = 31)</th>
<th>Placebo Respimat®* (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age, years</td>
<td>3.1 ± 1.5</td>
<td>3.1 ± 1.3</td>
<td>3.2 ± 1.4</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–&lt;3 years</td>
<td>15 (41.7)</td>
<td>12 (38.7)</td>
<td>10 (29.4)</td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th></th>
<th>Tiotropium Respimat® 2.5 μg* (n = 36)</th>
<th>Tiotropium Respimat® 5 μg* (n = 31)</th>
<th>Placebo Respimat®* (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–5 years</td>
<td>21 (58.3)</td>
<td>19 (61.3)</td>
<td>24 (70.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>19 (52.8)</td>
<td>21 (67.7)</td>
<td>21 (61.8)</td>
</tr>
<tr>
<td>Mean ± SD height, cm</td>
<td>100.0 ± 13.4</td>
<td>100.1 ± 10.8</td>
<td>100.2 ± 13.4</td>
</tr>
<tr>
<td>Mean ± SD weight, kg</td>
<td>16.4 ± 5.2</td>
<td>16.0 ± 3.5</td>
<td>16.3 ± 3.8</td>
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</tbody>
</table>

Exposure to second-hand smoke, n (%)

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
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<tbody>
<tr>
<td></td>
<td>31 (86.1)</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>28 (90.3)</td>
<td>3 (9.7)</td>
</tr>
<tr>
<td>Mean ± SD height, cm</td>
<td>100.0 ± 13.4</td>
<td>100.1 ± 10.8</td>
</tr>
<tr>
<td>Mean ± SD weight, kg</td>
<td>16.4 ± 5.2</td>
<td>16.0 ± 3.5</td>
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</tbody>
</table>

Exposure to household pets, n (%)

<table>
<thead>
<tr>
<th></th>
<th>No</th>
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<tbody>
<tr>
<td></td>
<td>28 (77.8)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>21 (67.7)</td>
<td>25 (73.5)</td>
</tr>
<tr>
<td>Mean ± SD height, cm</td>
<td>100.0 ± 13.4</td>
<td>100.1 ± 10.8</td>
</tr>
<tr>
<td>Mean ± SD weight, kg</td>
<td>16.4 ± 5.2</td>
<td>16.0 ± 3.5</td>
</tr>
</tbody>
</table>

Concomitant asthma therapies at baseline, n (%)

<table>
<thead>
<tr>
<th></th>
<th>ICS alone</th>
<th>ICS + 1 additional controller</th>
<th>ICS + LABA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 (55.6)</td>
<td>15 (41.7)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>20 (64.5)</td>
<td>9 (29.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mean ± SD height, cm</td>
<td>100.0 ± 13.4</td>
<td>100.1 ± 10.8</td>
<td>100.2 ± 13.4</td>
</tr>
<tr>
<td>Mean ± SD weight, kg</td>
<td>16.4 ± 5.2</td>
<td>16.0 ± 3.5</td>
<td>16.3 ± 3.8</td>
</tr>
</tbody>
</table>

Most frequent concomitant diagnoses at screening (>5% of total patients), n (%)

<table>
<thead>
<tr>
<th></th>
<th>Allergic rhinitis</th>
<th>Atopic dermatitis</th>
<th>Food allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (13.9)</td>
<td>5 (13.9)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>7 (22.6)</td>
<td>7 (22.6)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Mean ± SD height, cm</td>
<td>100.0 ± 13.4</td>
<td>100.1 ± 10.8</td>
<td>100.2 ± 13.4</td>
</tr>
<tr>
<td>Mean ± SD weight, kg</td>
<td>16.4 ± 5.2</td>
<td>16.0 ± 3.5</td>
<td>16.3 ± 3.8</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting β2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β2-adrenoceptor agonists; SD, standard deviation.
A70 - Effect of Tiotropium Respimat® on Seasonal Asthma Worsening in Pediatric Patients.

Szefler S.1, Goldstein S.2, Graham L.3, Vogelberg C.4, El Azzi G.5, Engel M.5, Zaremba-Pechmann L.6, Hamelmann E.7

1Department of Pediatrics, Children's Hospital of Colorado and the University of Colorado School of Medicine, The Breathing Institute – Aurora, USA; 2Allergy and Asthma Care of Long Island – Rockville Center, USA; 3Pediatric Pulmonology, Children’s Healthcare of Atlanta – Atlanta, USA; 4Department of Pediatric Pulmonology and Allergy, University Hospital Carl Gustav Carus, Technical University of Dresden – Dresden, Germany; 5TA Respiratory Diseases, Boehringer Ingelheim Pharma GmbH & Co. KG – Ingelheim am Rhein, Germany; 6Biostatistics, Boehringer Ingelheim Pharma GmbH & Co. KG – Biberach an der Riss, Germany; 7Klinik für Kinder und Jugendmedizin, Evangelisches Klinikum Bethel, Bielefeld – Allergy Center of the Ruhr University, Bochum, Germany

Background: Asthma exacerbations are a major cause of morbidity and increased healthcare costs in many patients, with a pattern for peaking during certain times of the year. Investigating asthma exacerbations in clinical trials can be difficult, especially in children, for whom long-term placebo-controlled exacerbation trials are difficult to justify. We aimed to investigate the adverse events (AEs) related to asthma exacerbations and asthma symptoms that were reported across several pediatric trials investigating the safety and efficacy of tiotropium. Of particular interest was the identification of any seasonality pattern in the reporting of these AEs, whilst also ascertaining whether tiotropium efficacy was consistent throughout the year.

Methods: We pooled data from 5 randomized, double-blinded, placebo-controlled trials investigating the safety and efficacy of tiotropium in pediatric asthma: NinoTinA-asthma®, a 12-week, Phase II/III trial in patients aged 1–5 years with persistent asthmatic symptoms (NCT01634113); CanoTinA-asthma®, a 12-week, Phase III trial in patients aged 1–5 years with persistent asthmatic symptoms (NCT01634139); VivaTinA-asthma®, a 12-week, Phase III trial in patients aged 6–11 years with severe symptomatic asthma (NCT01634152); RubaTinA-asthma®, a 48-week, Phase III trial in patients aged 12–17 years with moderate symptomatic asthma (NCT01257230); and PensieTinA-asthma®, a 12-week, Phase III trial in patients aged 12–17 years with severe symptomatic asthma (NCT01277523). In all trials, patients received once daily tiotropium (5 μg or 2.5 μg) or placebo, delivered via the Respimat® inhaler as 2 puffs, in addition to inhaled corticosteroids with or without additional controllers. AEs related to asthma exacerbations or symptoms were defined using a composite endpoint according to the Medical Dictionary for Regulatory Activities version 18.1 preferred term group ‘asthma exacerbations and asthma-related symptoms’. The number of asthma exacerbations reported as AEs were plotted by month, with data from the Southern hemisphere shifted by 6 months to align the seasons (Northern hemisphere: June = month 6; Southern hemisphere: December = month 6).

Results: Overall, 1,691 patients aged 1–17 years were included in the pooled analyses. The rate of patients reporting AEs related to asthma exacerbations and symptoms, number of patients with an event per 100 patient-years, was significantly reduced with tiotropium 5 μg (177 patients with event per 100 patient-years) compared with placebo (217 patients with event per 100 patient-years, rate ratio [RR] 0.76 [95% confidence interval (CI) 0.63, 0.93]). A similar, but non-significant, trend was associated with the tiotropium 2.5 μg dose (195 patients with event per 100 patient-years) compared with placebo (RR 0.87 [95% CI 0.72, 1.05]).

When analyzed by month, reports of AEs related to asthma exacerbations and symptoms were greatest in the placebo group in the spring, autumn and winter (Figure), and lowest in summer. With both doses of tiotropium, spring and autumn peaks were reduced.

Figure. Number of reported AEs related to asthma exacerbations and symptoms over 12 months

HR, hazard ratio; ICS inhaled corticosteroid; PBO, placebo; TioR, tiotropium Respimat®.
Conclusion: This analysis suggests treatment with tiotropium reduces AEs related to asthma exacerbations and symptoms in pediatric patients, with a particular effect in reducing spring and autumn seasonal peaks. As long-term asthma exacerbation trials in pediatric patients remain ethically challenging, this analysis highlights an alternative endpoint to investigate such efficacy in children. These data also highlight the importance of trial timing to account for seasonal exacerbation peaks when a 12-month study length is not practical.

A72 – Improvements in Reporting of Asthma Exacerbations in Efficacy and Safety Data with Tiotropium Add-on Therapy in Pediatric Patients.

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Background: Recurrent asthma symptoms and exacerbations cause substantial morbidity in pediatric patients with asthma, therefore, a primary treatment goal is to prevent these from occurring. The definition of exacerbations commonly used in clinical trials is worsening of asthma symptoms or reduction in lung function for a defined period, with severe events requiring systemic steroid treatment and/or hospitalization. However, this definition may be too strict for pediatric trials, where sample size and trial duration are limited by ethical considerations. Adverse events (AEs) related to asthma exacerbations and worsening symptoms are also recorded among safety assessments as standard in clinical trials, and this may be an alternative endpoint for clinicians to consider in assessing efficacy in terms of exacerbations in pediatric patients. Herein, we compare the reporting of asthma exacerbations as an efficacy endpoint using the standard definition, with reporting of AEs related to exacerbations and symptoms in Phase III trials of tiotropium add-on in children and adolescents.

Methods: This was an exploratory analysis of 5 Phase III trials comprising patients aged 12–17 years (RubaTinA-/PensieTinA-asthma®; moderate and severe asthma, respectively), aged 6–11 years (CanoTinA-/VivaTinA-asthma®; moderate and severe asthma, respectively) and 1–5 years (NinoTinA-asthma®; persistent asthmatic symptoms). Patients received tiotropium (5 or 2.5 μg) or placebo, as 2 puffs once daily via the Respimat® inhaler, as add-on to inhaled corticosteroids ± other controllers. Children <5 years old also used an AeroChamber Plus® Flow-Vu® spacer. Time to first asthma exacerbation, in all studies except NinoTinA-asthma®, was a pre-defined efficacy endpoint, with an exacerbation defined as an episode of progressive increase in ≥1 asthma symptom(s) lasting ≥2 consecutive days and/or a decrease in patient’s best morning peak expiratory flow (PEF) ≥30% from the patient’s mean morning PEF for ≥2 consecutive days. The number of patients reporting AEs related to asthma exacerbations or symptoms was recorded from start of treatment until 30 days after end of treatment; the AEs used in this analysis fell under an umbrella term of ‘related to asthma exacerbations or symptoms’, defined using a composite endpoint, according to the Medical Dictionary for Regulatory Activities version 18.1 preferred terms related to asthma exacerbations and asthma-related symptoms. In this analysis, the time to first asthma exacerbation occurrence was analyzed using the Cox proportional hazards model, with treatment as effect. AEs related to asthma exacerbations or symptoms captured by the safety reporting were analyzed to produce time-adjusted rate ratios (RR), that is, number of patients with the event per 100 patient-years at risk. The estimates and confidence intervals (CI) for RR are based on a Cochran–Mantel–Haenszel test (stratified by study in case of analysis for pool of studies). The study durations varied between 12 and 48 weeks, therefore, RR values were considered rather than hazard ratios (HR) alone.

Results: As an efficacy endpoint, the risk of exacerbation was generally reduced with tiotropium 5 μg add-on treatment compared with placebo (HR 0.60–0.82; Table 1), although these changes did not reach statistical significance. With tiotropium 2.5 μg, numerical reduction in risk of exacerbation was seen in 3 out of the 4 trials,
and this reached significance in VivaTinA-asthma® (HR 0.52; 95% CI 0.33, 0.82). When analyzing patients reporting AEs related to asthma exacerbations or symptoms, there was also a reduction with tiotropium 5 μg versus placebo across the trials (RR 0.35–0.89; Table 2); the reduction reached statistical significance in the youngest age group (RR 0.35; 95% CI 0.16, 0.76) and also when data were pooled across the 5 trials (RR 0.76; 95% CI 0.63, 0.93). With tiotropium 2.5 μg, a numerical reduction in AEs was observed in 4 of the 5 trials, reaching statistical significance in NinoTinA-asthma® (RR 0.35; 95% CI 0.16, 0.76) and VivaTinA-asthma® (RR 0.61; 95% CI 0.40, 0.94).

**Conclusion**: Overall, the data show that the 2 endpoints, exacerbations and AEs related to asthma exacerbations and symptoms, align and that treatment differences can be detected using AE reporting when exacerbation data as an efficacy endpoint are not, or cannot be, collected. Reductions in AEs related to asthma exacerbations or symptoms in safety reporting may be considered a useful alternative endpoint for clinicians and those conducting clinical trials to assess efficacy in terms of exacerbations in pediatric trials where sample size and trial duration may be limited.

Table 1. Children and adolescent patients reporting exacerbations during Phase III clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age, years</th>
<th>Asthma severity</th>
<th>Total patients treated, N</th>
<th>Placebo, n (%)</th>
<th>Tiotropium 5 μg, n (%)</th>
<th>HR 5 μg vs. placebo (95% CI)</th>
<th>Tiotropium 2.5 μg, n (%)</th>
<th>HR 2.5 μg vs. placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PensioTinA-asthma®</td>
<td>12–17</td>
<td>Severe</td>
<td>392</td>
<td>25 (16.82)</td>
<td>16 (11.64)</td>
<td>HR 0.80 (0.52, 1.24)</td>
<td>16 (11.64)</td>
<td>HR 0.80 (0.52, 1.24)</td>
</tr>
<tr>
<td>RabaTinA-asthma®</td>
<td>12–17</td>
<td>Moderate</td>
<td>397</td>
<td>37 (23.81)</td>
<td>30 (22.39)</td>
<td>HR 0.82 (0.51, 1.33)</td>
<td>34 (27.32)</td>
<td>HR 0.94 (0.65, 1.36)</td>
</tr>
<tr>
<td>VivaTinA-asthma®</td>
<td>6–11</td>
<td>Severe</td>
<td>400</td>
<td>47 (30.07)</td>
<td>35 (25.62)</td>
<td>HR 0.79 (0.44, 1.06)</td>
<td>29 (21.32)</td>
<td>HR 0.92 (0.33, 0.82)</td>
</tr>
<tr>
<td>CinoTinA-asthma®</td>
<td>6–11</td>
<td>Moderate</td>
<td>401</td>
<td>58 (38.1)</td>
<td>57 (42.22)</td>
<td>HR 0.77 (0.54, 1.10)</td>
<td>63 (46.87)</td>
<td>HR 0.68 (0.36, 1.24)</td>
</tr>
<tr>
<td>NinoTinA-asthma®</td>
<td>1–5</td>
<td>Persistent asthma symptoms</td>
<td>101</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NA, not applicable.

Table 2. Children and adolescents patients reporting AEs related to asthma exacerbations or symptoms during Phase III clinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age, years</th>
<th>Asthma severity</th>
<th>Total patients treated, N</th>
<th>Placebo, n (%)</th>
<th>Tiotropium 5 μg, n (%)</th>
<th>RR 5 μg vs. placebo (95% CI)</th>
<th>Tiotropium 2.5 μg, n (%)</th>
<th>RR 2.5 μg vs. placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PensioTinA-asthma®</td>
<td>12–17</td>
<td>Severe</td>
<td>392</td>
<td>26 (20.7)</td>
<td>20 (15.4)</td>
<td>RR 0.71 (0.40, 1.20)</td>
<td>23 (18.1)</td>
<td>RR 1.01 (0.44, 2.42)</td>
</tr>
<tr>
<td>RabaTinA-asthma®</td>
<td>12–17</td>
<td>Moderate</td>
<td>397</td>
<td>48 (34.8)</td>
<td>40 (30.9)</td>
<td>RR 0.85 (0.54, 1.32)</td>
<td>50 (40.0)</td>
<td>RR 1.28 (0.66, 2.40)</td>
</tr>
<tr>
<td>VivaTinA-asthma®</td>
<td>6–11</td>
<td>Severe</td>
<td>400</td>
<td>51 (36.1)</td>
<td>40 (30.3)</td>
<td>RR 0.75 (0.49, 1.14)</td>
<td>37 (27.2)</td>
<td>RR 0.61 (0.40, 0.94)</td>
</tr>
<tr>
<td>CinoTinA-asthma®</td>
<td>6–11</td>
<td>Moderate</td>
<td>401</td>
<td>30 (23.4)</td>
<td>26 (20.3)</td>
<td>RR 0.70 (0.43, 1.14)</td>
<td>26 (20.3)</td>
<td>RR 1.01 (0.44, 2.42)</td>
</tr>
<tr>
<td>NinoTinA-asthma®</td>
<td>1–5</td>
<td>Persistent asthma symptoms</td>
<td>101</td>
<td>20 (20.8)</td>
<td>9 (29.8)</td>
<td>RR 0.65 (0.16, 2.76)</td>
<td>12 (23.3)</td>
<td>RR 0.61 (0.30, 1.29)</td>
</tr>
<tr>
<td>Pooled studies</td>
<td>1–17</td>
<td>Moderate–severe</td>
<td>1,691</td>
<td>217 (26.9)</td>
<td>177 (21.6)</td>
<td>RR 0.76 (0.49, 1.19)</td>
<td>196 (29.4)</td>
<td>RR 0.87 (0.72, 1.09)</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence interval; RR, rate ratio.
6–17 years), as an example of how data from previous adult asthma studies can be extrapolated to pediatric asthma clinical trial programs.

**Results:** Several feasibility considerations were identified in the literature that can influence pediatric trial design. These ranged from low numbers of child participants in clinical research, poor long-term adherence in clinical trial settings, limited pediatric-specific resources at research centers and a lack of trial networks for pediatric research. Pediatric trials may also require the validation of specific endpoints for different age groups and associated stages of development.

While forced expiratory volume in 1 second (FEV1) is well accepted as an endpoint in clinical trials in adult patients, FEV1 response does not always correlate with asthma symptoms, and can often appear to be normal in children with asthma. In the tiotropium in asthma clinical trial program, improvements in peak FEV1(0–3h) and trough FEV1 following tiotropium add-on therapy were in a comparable range in adult patients and pediatric patients (Figure 1).

Alternative lung function measures suggested for pediatric patients include forced expiratory flow at 25–75% of the pulmonary volume (FEF25–75%), which reflects small airway function, and FEV1/forced vital capacity (FVC) ratio, which has been shown to be associated with asthma severity in children. In pediatric patients, tiotropium add-on therapy consistently improved trough FEF25–75% responses versus placebo. There was a strong association between improvements in trough FEF25–75% and trough FEV1 (Pearson correlation coefficient 0.735–0.799), and FEF25–75% improvements were largely more pronounced than trough FEV1 improvements. Moreover, tiotropium add-on therapy consistently improved trough FEV1/FVC ratio versus placebo in pediatric patients, although a high variability was noted in adolescent patients with severe asthma.

In addition to lung function-based endpoints, it is important to study patient-relevant outcomes such as exacerbations and symptoms. Assessing these endpoints in a confirmatory design can require a large sample size and a long study duration. Such trials would require giving some children placebo for long periods, which may be unethical, especially in the pediatric setting. Because asthma is a disease that follows a similar course in adults and children, and outcomes of treatments are comparable, a partial extrapolation concept was applied in the tiotropium in asthma clinical trial program. Thus, in adult patients, lung function, symptom and exacerbation endpoints were evaluated in a confirmatory manner, while in pediatric patients, only lung function endpoints were evaluated in a confirmatory manner, and symptom and exacerbation endpoints were assessed in an exploratory manner.

In adults (aged 18–75 years), tiotropium add-on therapy significantly improved pulmonary function and asthma control, and reduced exacerbation risk versus placebo. In pediatric patients (aged 6–17 years), tiotropium add-on therapy largely improved pulmonary function versus placebo, and there were trends for improved asthma control and reduced exacerbation risk versus placebo in a comparable range, as in adult patients.

**Conclusion:** The results from the tiotropium in asthma clinical program emphasize that successful clinical trials in pediatric patients with asthma can be performed. To assess lung function, FEV1 and FEF25–75% were shown to be reliable endpoints. In addition, there was a strong, positive correlation between trough FEF25–75% and FEV1, and trough FEF25–75% responses were generally more pronounced than FEV1 responses. The tiotropium asthma clinical program also demonstrated how a partial extrapolation concept may be applied for exacerbation and symptom endpoints, thereby keeping sample size and study duration reasonable and in line with ethical considerations.


**Figure 1.** Improvements in peak (a) and trough (b) FEV1(0–3h) response (% predicted) in adults, adolescents and children with tiotropium add-on treatment (5 μg)

CI, confidence interval; Tio R5, tiotropium Respimat 5 μg.

**A74 – Etiology Aspects of Asthma Exacerbations in Childhood.**

**Markova R.**

Pediatrics, 1-st Pediatric Consultative Clinic – Sofia, Bulgaria

The main cause for asthma exacerbations in childhood are viral infections. Their etiology profile has a significant epidemiological and therapeutic value.

**Material and methods:** In a clinical survey for a one-year period, 126 patients with bronchial asthma were followed. Their age was between
5 and 18 years. The patients were investigated according to clinical, functional and laboratory parameters. In order to assess certain etiological aspects of asthma exacerbations, serology tests were performed (ELISA tests) for: RSV, Adenovirus, Chlamydia pneumoniae, Mycoplasma pneumoniae, Influenza virus and Parainfluenza virus: IgM and IgG antibodies.

**Results:** The results were evaluated using statistical methods and SPSS software. Our results demonstrated: in 9.52% of asthmatics, acute RSV infections were found with positive/+/ IgM antibodies, in 42.1% – data for a past RSV infection – positive IgG antibodies. No patients with acute Adenovirus infection, positive IgG antibodies were detected in 22.2% of asthmatics.

Positive IgG titers for Chlamydia pneumoniae were found in 4% of patients. The results for M. pneumoniae proved /+ IgM in 0.8%, and /+IgG in 3.2% of asthmatics included in the clinical investigation.

Serology diagnosis for Influenza virus was positive in 1.6% for IgG, for Parainfluenza virus – positive IgG in 19.8%.

**Conclusion:** Serology tests revealed the leading role of past RSV infection in asthma exacerbations in an investigated group of asthmatics (42.1%), followed by Adenovirus infection (22.2%) and Parainfluenza virus infection (19.8%).

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**A75 – Exhaled Nitric Oxide among Bulgarian Children with Asthma Exacerbation.**

Markova R.
Pediatrics, 1-st Pediatric Consultative Clinic – Sofia, Bulgaria

Exhaled nitric oxide is an important non-invasive marker for bronchial inflammation in children with asthma.

**The aim of the study:** To investigate exhaled nitric oxide (FeNO) values among 126 patients with asthma exacerbation and to follow them over a 3-month period. To evaluate certain clinical, laboratory and functional parameters and their correlation with FeNO.

**Methods:** FeNO was measured by a single-breath on-line measurement. Laboratory tests included: leukocyte count, ESR, CRP. Total IgE levels were analyzed by ELISA. Pulmonary function tests (PFTs) were performed in all patients. Blood and sputum (nasal) eosinophils were counted. Serology tests for respiratory viruses were performed by ELISA.

**Results:** FeNO was significantly higher in the asthmatic group compared with the control groups. There was a positive linear correlation between age and FeNO values. Male gender was dominant (62.9%). Positive family history was observed in over half of the asthmatic patients (58.9%). Upper respiratory airways were involved in 46.24% with allergic rhino sinusitis. A number of asthmatics had a long duration of bronchial asthma (more than 5 years): 50.79%. Mean total IgE values were increased in the group of asthmatics (252.69IU/ml).

FeNO was the major parameter in the clinical study with mean values of 27.68 ppb. The 3-month follow-up showed a significant decrease in mean FeNO values from 27.68 to 17.21 ppb. Serological viral tests revealed the leading role of a past RSV infection (42.1%), followed by Adenovirus (22.2%) and Parainfluenza virus (19.8%).

**Conclusion:** We present some data regarding FeNO values for Bulgarian asthmatics in combination with clinical, laboratory and functional parameters.

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**A91 – No Effect of Variant Alpha-1 Antitrypsin Genotypes on the Frequency of Parental-Reported Wheezing and Breathlessness during the First Three Years of Life in the ALSPAC Birth Cohort.**

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**Background:** Alpha-1 antitrypsin (AAT) is the most common genetic cause of chronic obstructive pulmonary disease. Aside from the most important function as an inhibitor of proteinases, AAT is also implicated in the modulation of immune reactions and inflammation. Early-onset preschool wheeze has been suggested as being the first manifestation of COPD. Also, pilot data suggest that variant AAT genotypes may predispose children to more severe episodes of wheeze in early childhood. If this is the case, these children may be identified early in life by their wheezing characteristics and intervention measures might be applied to prevent the development of AAT-related chronic obstructive pulmonary disease.

**Materials and methods:** We chose to analyze the data from the ALSPAC cohort. AAT genotypes were determined from imputed genome data on the most common variant SNPs rs17580 (PiS) and rs28929474 (PiZ). Data on wheezing characteristics were obtained via questionnaire at several time points during the first 3 years of life. Associations among the most common variant AAT genotypes (PiMZ, PiZZ, PiMS, PiSS, and PiSZ) and wheezing characteristics (onset, number of wheezing episodes, duration of wheezing, and breathlessness during episodes of wheezing) were analyzed.

**Results:** A total of 6871 children had complete genetic data on the selected SNPs of which 2858 (41.6%) had at least one wheezing episode and 1033 (15.0%) experienced breathlessness due to wheeze during the first three years of life. Wheezing was prevalent in 487 (43.4%) of children with variant AAT genotypes compared with 2377 (41.4%) of children with a normal AAT genotype. Similarly, breathlessness did not differ between the groups (15.4% for variant and 15.6% for normal AAT genotype). Neither wheezing nor breathlessness due to wheeze (OR = 1.111, 95% CI 0.958 – 1.288, and OR = 0.929, 95% CI 0.759 – 1.137 respectively) was associated with a variant genotype of AAT. Finally, the proportions of wheezing days per year as well as the prevalence of breathlessness during wheezing attacks were similar in the normal AAT and variant AAT groups.

**Conclusions:** The data from the ALSPAC birth cohort do not show variant AAT genotypes to be associated with wheezing nor
breathlessness during the first three years of life and these characteristics are not useful in identifying children with variant AAT genotypes.

**A99 – Three Oxygen Saturation Targets for Discharge in Children with Wheeze – An Observational Study.**

Unger S.1, Twynam-Perkins J.1, Christie F.1, Cunningham S.2

1Respiratory Paediatrics, Royal Hospital for Sick Children – Edinburgh, United Kingdom; 2Child Life and Health, University of Edinburgh – Edinburgh, United Kingdom

**Objective:** To assess the potential effect of three guideline discharge oxygen saturation (SpO2) targets (≥90%, ≥94% and ≥94%) on length of hospital admission in children with acute wheeze.

**Methods and patients:** Children aged 1 year up to 16 years admitted with wheeze (requiring supplementary oxygen for SpO2 (≥94%)) were assessed in air every 4 h over nine months (11/14 – 08/15). Time from admission for SpO2 to become stable for at least 4 h at ≥90%, ≥92% and ≥94% was recorded. In addition, time to clinical stability was also collected, defined as requiring a frequency of four hourly salbutamol inhalers or less.

**Results:** 140 children, median age 2.8 years, were included. Median length of stay was 71 hours (h). Five children were admitted to high dependency. Sixty-three percent (88/140) had a viral or bacterial agent identified. Details on inhaler frequency were missing in five children and eleven children did not receive inhaled salbutamol during admission.

SpO2 became stable for at least 4 h at 8h (IQR 5–20), 17h (IQR 7–30), and 22h (IQR 11–33) for targets of ≥90%, ≥92% and ≥94% respectively. Time to achieve a stable SpO2 ≥90% was a median of 0h (IQR0–12h) and 4h (IQR 0–16h) sooner than SpO2 of ≥92% and ≥94%, respectively. There was a time lag in 47% (66/140) children between SpO2 targets of 90% and 92%, and 57% (80/140) between SpO2 targets of 90% and 94%. The median time lag in these children was 12h (IQR 8–19h) and 15.5h (IQR 8–24h) for SpO2 of ≥92% and ≥94% respectively.

The median time to stability of inhaler frequency in all children in whom this was recorded (n = 124) was 14h (IQR 10–21.5h). 68% (84/124) of children reached stability of inhaler frequency after achieving a stable SpO2 ≥90%, 51% (63/124) for ≥92% and 44% (54/124) for ≥94%. For those children with a time lag between different oxygen saturation targets, 58% (SpO2 90–94%) and 20% (SpO2 92–94%) reached stability of inhaler frequency after achieving a stable SpO2.

**Discussion and Reflections:** Our results show that reducing SpO2 targets could potentially reduce the length of stay in approximately 50% of children above 1 year of age with acute wheeze. However, in 58% of these children, clinical stability, as defined by only requiring regular four hourly salbutamol inhalers, was reached after achieving stable SpO2 reducing the potential number of children fit for earlier discharge at lower SpO2 targets to 25% (31/124) and 9% (11/124) for targets of SpO2 ≥ 90% and SpO2 ≥ 92% respectively. Results indicate the need to ensure wheeze control is achieved before a potential discharge at lower accepted SpO2 targets.

**Conclusions:** Allowing lower SpO2 of ≥90% as discharge targets could reduce length of stay in around a quarter of children with wheeze. Although this SpO2 target level has been shown to be safe in infants with bronchiolitis, safety and the effect on clinical status post discharge needs to be studied in older children with acute wheeze and a randomized control trial is merited to answer these questions.

**A102 – Heterogeneity of Childhood Asthma in Korea: Cluster Analysis of Children with Asthma from the Korean Childhood Asthma Study (KAS)**


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**Background:** Asthma is a heterogeneous airway disease with various clinical phenotypes in children. It is important to clearly identify clinical phenotypes to achieve better asthma management and to predict the prognosis. Investigating the asthma phenotype remains rarely understood in Korea. This study aimed to identify the phenotype of asthma in Korean school-aged children.

**Methods:** We enrolled 706 children with physician-diagnosed asthma from the Korean childhood Asthma Study (KAS) cohort which is a 3-year prospective follow-up study at 6-months intervals. At every visit, questionnaire survey and pulmonary function tests were conducted, and methacholine challenge test, blood tests, and skin prick tests were conducted at the first time visit. We classified 183 children with asthma from the Korean childhood Asthma Study (KAS) cohort into 4 clusters using hierarchical cluster analysis.
Results: Cluster analysis of the KAS cohort indicated four asthma phenotypes. Cluster 1 (40.3%) of children was characterized by late-onset, male-dominant, atopic asthma; cluster 2 (39.8%) was early-onset, male-dominant, atopic asthma with a history of bronchiolitis; subjects in cluster 3 (8.2%) consisted of puberty-onset, female-dominant atopic asthma having the lowest lung function; and cluster 4 (11.7%) was associated with early-onset non-atopic asthma.

Conclusions: Our results indicate that Korean children with asthma can be classified into four distinct clusters. Identification of asthma phenotypes may facilitate prediction of prognosis and response to treatment in heterogeneous phenotypes of asthma.

Funding: This study was supported by a grant (2016ER670300) from the Research of Korea Centers for Disease Control and Prevention, Republic of Korea.

Key words: Asthma, children, cluster analysis, classification, phenotype

A133 – Asthma Knowledge, Attitudes and Practices of Parents of Asthmatic Children in the Outpatient Department of a Tertiary Care Institution

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Introduction: Bronchial asthma is a common childhood respiratory condition. Objectives of management of patients with asthma include decreasing exposure to environmental triggers and decreasing the use of anti-inflammatory controller medications. The knowledge, attitudes and practices (KAP) of parents of asthmatic children have a big influence on the quality of life of asthmatic children as these determine the care that they give.

Objectives: This study investigated the asthma KAP of parents with asthmatic children who consulted at the outpatient department of a tertiary hospital. It determined if there was a difference in the asthma KAP of parents of children with controlled versus uncontrolled asthma and if there was a correlation between the asthma KAP of parents of asthmatic children and the number of emergency room (ER) consults and hospital admissions for asthma in the immediate past year.

Methods: In this descriptive, cross-sectional study, parents of patients one-year-old and older diagnosed with bronchial asthma during the past six months were included. Excluded were parents who were younger than 18 years old and those whose children had other active chronic conditions aside from asthma.

Results: A total of 66 subjects participated in the study. Partly and uncontrolled asthma was observed in 21.2% of the subjects’ children. Most parents had a good knowledge of asthma, its signs and symptoms (87.9%), and its management (86.4%). Half of the parents (50%) were anxious about their children practicing physical activities for fear that these will provoke an asthmatic attack. The majority of parents were able to initiate home measures (80.3%), administer the correct drug in the proper timing (98.5%), seek the physician early on (92.4%), institute early treatment in mild symptoms (92.4%), and adhere to the physician’s medication orders (97%) to decrease the occurrence of attacks. There was no difference in the asthma KAP of parents of children with controlled versus uncontrolled asthma. Among the subjects with children with frequent ER consults and hospital admissions, their asthma KAP scores were higher than those with no ER consults and hospital admissions, although these variables were not statistically significant.

Conclusion: Parents of asthmatic children in a tertiary hospital had a good level of KAP on bronchial asthma comparable to those in other countries. The asthma KAP of parents with children whose asthma was controlled did not differ from those whose children had uncontrolled asthma. Frequent ER consults and hospital admissions may provide parents with opportunities to achieve higher asthma KAP scores.

A150 – The Prevalence of Passive Smoke and Impact on Childhood Asthma Symptoms

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Introduction: Asthma is a chronic, frequent disease with high morbidity in childhood. Indoor exposure to allergens and irritants, including cigarette smoke, affects the control of asthma symptoms.

Objective: We aimed to verify the prevalence of passive smoke and repercussions on childhood asthma symptoms.

Methods: The sample consisted of 384 asthmatic patients, aged 2 to 14 years. A complete interview with the child and his/her parents regarding asthma symptoms, treatment in use, exacerbations and hospitalizations as well as a clinical evaluation were performed. Social and economic aspects were also evaluated.

Results: Exposure to passive smoking was present in 55% of the children. Household agglomeration, lower family income, lower level of maternal and paternal schooling were significantly observed in the exposed group. The exposed population showed a higher frequency of asthma classified as moderate, greater use of inhaled corticosteroids and greater frequency of diurnal symptoms (present at least once a week in 60% of patients).

Conclusion: The prevalence of asthmatic children exposed to passive smoking was high. Low socioeconomic condition was confirmed in the exposed group. Moderate severity, greater use of inhaled corticosteroids and greater frequency of diurnal symptoms were observed in the exposed group. Effective measures to combat passive smoking should be taken immediately as an essential strategy for the control of childhood asthma.

A151 – Clinical, Functional and Sputum Cytology Evaluation in Patients with Post-infectious Bronchiolitis Obliterans.

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Introduction: Post-infectious bronchiolitis obliterans is a rare lung disease that occurs after severe insult to the small airways caused by viral bronchiolitis or viral pneumonia before 3 years of age. It is characterized by respiratory symptoms compatible with lower airways obstruction, lung function tests (LFT) demonstrating obstructive pattern and tomographic changes such as mosaic attenuation, bronchial thickening, bronchiectasis and atelectasis.

Objective: The aim of this study was to evaluate the clinical findings, lung function and sputum cytology in patients with bronchiolitis obliterans who attend an outpatient clinic.

Methods: Twenty-three patients aged less than 21-years-old diagnosed with bronchiolitis obliterans were invited to participate. They underwent LFT, CT scan, skin prick test (SPT) for aeroallergens, induced sputum using Pizzichini et al. methodology, and were classified according to Spanevello et al.

Results: Thirteen patients were included and signed the consent, 12 underwent LFT and all had an induced sputum sample collected. Three sputum samples were discarded due to low cellular viability. Five (38%) patients reported daily symptoms while 8 (61.5%) reported symptoms during physical activity. All patients showed tomographic alterations, mosaic pattern (84%) and bronchial thickening (76%). Nine (90%) demonstrated obstructive ventilatory disorder and 4 (25%) had positive bronchodilator LFT. Four sputum samples showed a neutrophilic cytological pattern, while 2 were eosinophilic, and 4 were mixed (eosinophilic-neutrophilic). Eight patients reported associated allergic diseases and were positive for SPT.

Conclusion: A correlation was not demonstrated between daily symptoms or exercises, severity of the obstructive ventilatory disorder, tomographic findings and cytological sputum patterns. There is a possibility of asthma and bronchiolitis obliterans coexistence.

A171 – Vitamin D Levels in Asthmatic and Healthy Children in Singapore.

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Background: Asthma is one of the most common chronic diseases affecting children, and there has been much interest in the relationship between vitamin D and asthma symptoms. Vitamin D is involved in the support of immune regulation, by regulating the actions of lymphocytes, mast cells, antigen-presenting cells and structural cells to dampen excessive inflammatory responses. Establishing a causal relationship between vitamin D and asthma could result in a simple yet important preventive and therapeutic strategy in the management of asthma. Several case-control studies showed that vitamin D insufficiency is more prevalent among asthmatic children. However, there is a lack of uniformity among studies in the current literature body in demonstrating correlation between vitamin D levels and control of asthma. Obtaining local data on the prevalence of vitamin D insufficiency in both asthmatic and control populations is important in justifying further research on this relationship, as this is currently unknown in Singapore. Our hypothesis was that asthmatic children had significantly lower vitamin D levels than controls.

Methods: We conducted a cross-sectional study with a case-control design on children aged 7–16 years of age attending pediatric outpatient clinics at a tertiary hospital in Singapore. Children were recruited as cases if they fulfilled the following criteria: they had a diagnosis of asthma made on clinical grounds, and either (1) uncontrolled asthma, as defined as an Asthma Control Test score of 19 or less, or (2) asthma requiring control with at least 200mcg of inhaled beclometasone-equivalent dose per day at time of entry into the study. Serum 25-hydroxy vitamin D (25-OH vitamin D) levels were measured by the hospital laboratory from blood samples taken by venepuncture from these children. Vitamin D levels were categorized as sufficient (30 μg/l or greater), insufficient (20–30 μg/l), or deficient (20 μg/l). Controls were selected to match the age, gender and ethnicity of cases. Children were excluded if they had a history of consumption of calcium and vitamin D supplementation or drugs that modulate vitamin D levels, a history of significant chronic medical diseases (other than asthma in cases), or had a first-degree family history of vitamin D deficiency.

Results: 20 cases of children with asthma who fulfilled the inclusion criteria were recruited for the study. This group was comprised of 12 males and 8 females. Nine children were of Chinese ethnicity, 9 were of Malay ethnicity, and 2 were of Indian ethnicity. Age range was 8 years 0 months to 16 years 11 months (men age 12 years 5 months). The control group consisted of 20 healthy children who were age, gender and ethnically matched (age range 8 years 11 months to 16 years 11 months, mean age 11 years 11 months). There was no significant difference in household income between the two groups (p = 0.53). The mean vitamin D level for the asthma group was 23.5 μg/l (range 8.4–44.5 μg/l, standard deviation 9.47 μg/l), and the mean level for the healthy controls was 20.1 μg/l (range 5.3–31.9 μg/l, standard deviation 7.63 μg/l). There was no significant difference in vitamin D levels between the two groups (p = 0.27). Thirty-three of the 40 children (82.5%) had vitamin D levels that fell below our threshold for sufficiency (30 μg/l), with 6 children from the asthma group showing vitamin D deficiency (<20 μg/l) and 8 healthy controls showing vitamin D deficiency.

Discussion: A recent systematic review on vitamin D levels and asthma in children found that mean vitamin D levels pooled from 10 case-control studies had shown significantly lower vitamin D levels in asthmatic children compared to non-asthmatic children. However, taken separately, five of these studies showed no significant difference in vitamin D levels between asthmatic and non-asthmatic children. Our data did not show a significant difference in vitamin D levels between asthmatic and non-asthmatic children, consistent with the findings of these studies. We have therefore not shown an association between vitamin D levels and asthma in our study population. The sample size was small, and this may account for the statistically non-significant association. What our study did show, however, was a high prevalence...
of vitamin D insufficiency and deficiency in our study population, regardless of whether the children were asthmatic or not. Our data is at the higher end of the spectrum of prevalence of vitamin D deficiency and insufficiency compared to other studies in the literature body looking at vitamin D deficiency among asthmatic and non-asthmatic children. The prevalence is slightly higher than a previous study in Singapore which showed a prevalence of 76.1% for vitamin D insufficiency and deficiency in adults. In studies looking at vitamin D deficiency in tropical countries, several factors have been postulated to contribute to poor vitamin D status—unfortified food in the local diet and a lack of sun exposure due to lifestyle habits being two of the more likely factors. While these may account for the high prevalence of vitamin D insufficiency found in our study participants (children in Singapore tend to spend more time indoors than outside the home due to the hot weather and high humidity), we did not investigate for these factors in our study, and can therefore not draw conclusions from our data.

Conclusion: There was no significant difference in vitamin D levels in asthmatic children compared to non-asthmatic healthy controls in our population. However, the prevalence of vitamin D insufficiency is high. Further studies are needed to investigate why vitamin D insufficiency is so highly prevalent in children living in a tropical country such as Singapore.

A176 – Inflammatory Phenotypes and Instability of Induced Sputum Inflammation in Children with Severe Therapy-Resistant Asthma: A Case-Control Study.

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Background: Induced sputum (IS) has been an important tool to assess airway inflammation in children with asthma. However, the pattern of airway inflammation in children with severe therapy-resistant asthma (STRA) has not been widely studied. We report in this study the characteristics of the inflammatory pattern and granulocytic cell counts in children with severe asthma compared to mild to moderate asthma, including sequential sputum procedures.

Methods: Children and adolescents (6–18 years) with STRA and mild to moderate asthma (MMA) were selected according to GINA and ERS/ATS criteria. Induced sputum was collected from all patients, and was repeated between 6 and 12 months in a sub-group of subjects. The type of inflammation, granulocytic cell counts and instability of inflammation of the induced sputum was analyzed. The association of inflammatory cell counts and lung function results was also assessed.

Results: 99 subjects were selected, with a mean age of 11.3 ± 2.1 years, and 53% female subjects (STRA: n = 23 and MMA: n = 76); 182 induced sputum procedures were performed (success rate: 64%). The group of STRA children exhibited the following inflammatory phenotypes: 6/23 (26%) were eosinophilic, 26% neutrophilic, 4/23 (17.5%) mixed and 7/23 (30.5%) pauci granulocytic. There was no significant difference in the inflammatory phenotypes, eosinophil number and neutrophil counts in induced sputum between the STRA and MMA groups. When abnormal lung functions were selected, neutrophil counts were significantly and negatively correlated with FEV1 (r = −0.69, p = 0.01). In those STRA children with sequential sputum performed, 10/12 (83%) subjects changed inflammatory phenotype. All children with neutrophilic sputum did not respond clinically to a trial of macrolide therapy.

Conclusions: The inflammatory phenotype of induced sputum in children with asthma is very heterogeneous, regardless of the severity of disease, and most children with STRA changed inflammatory phenotype in sequential induced sputum procedures. The role of induced sputum in the management of children with STRA is still unclear, and the understanding of neutrophilic inflammation should be better explored in this group of patients.

A187 – Defining and Diagnosing Asthma in the Infant and the Preschooler: A Systematic Review.

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Introduction: There is disagreement among Spanish pediatrician experts relative to asthma diagnosis in infants and preschoolers. We present the results of a systematic review of asthma guidelines to answer some key questions regarding the diagnosis of asthma in infants and preschoolers, as a preliminary step to reaching a consensus among Spanish pediatricians on this subject.

Methods: Key questions:

Is there a specific definition for asthma in children under 6 years old?

Is it possible to diagnose asthma at any age, including the first year of life?

Is it necessary to perform pulmonary function tests in order to make the diagnosis of asthma in children under 6 years of age?

Are there defined and objective criteria for the diagnosis of asthma in children under 6 years old?

Is it possible to diagnose asthma in preschoolers even though the disease may remit at 6 years of age or later?

Search strategy: We performed a systematic search of scientific literature published between 2007 and 2016 to identify and select clinical practice guidelines (CPGs) related to asthma management. We initially searched in the database of clinical guidelines Trip Database
and the US National Library of Medicine database MEDLINE (through PubMed) using a combination of text-free terms and their corresponding medical subject heading (MeSH) terms and limiting the results with a filter to retrieve guidelines as follows: (Practice Guideline OR Guidelines OR Practice Guideline OR Guideline OR Consensus Development Conference OR Practice Guidelines as TopicMeSH) AND ("Asthma"Mesh OR asthma*t), without restriction of languages. A manual search was subsequently performed.

Inclusion and exclusion criteria: We included CPGs that aimed to provide diagnostic and therapeutic recommendations on the care for children and/or adolescents and adults. The documents were considered as a guideline if they met the following criteria: provided practical clinical recommendations for children, adolescents or adults, and collected all related documents and supporting materials. We excluded documents without information regarding the concept or diagnosis of asthma in childhood, including the first 6 years of life.

Analysis: The guidelines included in the review were subjected to several exploratory analyses conducted by LM, with the participation of all the researchers. Given the descriptive nature of the sections related to the concept and diagnosis of asthma, questionnaires were designed to find out how the guidelines considered the diagnosis of asthma in young children, especially in terms of the age at which it could be established, the diagnosis and the premises (clinical criteria or complementary tests) to make this diagnosis. The authors responded to these questionnaires and they contributed with comments via e-mail to clarify the discrepancies. Discrepancies were resolved by agreement among reviewers.

Results: We obtained 2338 references with the initial search in Trip Database and PubMed (Figure 1). Through manual search, we added 7 more guides. Finally, 22 documents were analyzed and grouped into 20 guides, given that 2 of the guides were considered to be integrated by 2 different documents whose contents were judged as complementary. Nine guidelines referred to patients of all ages, 8 were pediatric and 3 were dedicated exclusively for preschoolers. Regarding questions, the results were:

In most guidelines, the concept and definition of asthma are closely linked to their diagnosis. In the general guidelines, distinction is not made between the definitions of adult or pediatric asthma.

Most asthma guidelines recognize, generally implicitly, that there is not an age limit to establish the diagnosis of asthma, but highlight the difficulty to establish the diagnosis under 5–6 years.

Spirometry is not considered essential to establish the diagnosis in preschoolers, although the difficulty in carrying it out is an inconvenience that makes it difficult to confirm the diagnosis.

In most of the guidelines, asthma diagnosis in preschool children is based on the subjective interpretation that the pediatrician makes of the clinical findings, treatment response and exclusion of other alternative diagnoses. They also rely on the performance of some complementary tests that rule out or increase the probability of diagnosis.

The ERS guideline on preschool wheezing is the only one to indicate that the disappearance of symptoms in later years is what distinguishes those who really suffer from asthma from those who do not. Some guidelines accept that asthma may remit over time (for example, ICON and Japan’s child) and, therefore, it would not be an impediment to establish the diagnosis.

Conclusion: There is an apparent agreement among most national and international guidelines to consider that the diagnosis of asthma in preschool child is syndromic and that it can be established at any age, even though respiratory function tests cannot be performed.

Reflection: We believe that there is, therefore, a good basis for the performance of a consensus that formalizes the findings of this review.

3. BRONCHOPULMONARY AND PLEURAL INFECTIONS (INCLUDING TUBERCULOSIS)

C8 – Randomized, Double-blinded, Placebo-controlled Trial of Arginine as an Adjunct Therapy for Pediatric Patients with Healthcare-Associated Pneumonia.

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Background: Research has been made regarding the immunomodulatory properties of amino acids that possess pharmacological effects on pathophysiological abnormalities. These amino acids included arginine,
glutamine and branched-chain amino acids (Gardiner & Barbul, 2001). These amino acids have been used in sepsis, burn, surgical and trauma patients who presented with a significant decrease in their plasma arginine level, which correlated with their state of immunosuppression incurred by the initial insult.

This study evaluated Arginine supplementation as an adjuvant therapeutic option among patients with healthcare-associated pneumonia as a potential agent to specifically alter the inflammatory response and immune function of an individual during the disease process that is measured indirectly by soluble human leukocyte antigen type DR (sHLA-DR) level.

**Objective:** To determine the effect of adjunctive arginine therapy on the immune status of pediatric patients diagnosed with healthcare-associated pneumonia.

**Study Design:** Randomized, Double-Blinded, Placebo-Controlled Trial

**Methods:** All patients aged 1 month old to 18 years old admitted at the Pediatric ER, Wards 6, 9, 11, Trauma and Burn Unit, diagnosed with a first bout of healthcare-associated pneumonia regardless of the current hospital stay, empirically treated with IV antibiotic and on enteral nutrition either per orem or through feeding tubes, were included in the study. Patients who were enrolled in the study were randomized into two (2) groups by means of a computer-generated randomization table. One group received the dietary supplement and the other the placebo. The dietary supplement group received L-arginine 200 mg/kg/day three times a day per orem for 7 days as an adjunct to the appropriate intravenous antibiotics not exceeding 3 grams/day. Blood samples were collected from all recruited subjects for baseline levels of plasma arginine and serum sHLA-DR and repeat blood extraction after 7 days of supplementation and treatment for healthcare-associated pneumonia.

Data were encoded in Microsoft Excel and analyzed using SPSS. All variables were numerical variables and expressed as mean and standard deviation. All variables underwent T-test for numerical variables. Pearson correlation was also used to test the relationship of the plasma level of L-arginine with sHLA-DR level between the dietary supplement and placebo groups.

**Results:** There were a total of 40 patients recruited in the study. Seven (7) subjects were withdrawn from the study; five (5) of whom were due to protocol non-compliance and two (2) had deceased due to acute respiratory failure as complication of the underlying disease, thus only 33 subjects were included. There were 16 and 17 subjects recruited to the respective supplement and placebo groups. There was no significant difference between the two groups in terms of age, weight, gender and use of oxygen support.

The Arginine levels on Day 1 of both supplement and placebo groups were the same and showed no significant difference (p value = 0.71). The Arginine levels on Day 8 of the supplement group however had a higher level compared to the placebo group but was not statistically significant (p value = 0.27). Regarding the sHLA-DR levels of both groups, the supplement group had a lower level on Day 1 as well as after supplementation (Day 8) compared to levels of the placebo group. Both sHLA-DR levels of the two groups were not statistically significant. However, both sHLA-DR levels of both groups were below the set threshold level, hence both groups had low sHLA-DR levels.

Further analysis of the data comparing arginine and sHLA-DR levels on day 1 to levels after 7-day supplementation (Day 8) showed that, in the supplement group, arginine levels at baseline and after 7 days of supplementation increased which was statistically significant (P value = 0.04). In the placebo group, the Arginine levels at baseline and after 7 days of supplementation also increased, however they were not significantly different (P value = 0.31).

Data on arginine and sHLA-DR levels both at baseline (Day 1) and after 7 days of supplementation (Day 8) were compared although showed no correlation between the level of arginine and sHLA-DR in both groups with Pearson’s r values of less than 0.8.

**Conclusion/Recommendations:** In this study, the data of 33 patients were analyzed. There was no general trend and no correlation between arginine level and soluble HLA-DR level from baseline and after 7 days of supplementation. In conclusion, arginine supplementation as an adjunct to IV antibiotics did not improve the immune status of patients with healthcare-associated pneumonia. Further studies are needed focusing on the dietary intake of each subject prior to supplementation as well as during the duration of therapy. It is recommended that future studies have a longer duration of supplement intake. Furthermore, arginine and sHLA-DR levels should be monitored even after 7 days of supplementation as well as a greater number of patient subjects recruited for the study.

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**C9 – Lobectomy as a Life-Saving Procedure Following Life-Threatening Necrotizing Pneumonia in a Toddler – A Case Study.**

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Necrotizing pneumonia is a severe form of pneumonia caused by highly virulent bacteria, mainly *Streptococcus pneumoniae* and *Staphylococcus aureus*. Treatment is primarily conservative, while surgical intervention is still controversial.

We report a unique case of necrotizing pneumonia due to group A streptococcus infection in an 18-month-old boy. Severe respiratory failure required extracorporeal membrane oxygenation (ECMO) support as a bridge to recovery. Following surgical lobectomy, the child was weaned off ECMO and recovered uneventfully. Cases of necrotizing pneumonia requiring ECMO support present a unique clinical challenge. A conservative approach includes watchful waiting for respiratory improvement while on ECMO support. However, an alternative approach stipulates surgical intervention to facilitate ECMO withdrawal.
Our patient's necrotizing pneumonia was successfully treated by surgical lobectomy while he was on ECMO support. Thus, we suggest surgical lobectomy as a suitable option in select cases of necrotizing pneumonia not responding to conservative medical treatment.


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Background: Tuberculosis or TB is an infectious disease caused by the bacteria called Mycobacterium tuberculosis which is a curable and preventable. Extra-pulmonary TB (EPTB) refers to tuberculosis involving organs other than the lungs. According to the Department of Health (DOH Philippines, 2014), tuberculosis remains a major public health problem in our country. In 2010, TB was ranked as the 6th leading cause of mortality across all ages, with 26.3 deaths for every 100,000 population and accounted for 5.1% of all total deaths. There may also be an increased risk of having more cases of EPTB in our country. This study aims to provide an overview on the prevalence of EPTB among pediatric patients and help increase awareness of the magnitude of the problem in order to improve management of Tuberculosis programs among the pediatric population in the country.

Objective: To describe the prevalence of extrapulmonary tuberculosis among pediatric patients aged 1–18 years old in a tertiary government hospital.

Study Design: Retrospective, descriptive study (chart review).

Setting: A Tertiary Government Hospital in Manila (Ospital ng Maynila Medical Center)


Study Methods: Permission was obtained from Ospital ng Maynila Medical Center. The consent of all patients who were admitted at Ospital ng Maynila Medical Center with the diagnosis of extrapulmonary TB from year 2014–2016 was obtained. The charts or patient’s file were retrieved from medical records. Demographic and socio-economic features, clinical findings, laboratory, treatment and outcome information were obtained. Data were arranged in tables expressed as proportions and percentages.

Results: This study showed that there was a prevalence rate of 0.35% for extrapulmonary TB among all pediatric admission for the years 2014–2016. The majority of the cases were children aged 1–5 years old, 64% with a mean age 10 years old. There appeared to be no sex predilection with regards to extrapulmonary TB. A majority of the cases had no known TB disease or TB exposure. Common cases of EPTB included TB meningitis (84%) presenting with changes in behavior or decrease in sensorium. Gastrointestinal TB (8%) presented with abdominal distention and one case of TB Uveitis who presented with whitish lesion in the cornea of the eye. Among these patients, 33% were discharged as improved including and 42% died all of whom were TB meningitis patients.

Conclusion: With these data, we can say that there is a need to strengthen the National TB program in terms of active case finding so that we can further decrease the transmission of TB in the country and initiate early treatment. There is also a need to educate health care workers to identify possible cases of EPTB to prevent possible fatal outcomes. Since TB meningitis has a poor outcome, health care professionals should be vigilant and be more aggressive in treating these cases.

C33 – Effect of Passive Smoking Exposure on Development of Childhood Pneumonia and Illness Severity.

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Objective: Previous research has shown that passive smoking exposure is associated with wheezing, chronic cough, asthma and bronchiolitis in children. Research studies on pneumonia are limited and based on questionnaire studies. Since 2008, smoking cessation has begun to be applied in closed areas in Turkey. In previous studies, urine cotinine / creatinine threshold value, which shows passive smoking exposure in children, was evaluated as 60 ng / mg in our country. Our aim is to objectively evaluate the effect of passive smoking on pneumonia development and illness severity in childhood.

Methods: Between December 2015 and April 2016, children under the age of 5 with pneumonia and age-matched healthy controls were included in the study in three pediatric pulmonology centers. A questionnaire was applied to the parents regarding demographic data and smoking status at home. Urine cotinine / creatinine levels were measured as objective indicators of passive smoking exposure. The pneumonia group was grouped as mild and severe according to disease severity. The data of patient and control groups as well as children with mild and severe pneumonia in the pneumonia group were compared with each other.

Results: There were 74 children in the study group and 153 children in the control group. Overall, 52% of children in the study group and 54% of children in the control group had passive smoking exposure. Urine cotinine / creatinine levels of children exposed to passive smoking were higher than unexposed children. There was a significant difference between the study and control groups in terms of age, monthly income, number of people living at home, age of mother and father, and time spent outside the home (p < 0.05). The cotinine /
creatinine level of the study group was higher than the control group. There was a significant difference between age and urine cotinine / creatinine levels in mild and severe cases in the study group (p < 0.05); 64.1% of the children with smoking exposure had severe pneumonia while 35.9% had mild pneumonia. ROC analysis revealed a urine cotinine / creatinine threshold of 2.47 ng / mg for passive smoking exposure.

Discussion: Objectively, it was shown that passive smoking exposure is associated with the development of severe pneumonia in children. The present findings are considered as promising given that the threshold value of passive smoking exposure after smoking cessation in our country was considerably lower than in previous studies.

C39 – Necrotizing Pneumonia Caused by Refractory Mycoplasma pneumoniae Pneumonia in Children.

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Objectives: The aim was to evaluate the clinical features of necrotizing pneumonia (NP) caused by refractory Mycoplasma pneumoniae pneumonia (RMPP).

Methods: A retrospective, observational study of NP cases caused by RMPP, who were hospitalized in our hospital from January 2008 to December 2015 was conducted, and clinical manifestations, laboratory data, imaging performance, hospital course and outcomes were analyzed.

Results: A total of 25 NP cases caused by RMPP were identified, with a median age of 5.1 (4.0 ~ 7.9) years. The mean length of total fever days and hospital stay days of these patients were 21.0 ± 8.9 days and 19.9 ± 9.9 days, respectively. The abnormal laboratory findings of elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), interferuk (IL)-6, IL-10 and interferon gamma (IFN-γ) were observed in many of our patients. Meanwhile, pleural fluid characteristics associated with NP in the present study, particularly the high value of pleural fluid cell count, LDH and protein, was also observed. Most of the patients (80.0%) in our study were associated with pleural effusion, and had a high incidence of lobar atelectasis and pulmonary consolidation. Interestingly, the mean delay time for detecting necrotic lesions from onset of symptoms was 21.0 ± 6.9 days. Eighty percent (80.0%) of patients were administered corticosteroids and 100% of patients underwent bronchoalveolar lavage (BAL). Of the 20 patients who presented with pleural effusion, 11 had thoracicocentesis alone and 2 had chest drainage. All patients received prolonged course of antibiotics (32.2 ± 8.7 days), and discharged without death. Follow-up studies showed that all patients recovered without surgical intervention, and chest radiographs revealed resolution or only minimal residual fibrotic change within 3.0 (2.0 ~ 6.0) months.

Conclusions: NP caused by RMPP should be recognized as a severe, yet self-limiting and reversible disease through appropriate managements.

C52 – Determinants of Pulmonary Complications in Childhood Mycoplasma pneumoniae Pneumonia

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Background: Mycoplasma pneumoniae (MP) is the major pathogen causing community-acquired pneumonia in children. Although Mycoplasma pneumoniae pneumonia (MPP) is usually benign and self-limited, it may develop into pulmonary complications. The aim of this study was to elucidate the clinical and laboratory characteristics of patients with early-onset (pleural effusion, necrotizing pneumonia, and acute respiratory failure) and late-onset (bronchiectasis and bronchiolitis obliterans) pulmonary complications after MPP.

Methods: A retrospective analysis was performed in children with MPP who were admitted to our hospital from January 2011 through December 2016. Of a total of 464 patients, 85 and 11, respectively, had early and late-onset pulmonary complications.

Results: The median age was higher in patients with early-onset complications (ECx) than in those without ECx, while it was not different between patients with and without late-onset complications (LCx). The median levels of lactate dehydrogenase (LDH), C-reactive protein, ferritin, C-X-C motif ligand 9, C-X-C motif ligand 10, interleukin (IL)-2Ra, IL-10, IL-18, interferon-γ and the median percentage of neutrophils in patients with ECx were higher than in those without ECx. In logistic regression analysis, ferritin >370.1 pg/mL (OR 11.75, 95% CI 1.07–229.29) and IL-10 >809.13 pg/mL (OR 6.57, 95% CI 1.05–50.58) increased the risk for ECx while LDH >1002IU/L (OR 20.31, 95% CI 3.45–386.38) increased the risk for LCx. Cox regression analysis showed that macrolide treatment for over 15 days (HR 13.83, 95% CI 1.68–113.61) and LDH >1002IU/L (HR 27.41, 95% CI 3.23–232.86) were significant determinants for LCx.

Conclusions: During the course of MPP, ferritin >370.1 pg/mL and IL-10 >809.13 pg/mL may promote timely recognition of early-onset complications and LDH >1002IU/L might be the significant predictor of late-onset complications.

C63 – Multidrug-Resistance in Congenital Disseminated Tuberculosis: A Rare Case Report from Indonesia

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Introduction: Recently, although childhood Multidrug-Resistance (MDR) Tuberculosis (TB) is increasing in Indonesia, congenital MDR TB however is still rare. We report a late diagnosed congenital
ABSTRACT

Objective: To investigate the epidemiology and characteristics of miliary tuberculosis in children in an Indonesian top referral hospital, Cipto Mangunkusumo Hospital (CMH).

Methods: A retrospective study from 2014 to 2017 was performed to investigate the profile of miliary tuberculosis in children.

Results: From 2014 to 2017, 483 children were treated as tuberculosis. Miliary tuberculosis was diagnosed in 21 children (4.35%). Among these, 57% were female, 23.8% were under 2 years of age, while a majority (61.9%) were older than 10 years old. BCG vaccination was administered in 61.9% of children. Forty-two percent were mildly malnourished, and 38% were severely malnourished. No HIV infection was found in these patients. GeneXpert was positive in 47% and all were rifampicin-sensitive. Only 9 children underwent a tuberculin test, which yielded a positive result in 1 child. Mortality rate among miliary tuberculosis children was 28.6%.

Conclusions: Miliary tuberculosis is prevalent among children older than 10 years old (adolescents). Most of these children are female, and have been vaccinated. Bacteriological confirmation should be performed in miliary tuberculosis patients since positive results are high. Almost 30% of the cases result in mortality. This may raise the notion for prophylaxis among adolescents in high endemic countries.

Keywords: tuberculosis, miliary, adolescent.

C87 – Pulmonary Tuberculosis and Scrofuloderma in Marasmic Kwashiorkor Children: A Case Report.

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Background: Pulmonary tuberculosis (TB) and extrapulmonary TB can sometimes simultaneously occur, especially in child malnutrition. Scrofuloderma is one form of cutaneous TB whose infection route is always endogenous, usually secondary to joint and lymph node TB and dependent on individual immunity and environmental factors. Clinical lesions appear as nodules, gumma and ulcers due to fistulae, occurring in children and young people. Very few pediatric patients with pulmonary TB and scrofuloderma have been reported.

Case: A 10-year-old boy was referred to the department of child health with shortness of breath, abdominal enlargement and swelling of the leg, with normal urination and defecation, for 2 weeks. History of low grade fever, chronic cough, loss of appetite, decreased body weight, nodules in the neck, armpit, upper chest, no pain, since 1 year. Then, in 1 month, the nodules became reddish and ruptured, discharging pus, after which other nodules started to appear. We found signs of dyspnea with rales, multiple hypertrophic crusted ulcers with skin tract at the colli, axilla and infraclavicular regions, abdominal enlargement due to ascites and edema of the leg, and clinical marasmic kwashiorkor. Tuberculin skin and HIV rapid tests were negative, a rapid molecular test detected very low Mycobacterium tuberculosis (Mtb), and hypoalbuminemia. Skin biopsy showed specific chronic...
inflammatory granulomatous. Anti-tuberculosis therapy (ATT), albumin, antibiotic, and nutritional therapy was administered. Significant improvement was observed after 1 week of treatment.

**Discussion:** One-third of the world’s population is infected with Mtb and the global burden of the disease continues to grow, depending on the individual immunity and environmental factors of the children. The typical patient is adolescent with malnutrition and low socioeconomic conditions from crowded environments. In the present case, specific scrofuloderma lesions, skin biopsy results, positive rapid molecular Mtb test and a good response to ATT favored the diagnosis of pulmonary TB and scrofuloderma in a marasmic kwashiorkor child. Scrofuloderma must be differentiated from some other similar lesions such as sporotrichosis and hiradenitis suppurativa by skin biopsy.

**Keywords:** pulmonary tuberculosis, scrofuloderma, marasmic kwashiorkor, children

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**C121 – Pneumological Endosonography in a Child with Tuberculosis – A Case Report.**

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**Background:** Endobronchial ultrasound (EBUS & EUS-B) is an essential part of the bronchoscopic diagnosis of lung cancer and mediastinal lymphoma, especially in sarcoidosis and tuberculosis. To date, the possible uses in children have only been explored through a limited number of individual case reports, one prospective multicenter study (1) and one retrospective analysis (2).

**Methodology:** We report on a three-year-old boy with mitochondrialopathy and suspected tuberculosis due to contact with a tuberculosis patient and prolonged cough. Further diagnosis revealed a positive tuberculin skin test, a right lobe atelectasis and a bilateral hilum prominence. Gastric aspirates remained without germ detection. Despite triple therapy with INH, RMP and PZA, an increasing stenosis of the left main bronchus developed after 2 months. Bronchoscopically, lymph node penetration was the cause of the stenosis. Endosonographically (EBUS PENTAX), it was possible to visualize pathological lymph nodes via EBUS and EUS mediastinally on the left (position 2L, 7 and 9) and to perform a transesophageal EUS-B-FNA from position 7 and 9.

**Results:** Bronchoalveolar lavage showed acid-fast bacilli. The PCR for M. tuberculosis complex was positive. The EUS-B-FNA revealed a granulomatous inflammation of the TB type as well as the molecular pathological evidence for tuberculosis. Resistances were not found. After escalation of the therapy with EMB and passable prednisolone, the local findings and clinical picture improved.

**Conclusion:** The course shows that EBUS can be helpful in pediatric pulmonology. However, transesophageal puncture has to be preferred in very small patients, to reduce possible complications, especially bleeding, and to account for device limitations because of limited airway diameter. Further diagnosis of mediastinal lymphoma is also possible in children and recommended due to the broad range of possible causes.


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**C126 – Clinical Features of Tuberculosis in Pediatrics.**

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**Background:** Tuberculosis (TB) infection and disease are still a global health problem in Indonesia, especially in children. Clinical presentation for childhood TB may vary depending on the epidemiological situation of TB.

**Objective:** To study the clinical features and investigation profiles of pediatric TB patients at various ages.

**Methods:** Retrospective analysis of 50 children with TB who were admitted to the Dr. Moewardi Hospital from November 2016 to November 2017 and included in the study. Clinical features and investigation profiles of patients were obtained.

**Results:** From the overall 50 pediatric TB patients, 20 were males and 30 were females. Pulmonary TB was more common (76%) than extrapulmonary TB (24%). BCG scar was present in 50% of cases. History of TB contact was present in 2%. The most common symptoms were fever (72%), cough (70%) and malnutrition (40%). Tuberculin skin testing was positive in 68%. GeneXpert was positive in 46%.

**Conclusion:** Fever is the most common presentation of pediatric TB, but it is not a specific symptom. GeneXpert and tuberculin skin tests are important diagnostic tools.

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**C127 – Characteristics of Tuberculosis in Children in Kariadi Hospital Semarang Indonesia.**

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**Background:** Tuberculosis (TB) still remains a major problem in Indonesia, especially in children. Characteristics of the disease may differ between regions as well as site of infection.

**Objective:** To report the characteristics of pulmonary and extrapulmonary TB in children.

**Methods:** A retrospective descriptive study was undertaken in children aged 0 to 18 years admitted to Kariadi Hospital between 2015 and 2017. Data regarding TB, nutritional status, history of contact, demographics, sputum smear and GeneXpert result, HIV status and Tuberculin Skin Test (TST) were recorded. Chi-square was performed to analyze the variables.
Results: Of 215 children admitted with TB, 64.2% showed pulmonary TB and 35.8% extrapulmonary TB. There were 119 (55.3%) males and 96 (44.7%) females, with a median age of 6 years (range 0–18 years). Nutritional status was 47% mild-moderate and 25.6% severe malnourished. HIV status was 6% positive, and 92.3% were pulmonary TB. History of TB contact was only 60% of whom 61.4% had positive TST. Positive sputum smear was found in 15.8% cases and GeneXpert was positive in 10.2% with 1 Rifampicin resistance. There was a statistical difference between pulmonary and extrapulmonary TB with regard to history of contact (p = 0.01). Fifty-five percent of over 14-year-old children had extrapulmonary TB compared to 26% and 37.1% in under 5 years old and 5–14 years old, respectively (p = 0.03).

Conclusion: Incidence of extrapulmonary TB was found higher in adolescence, and history of contact was higher in pulmonary TB.

Keywords: Pulmonary TB, extrapulmonary TB, children

C128 – Disseminated Tuberculosis in a Boy with HIV.

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Background: HIV alters the pathogenesis of TB, increasing the risks of developing severe disseminated TB.

Objective: To describe a case of disseminated tuberculosis in a boy with HIV.

Case: A 3-year,10-month-old boy was referred to the Kariadi Hospital with swelling in the left knee, chronic diarrhea, and severe malnutrition. Physical examination: oral thrush, multiple cervical lymphadenopathy, diffuse rales and crackles, inflamed left knee; ulcer with necrotic tissue and pus. TST was negative. Anthropometric score showed severe chronic malnutrition (WAZ –6.39 SD, HAZ –6.12 SD, WHZ –5.71 SD). He had normocytic normochromic anemia (5.4 gr/dL), a CD4 count 167 cells/ uL and HIV screening was indeterminate although HIV viral load level was 9,060,457 copies/ mL. Sputum smears revealed no AFB, and culture showed Klebsiella pneumoniae (ESBL). Left knee X-ray results suspected peristeal osteomyelitis; sonography suggested septic arthritis and periosteal reaction. Wound swab smears revealed positive AFB. Knee effusion staining was positive for AFB with Xpert MTB-RIF high detection of MTB but no rifampicin resistance. Biopsy of the left knee resulted in non-specific chronic inflammation. Wound culture and blood culture revealed Staphylococcus aureus (MRSA). Stool smears were positive for AFB and Cryptosporidium sp cyst. The patient was treated with cefoperazone sulbactam and vancomycin intravenously; RHZE, ART (zidovudine, lamivudine, efavirens); azithromycin and paromomycin for cryptosporidiosis; and cotrimoxazole. He was programmed for debridement and drainage, with application of back slab splinting. After 4 weeks, the child was discharged with improved condition. After 9 months of TB treatment, his left knee was no longer inflamed and the wound was improving, with X-ray showing no periosteal inflammation although there remains joint effusion; no AFB was detected in wound swab smears. Physiotherapy was subsequently programmed. He still continues the maintenance phase of TB treatment and ART.

Keywords: Disseminated TB, HIV, children

C140 – Outcomes of Children Hospitalized with Pneumonia in West Nusa Tenggara Province General Hospital Indonesia.

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Background: Pneumonia is a major cause of death in children younger than 5 years old, particularly in developing countries. Aside from a high mortality rate, pneumonia also causes a significant number of hospitalizations. We conducted this study to present the outcomes of children hospitalized with pneumonia in West Nusa Tenggara Province General Hospital.

Methods: A respirology registry of children aged 2 months to 15 years of age admitted with pneumonia from January 2015 to December 2016 was retrospectively reviewed. Demographic data, physical examination, laboratory and radiology findings, and outcomes were carried out in all children admitted with pneumonia.

Results: Out of the 392 children admitted with pneumonia, 187 (47.7%) were admitted in 2015 and 205 (52.3%) in 2016. The majority were male – 224 (57.1%), aged between 2 and 12 months – 259 (66.1%), and had Fe deficiency anemia – 215 (54.8%) as co-morbidities. Nine of 392 (2.3%) had very severe pneumonia, while 383/392 (97.7%) were admitted with severe pneumonia. About 208/392 (53.1%) were hospitalized for more than 5 days, with an average length of hospital stay of 7.4 days (2015) and 6.8 days (2016). Overall, the mortality rate was 24/392 (6.1%), with 8/187 (4.3%) in 2015 and 16/205 (7.8%) in 2016, respectively. Eighteen of 24 (75%) were aged between 2 and 12 months, of whom 6/24 (25%) were admitted with very severe pneumonia, and 18/24 (75%) with severe pneumonia with two or more co-morbidities.

Conclusions: Although the mortality rate of children hospitalized with pneumonia in our hospital had increased from 2015 through 2016, the average length of stay in hospital nevertheless declined. These findings highlight the need for further prospective studies to identify the risk factors of prolonged hospital stay and mortality as poor outcomes in children hospitalized with pneumonia.

Keywords: outcome, pneumonia, hospitalized, children

C163 – Characteristics of Children Who Are in Close Contact with MDR TB Patients in Persahabatan Hospital.

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Background: There are increasing MDR TB cases in Indonesian adults, which render the need for children who are in close contact with these MDR TB cases to be closely observed, because of the risk of contracting MDR TB from adult patients.

Objective: To examine the pediatric population in the household of adult MDR TB patients.

Method: This is an observational cross-sectional study which was held from January 2017 to February 2017 in Persahabatan General Hospital, Jakarta, Indonesia involving 68 household children from 47 MDR TB adult patients. We examined the children, including careful history of exposure and physical examination, Tuberculin Skin Test (TST), chest X-ray and, if the children had signs and symptoms of tuberculosis, acid fast bacilli stain examination, sputum culture and resistance test and GeneXpert sputum test were also added.

Results: From the 68 children, there were 7 children (10.29%) diagnosed with TB, although none had MDR TB. In children who were diagnosed with TB, all had chronic cough and positive TST, 2 children had prolonged subfebrile fever (18.2%), 2 children had multiple lymphadenopathy (18.2%), 5 children had poor housing ventilation (72%), 2 of whom their parents complied with wearing a surgical mask for transmission prevention (18.2%), 2 did not have BCG scar (18.2%), and 1 child with suggestive TB from chest X-ray (14.3%). Of the 68 children, TB prophylaxis was administered in 20 children who were under 5 years old, and close observation was maintained in 41 children.

Conclusion: There were 7 children (12.7%) of household adults with TB MDR who were diagnosed with TB and none had MDR TB.

C167 – Follow-Up of Viral Pneumonias and Identification of Late Complications at a Portuguese Tertiary Pediatric Hospital.

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Introduction: Viral pneumonia can vary from a mild and self-limited illness to a life-threatening disease. Morbidity is high and the evaluation of childhood pneumonia interventions should include potential impact on long term respiratory sequelae, which are more likely in children requiring hospital admission. Identification of the agent is also important since different viruses have different rates of complications, with adenovirus pneumonia being associated with the highest risk of sequelae. The most commonly isolated viruses in childhood pneumonia requiring hospitalization are respiratory syncytial virus (RSV), rhinovirus, human metapneumovirus, adenovirus, influenza viruses, parainfluenza and coronavirus. This study intends to evaluate the follow-up of children with viral pneumonias that required hospitalization in a tertiary pediatric hospital as well as long term respiratory complications, particularly post-infectious bronchiolitis obliterans for its usual severity and major impact in children and families.

Methods: We retrospectively studied clinical records of children admitted in a Portuguese tertiary pediatric hospital from July 2013 to June 2017 and whose diagnosis at the time of discharge was viral pneumonia. Children with previously known comorbidities were excluded. The diagnosis of viral infection was established clinically and by imaging features suggestive of viral infection (bilateral interstitial infiltrates and alveolar infiltrates). Quantitative real-time polymerase chain reaction of nasopharyngeal swab specimens for viruses and Mycoplasma pneumoniae was performed in all children. Demographic and clinical data, imaging and laboratory results, treatment and clinical course during hospitalization were analyzed. Follow-up and identification of late sequelae were also studied.

Results: A total of 77 children fulfilled the study criteria, with a median age of 19 months, 55% being girls. The most frequently identified virus was RSV (n = 42) followed by adenovirus (n = 23), rhinovirus (n = 22), parainfluenza (n = 12), influenza A (n = 10), metapneumovirus and coronavirus (both with n = 9). Mycoplasma was identified in two children. Most patients (60%) had more than one virus identified, and three children had no identified pathogen. Median time of hospitalization was five days, ranging from one to 17 days. Most children were treated with supportive measures, but three children needed mechanical ventilation. Fifty-three children were followed-up at our hospital. Of those, 20 are still followed at the Pulmonology Outpatient Clinic: 2 with post-infectious bronchiolitis obliterans (both diagnosed clinically and with CT scan) and the remaining for recurrent wheezing and/or cough not present before the pneumonia. The remaining children maintain follow-up at a primary care or local hospital but none of them has been identified with respiratory sequelae.

Conclusion: Viruses are common pathogens in childhood pneumonia and the need for hospitalization is common. In our sample, two children (3%) developed post-infectious bronchiolitis obliterans and 26% of children maintain follow-up for recurrent respiratory symptoms. These findings highlight that all children with viral pneumonia who need hospitalization should be considered at risk of long term complications and require follow-up.

C174 – Polyserositis Tuberculosis in a Teenager.

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Introduction: Tuberculosis still remains a serious public health problem worldwide, especially in third world countries, and it is estimated that 1/3 of the world’s population has already been infected by Koch’s bacillus. Polyserositis tuberculosis, an uncommon condition, is a form of extrapulmonary tuberculosis that can occur at any age. Young children and HIV-positive adults are particularly susceptible. About 25% to 30% of children with tuberculosis manifest an extrapulmonary form. After penetrating the body via the respiratory tract,
Mycobacterium tuberculosis can spread and settle in any organ, either during the first infection, when specific immunity is not yet developed, or thereafter, at any time, if there is an ability of the host to maintain the bacillus in its implantation sites. The definitive diagnosis of extrapulmonary tuberculosis is very difficult: it can be presumptive, as long as other conditions are excluded. The treatment consists in the RIPE regimen (rifampicin, isoniazid, pyrazinamide and ethambutol) and can be started only with the presumptive diagnosis, assisting the completion of definitive diagnosis. The objective of this work is to report the case of a teenager with tuberculosis polyserositis.

Case report: J.V.M.M., 15-year-old teenager, male, black, from Rio de Janeiro- Brazil, admitted to the Jesus Municipal Hospital, RJ, on December 2017 for ascite symptoms investigation. His mother reported that he had been affected with fever, nausea and vomiting for 10 days. He sought immediate medical attention and was released after intramuscular benzathine penicillin injection. Without improvement, he sought new care the following day, being given the diagnosis of urinary infection. A dose of ceftriaxone was administered and he was sent home with a seven-day course of ciprofloxacin prescription. With no response to medication, on the fourth day of treatment with ciprofloxacin, he started having ascites. On the seventh day of treatment, the ascites were already large and the previous symptoms, such as fever and night sweats, persisted. He sought emergency care, being hospitalized and referred to this unit for investigation.

Physical examination on admission: Thin, eupneic (FR = 16irpm), good perfusion, acyanotic, hypotropical (+/- 4), massive ascites, abdominal circumference measuring 88 cm, remainder of the exam without other abnormalities. Ciprofloxacin maintained. Complementary examinations demonstrated: non-specific blood count, HSV = 105 mm, TGO = 36U/l, TGP = 26U/l, DHL = 636 U/l, FA = 114U/l, albumin = 2.8g/dl, negative rapid test for dengue, negative tuberculin test and negative serologies for hepatitis and HIV. Image exams: chest X-ray with small calcified lymph nodes in the mediastinum. Abdominal USG only proved the voluminous ascites. Chest CT was performed after 10 days of hospitalization, which demonstrated extensive pleural effusion in the left hemithorax. Transthoracic echocardiogram demonstrated compacted cardiomyopathy, and patient started on captopril.

Diagnostic puncture of the ascites fluid was performed, which showed an increase in cells with mononuclear predominance and adenosina deaminase (ADA) = 113U/l, justifying the empirical treatment with RIPE; rifampicin, isoniazid, pyrazinamide and ethambutol. Clinical improvement was observed quickly and the patient no longer had a fever and with 5 days of treatment, presented a drastic reduction in ascites, going from 88 cm of abdominal circumference to 77 cm.

Conclusion: In the case described, it is important to draw attention to the differential diagnosis of ascites. In the present case, the family history of tuberculosis was negative, however, due to the high prevalence of the disease in Brazil, tuberculosis was investigated. The inflammatory tuberculosis effusion can also occur in any of the serous cavities: pleural, pericardial or peritoneal. Clinical presentation of polyserositis is the sum of symptoms from the involvement of each serous.
Nocardia is a gram-positive bacterium from the genus of aerobic actinomycetes found in soil that has the ability to cause localized suppurative disease (mostly pulmonary, central nervous system, cutaneous or lymphocutaneous involvement) or systemic disease. There are currently 85 species of Nocardia, 25 of which cause disease in humans. Despite being associated with immunodeficiency, one third of the patients are immunocompetent. The authors report a case of a pulmonary abscess in a previously healthy adolescent caused by Nocardia (polymerase chain reaction (PCR) confirmation).

Purpose of the case: This case emphasizes the importance of considering Nocardia in differential diagnosis of pulmonary abscess, especially in the absence of response to empiric therapy.

Case report: We report a case of a previously healthy 17-year-old adolescent who was admitted in the ER with a history of fever, odynophagia, vomiting, cough and thoracic pain. The patient was on day 2 of amoxicillin/clavulanate for a pultaceous tonsillitis. On admission, exudate was observed on the tonsils but there were no signs of peritonsillar abscess. The pulmonary auscultation was normal. On blood tests, the total white cell count was 12,020/µL with 86.5% neutrophils and 2.8% lymphocytes (340/µL). Serum C-reactive protein (CRP) was 130.2 mg/L. Heterophile antibody test was negative and chest X-ray revealed an interstitial infiltrate in the right upper lobe. The patient was discharged with increased dose of amoxicillin/clavulanate.

The adolescent returned to the ER eight days later with recrudescence of fever, dyspnea and thoracic pain. On blood tests, the total white cell count was 19,500/µL with 76.9% neutrophils and 12.1% lymphocytes (2,360/µL). CRP was 90.2 mg/L. The chest X-ray revealed a cavitory lesion on the right upper lobe. The pulmonary computerized tomography (CT) scan revealed a lesion measuring 60 x 50 x 50 mm. There was no mediastinal or hilar lymphadenopathy. Empiric antimicrobial therapy with intravenous (IV) ceftriaxone and clindamycin was initiated, without evident clinical improvement. A CT-guided biopsy of the lesion was conducted. Mycobacterial, aerobic and anaerobic cultures of the pulmonary tissue and blood cultures were all negative. The histopathology analysis of the biopsy excluded malignancy and PCR of the biopsy revealed nocardiosis. All other PCR studies were negative. Autoimmune disease and immunodeficiency were excluded by normal findings, including negative serum examination and PCR detection for HIV. Brain CT, echocardiogram and cervical Doppler ultrasound were normal. The treatment was changed to IV imipenem and oral sulfamethoxazole/trimethoprim (TMP/SMX) for two weeks. The total therapy period was 3 months with TMP/SMX. There was full clinical recovery of the patient. Follow-up appointments were scheduled.

Discussion: We present a case of pulmonary nocardiosis in an immunocompetent adolescent. The clinical presentation of pulmonary nocardiosis is non-specific and chest radiograph normally reveals lesions in the superior lobe that are often attributed to other causes, which delays the correct diagnosis. The difficult isolation of the bacterial agent and its slow growth in culture makes it a challenging diagnosis. In this case, the lack of response to empirical antibiotic therapy justified an invasive procedure (pulmonary biopsy) to obtain samples for culture identification and molecular diagnostic methods.

Nocardia is a gram-positive bacterium from the genus of aerobic actinomycetes found in soil that has the ability to cause localized suppurative disease (mostly pulmonary, central nervous system, cutaneous or lymphocutaneous involvement) or systemic disease. There are currently 85 species of Nocardia, 25 of which cause disease in humans. Despite being associated with immunodeficiency, one third of the patients are immunocompetent. The authors report a case of a pulmonary abscess in a previously healthy adolescent caused by Nocardia (polymerase chain reaction (PCR) confirmation).

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new samples for in vitro culture and PCR. A positive PCR result for Nocardia sp. led to the final diagnosis of pulmonary nocardiosis. The culture was negative. To improve the culture rate identification of Nocardia, it is necessary to notify the laboratory regarding the clinical suspicion. This allows the establishment of an adequate incubation time and avoiding the use of decontamination solutions that are toxic for Nocardia sp. There are few documented cases of pulmonary nocardiosis affecting adult immunocompetent patients and usually associated with pulmonary chronic disease. To our knowledge, this is the first report of pulmonary nocardiosis in a previously healthy pediatric patient. This clinical case highlights key points that should be considered by the pediatric pneumologist in a similar context: 1) consider unusual agents that cause pulmonary abscess, even in the absence of known risk factors; 2) recognize the importance of using PCR, especially if antibiotic treatment has been previously initiated; 3) promote a close partnership between the attending clinician and microbiologist to efficiently explore the samples obtained from the patient.

C196 – Extrapulmonary Tuberculosis in Children < 13 Years Old in Costa Rica: A Retrospective Study of a not so Rare Pathology in Low Middle-Countries.

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Background: Tuberculosis (TB) in childhood is clinically challenging, but it is a preventable and treatable disease. The most common form of pediatric TB is pulmonary disease; however, other extrapulmonary forms of TB such as miliary, lymphatic, meningeitis and others are also common, particularly in children. According to WHO, Costa Rica is considered a low TB incidence country (9.5 cases per 100,000). Nevertheless, this disease should be considered to be a public health threat in any country. In Costa Rica, epidemiological and clinical information related to pediatric extrapulmonary tuberculosis (EPTB) is scarce.

Aim: To describe the clinical characteristics, epidemiology, diagnostic approach, laboratory studies and treatment for extrapulmonary and miliary tuberculosis in children under 13 years old.

Methods: A 12-year (2003–2015) retrospective study of children under 13 years old with suspected extrapulmonary tuberculosis in Costa Rica’s National Children Hospital was undertaken. Information regarding clinical and pathological history, laboratory and complementary studies, and treatment was obtained from medical records and laboratory databases. Cases were defined based on World Health Organization (WHO) recommendations for diagnosis based on clinical data, contact with a positive case, laboratory, radiological or other histopathological findings, in association with the presence of Mycobacterium tuberculosis confirmed by positive Auramina or Ziehl-Neelsen staining, positive culture on Loewenstein-Jensen medium of specific tissues or fluids.

Results: A total of 54 cases of diagnosed extrapulmonary disease were identified, of which 20 (37%) were miliary TB, followed by 14 (25.9%) cases with meningeal tuberculosis, 13 (24.1%) with tuberculous lymphadenitis, 3 (5.6%) pleural TB, 2 (3.7%) osteoarticular TB, and gastrointestinal and skin involvement in equal proportions in 1 (1.9%) patient. The mean age of diagnosis was 5.2 years (range, 0.4–12.8 years). A slight predominance of male sex prevalence was observed, with 57.4% in comparison to 42.6% female distribution. As expected, the majority of patients (47, 87.0%) were from Costa Rica. Immigration is also common in the region, from our cohort: 5 (9.2%) were from Panama and 2 (3.7%) cases from Nicaragua. There were 15 (27.7%) cases of extrapulmonary TB among the indigenous population, 3 (20%) came from Panama. No HIV positive cases were found, and malnutrition was present in 22.2% of cases.

Information collected regarding the adult index case was available for 50 patients of which only 29 (58%) had a positive index case.

The most frequent symptom was fever in: 75% of miliary cases, 66.7% of pleural tuberculosis, 64.3% meningeal presentation, and 46.2% in ganglionar disease. As for miliary tuberculosis, chronic cough was present in 60% of cases and weight loss in 45% of cases, with respiratory distress and enlarged liver in 35% of cases. Lymph node tuberculosis was characterized by weight loss and sweating in 15.4%, and 100% of patients had cervical lymphadenopathies. Meningeal presentation had seizures as main symptom in 64.3% of cases, vomiting in 57.1%, and 42.8% had either altered mental status or loss of appetite. Up to 78.6% patients had cranial nerve focality. Chronic cough was present in 100% of pleural tuberculosis and 66.7% associated chest pain, fever and poor appetite. Moreover, weight loss, abdominal pain and bloody stools were documented in 100% of gastrointestinal tuberculosis cases. Skin and bone tuberculosis had no specific symptoms at presentation, but 100% of the latter associated edema, erythema and local elevated temperature.

Chest X-ray was abnormal in 29/39 (74.4%) of patients. It was abnormal in 100% of miliary and pleural cases, 50% of meningeal and osteoarticular TB, and 42.8% of ganglionar diagnosis. Tuberculin skin test (TST) was positive in 20/42 (47.6%) of cases. It was 100% positive in patients with bone, skin and pleural tuberculosis, 50% positive in meningeal disease, 44.4% in lymph node TB, and 33.3% in miliary. Gastric lavage was positive in 14/31 (45.2%) patients. Those with miliary TB had the highest positive results (78.6%), a total amount of 7 positive cultures were documented, 5 having miliary disease, and in 4 cases molecular studies were positive, all of miliary presentation. This was also observed with bronchoalveolar lavage. A total of 20 cases were analyzed: 6/14 (42.8%) had positive cultures and 2/18 (11.1%) had positive PCR for M. tuberculosis.

All patients completed direct observed treatment (DOTS) as per WHO recommendations. Of our cohort, one patient (1.8%) died with meningeal TB.
Conclusion: The epidemiological characterization of pediatric patients with extrapulmonary TB helps achieve a better diagnostic approach to this population. It is clear that bacterial confirmation is difficult in children with disseminated disease; therefore, contact history, clinical features, radiology and TST may be sufficient to establish a diagnosis and initiate treatment. In our study, although microbiological isolation was low, it was slightly higher to other similar reports. The role of molecular biology for TB diagnosis is an important development, however, in our study, this technique was not available during the whole study period. We found that prompt diagnosis is dependent on a high index of suspicion as clinical signs may be non-specific and microbiological confirmation is difficult. Furthermore, the tuberculin skin test and chest radiograph may initially be negative in as many as 40% of pediatric patients. Treatment was well tolerated in most patients.

4. NON-INFECTIOUS RESPIRATORY DISORDERS

D17 – IgG4-Related Lung Disease in an Adolescent Male.

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IgG4-related disease (IgG4-RD) is a recently recognized systemic immune-mediated condition characterized by lymphoplasmacytic infiltrate in various organs with IgG4-positive plasma cells, different degrees of fibrosis, obliterative phlebitis and elevated serum level of IgG4 in up to 60% of patients. Lung involvement is rare, difficult to diagnose and can mimic primary lung malignancy on imaging.

A 16-year-old adolescent with no significant past medical history was incidentally found having bilateral nodular lesions in the right lower lobe and the upper lobe of the left lung on chest radiograph. X-ray was performed following positive test with 2TU (Mantoux). The patient had no complaints and physical examination revealed no abnormalities. Computed tomography (CT) demonstrated nodules in S5,6,8 of the right lung with a maximum size of 5.5 cm with large petrification in S8 and S2,6 in the left (Fig. 1a,b).

The patient underwent right bilobectomy for assumption of malignancy. Inflammatory pseudotumor was an initial histological diagnosis. However, due to high clinical suspicion of primary lung malignancy, combined partial resection of the left lung was performed. The second revision of the histological material suggested a fungal nature of the disease (sporotrichosis). Despite the absence of clinical signs of immunodeficiency, mycological examination was conducted. BAL microscopy, PCR, bacteriological culture, galactomannan test, revision of histological material with a specific Grocott’s stain were performed. On the follow-up CT examination, a nodule in the S2 left upper lobe was found (Fig 2). Specific processes and postoperative changes were found in differential diagnosis. The third expert pathology review of the histological samples was requested. Histological examination revealed significant lymphoplasmacytic infiltrate with lymphoid follicle formation, peribronchial fibrosis, vascular obliteration (Fig. 3a).

Immunostaining showed infiltration in the interstitium of IgG4-positive plasma cells. The mean number of IgG4+ plasma cells per high power field (HPF) was within 150–350. The diagnosis of IgG4-related lung disease was made.

To understand the etiology of the nodule in S2 of the left lung, positron emission tomography was performed. No lesions in the lungs or other organs including pancreas, kidney, thyroid and salivary gland were identified. The patient’s serum IgG4 level was 1.11 g/l which is in normal reference range (0.049 – 1.985 g/l). Recent international consensus for management of IgG4-related diseases states that all symptomatic and
subset of asymptomatic patients require treatment. IgG4-related disease shows a good response to steroid therapy. Some may require additional immunosuppressive agents, such as Rituximab. By the time of the presentation, the patient is under a careful clinical surveillance with no treatment.

**Conclusion:**
IgG4-related disease is a rare disease, especially cases with lung involvement. It can mimic malignancy, infection or inflammatory disorders. Isolated pulmonary disease is most frequently seen in middle aged and older men but young people can also present with this disease. Biopsy is required for the diagnosis of IgG4-related disease. Morphological features of the disease include dense lymphoplasmacytic infiltrate, "storiform" fibrosis, obliterative phlebitis and immunohistological expression of IgG4 in plasma cells. Awareness of this pathology allows avoiding unjustified surgical interventions.

**D18 - Clinical Manifestation of Pediatric Mediastinal Tumors.**
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**Background:**
Mediastinal tumors are uncommon in children but may potentially cause serious consequences owing to cardiopulmonary compromise. Predicting long-term outcome through initial clinical manifestations may be contributory to clinical decision-making. In this study, we aimed to analyze clinical presentations of various types of pediatric mediastinal tumors and develop useful predictive prognostic factors.

**Method:**
Patients under 18 years of age with diagnosis of mediastinal tumors at the China Medical University Children's Hospital between 2001 and 2016 were enrolled in this study. Patients’ gender, age of disease onset, initial clinical symptoms and signs, and outcome during the hospital course were reviewed and analyzed.

**Results:**
A total of 40 patients were enrolled into our study. The median onset age of mediastinal tumors was around 13 years-old. Male to female ratio was 3 to 1. The overall mortality rate was up to 40%. Only two cases were benign in origin. The most common tumor type was lymphoma (40%), followed by germ cell tumors (12.5%), neuroblastoma (12.5%), and thymoma (7.5%). Neuroblastoma was more prevalent in girls younger than 5 years-old. The initial presentations of these patients included respiratory distress (60%), productive cough (47.5%), pleural effusion (42.5%), superior vena cava (SVC) syndrome (35%), neck mass (35%), airway compression (32.5%), fever (30%), chest pain (25%) and pericardial effusion (25%). Lymphoma, compared to other types of tumors, was more likely to be accompanied with neck mass (52.6% vs. 19.0%, P = 0.026) and SVC syndrome (52.6% vs. 19.0%, P = 0.026), yet had better one year-survival rate (68.4% vs. 52.4%, P = 0.021).
Conclusion:
Pediatric mediastinal tumors often involve the respiratory system. Overall, lymphoma should be highly suspected when children present with neck mass and SVC syndrome, and are more common in male teenagers. Lymphoma also has better prognosis compared to other types of malignancy. Neuroblastoma, from posterior mediastinal origin, should be considered in priority among children younger than 5 years old.

D28 – Pleural Effusion and Displacement of Ventriculo-Peritoneal Shunt. A Pediatric Case Report and Review of Literature.

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Introduction: Thoracic complications of ventriculo-peritoneal (VP) shunt have rarely been reported and include pleural effusion, bronchial perforation, pneumothorax and pneumonia [1]. These complications can occur at any period of time after the procedure and three possible mechanisms have been postulated: intrathoracic trauma during shunt placement, dislocation of the peritoneal catheter into the chest and fluid shift from the peritoneal cavity to the pleural cavity [2].

Case report: Herein we report the case of a 2-year-old Caucasian female patient with Pfeiffer syndrome and VP-derived hydrocephalus who was admitted at our Respiratory Unit for irritability, tachypnea with need of mechanical ventilation and increased baseline oxygen requirement and vomiting. She was afebrile and cardiovascular examination was unremarkable. Normal lung sounds and good ventilation were noted bilaterally; no dullness to percussion was reported. The remainder of the physical examination was negative. Results of venous blood gas and routine blood tests were normal. Thorax X-ray showed a complete opacification of the right hemithorax with mild associated compressive atelectasis. A large right-sided pleural effusion was detected on thorax CT scan and an abdomen CT scan revealed the dislocation of the distal tip of the VP shunt (Figure 1). A thoracentesis was performed and the analysis of pleural fluid confirmed the CSF leakage. Because of right recurrent effusion, the distal end of VP shunt was positioned back into the abdomen and a ventriculo-atrial (VA) shunt was established in order to prevent a recurrent pleural effusion.

Discussion: pleural effusion due to VP shunt insertion is a rare and potentially life-threatening condition that should be suspected in any patient with VP shunt and respiratory failure. Overall, 21 studies have been published in the pediatric age. The timing of occurrence of this chest complication is variable and dislocation of the distal tip of the VP shunt is not prevalent. Beta-2 transferrin assay and radionuclide shuntography are useful techniques to diagnose CSF leakage and verify shunt patency and course. The diagnostic work-up should also include investigations excluding peritoneal-thoracic fistula. Thoracentesis is a useful tool to treat massive pleural effusion other than to define its source. Revision of the distal tip of the VP catheter may be sufficient when malfunction is suspected, especially when the effusion is not massive and the clinical picture does not suggest catheter infection. Its removal from the pleural space and repositioning back into the abdomen or in the right atrium is considered when dislocation is showed or CSF hydrothorax is recurrent [3]. Positive pressure ventilation is also reported as a possible therapeutic approach because of its effect on conversion of negative intrathoracic pressure to positive, preventing fluid shifts [4].

References:

Figures:
Figure 1. a) Chest CT scan demonstrating a large right pleural effusion causing mediastinal shift and compression of the heart. b) Abdomen CT scan 3D reconstructions showing the distal end of the VP shunt situated over the diaphragmatic cupola and within the pleural cavity.
Introduction: Atelectasis is a non-ventilated lung parenchyma that can occur from several causes in children. Diagnosis and treatment are very important as it can cause lung damage.

Aim: We aimed to evaluate the etiology, diagnostic methods, treatments and outcomes of patients with atelectasis in childhood.

Methods: Data of children with atelectasis in a tertiary pediatric pulmonology center between 2007 and 2015 were evaluated.

Results: In this period, 194 patients were diagnosed with atelectasis and mean age was 5.8 ± 4.0 years. The most common complaint was coughing. Ninety-five patients had pneumonia and 23 patients had acute asthma exacerbation during diagnosis. The underlying diseases were asthma, primary ciliary dyskinesia, neuromuscular disease such as hypotonia or myopathy, congenital heart disease, bronchopulmonary dysplasia, tracheal bronchomalacia, cystic fibrosis, and other rare causes. Diagnosis was made via bilateral chest X-ray in 76% of the patients and computed tomography in 23%. The most common atelectasis was observed in right middle lobe. If present, the underlying condition was treated, all patients were treated by chest physiotherapy and mucolytic treatment and 10% of the patients had bronchoscopy while 7% had dornase alpha treatment in addition to these treatments. Twenty-two patients had recurrent atelectasis, and in 37 patients atelectasis did not resolve.

Conclusion: It is important for clinicians to keep in mind that atelectasis may have different radiological findings. Recognizing radiological findings is important both for treatment and unnecessary further studies involving high-dose radiation. Patients with impaired mucociliary function may have recurrent or non-recovering atelectasis.

D36 – Tracheomalacia in Children – Long-term Retrospective Clinical Follow-up.

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Introduction:
Tracheomalacia (TM) is a fairly common airways disorder, identified in 1 to 2100 – 2500 children. Moreover, TM diagnosing has been increasing in the last decade with the improvement of imagining capabilities (fiberobronchoscopy, radiology procedures) and with the growing awareness of this disorder among clinicians. TM can be established as primary or secondary (e.g. secondary to trachea compression by great arteries). Regardless of pathophysiology, tracheal walls are softer than normal in TM and more susceptible to collapse. Clinical symptoms due to dynamic cross-sectional narrowing of the trachea are usually observed when intrathoracic pressure exceeds intraluminal pressure of the trachea, which is mostly seen during vigorous exercising, prolonged forced expiration or cough.

Clinically, TM produces recurrent cough, wheeze or stridor, thus the symptoms are commonly seen in children with other respiratory disorders. It is believed that TM is a mild disease with a tendency to resolve spontaneously in the first two years of life. However, recent studies indicate that some TM symptoms (cough during exertion, prolonged cough after respiratory tract infection, exertional dyspnea) could be observed even in older children.

The aim of this study was to characterize the clinical features of children with TM in the long-term follow-up period.

Methods:
Children with TM were identified in the dataset of fiberobronchoscopic examinations performed between 2005 and 2015 at the University Children’s Hospital in Krakow. Children with tracheostomy, immune deficiency disorders, cystic fibrosis were excluded from the analysis. Parents of children older than 6 years were surveyed by an authorial questionnaire. They were asked about presence, type and severity of respiratory symptoms in their children in two-time points: in the first year after TM diagnosis and in the last year preceding the survey. They were requested to evaluate their children’s respiratory problems in relation to their general judgment and concern to health conditions. Construction of questions was various (yes/no questions, multiple choice questions, open questions, questions with graphical scale).

Out of 55 identified children with TM, 24 (44%) constituted the study group, 13 of whom were boys (54%). In these children, TM was diagnosed at the median age of 1.4 years [interquartile range (IQR): 0.5 - 6.9], the survey was conducted at the median age of 8 years [IQR: 6.9 - 8.9], thus the median follow-up period was 6.2 years [IQR: 3.3 - 6.8]. There was primary TM in 21 children and secondary TM – in 3 (2 children with vascular rings, 1 child after surgery of esophageal atresia with tracheoesophageal fistula). In 9 (36%) children, accompanying laryngo- and/or bronchomalacia was identified (laryngomalacia in 2, bronchomalacia in 6, both in 1).

It should be noted that the group of children for whom parents did not return the questionnaire (n = 31) was not significantly different from the study group in terms of: gender (16 (52%) boys, p = 0.85), the median age at the time of TM diagnosis (0.8 years [IQR: 0.1 - 4.8], p = 0.08), the ratio of primary to secondary TM (primary TM was in 26 children, secondary TM in 5 and between them: 3 children with vascular rings, 2 children after surgery of esophageal atresia with tracheoesophageal fistula, p = 0.7) and coexistence of laryngo- or bronchomalacia (laryngomalacia in 6, bronchomalacia in 11, p = 0.2).

Results:
Parents reported a high frequency of respiratory tract infections in the first year after TM diagnosis in 17 (71%) children and in 13 (54%) in the last year preceding the survey. In comparison to the first year after TM diagnosis, respiratory tract infections in the last year preceding the
survey were reported less frequent in 13 (54%) children and less severe in 9 (38%). The most common respiratory tract infections diagnosed by physicians were: viral wheezy bronchitis in 18 (75%) study children, recurrent acute bronchiolitis in 13 (54%), rhinosinusitis in 11 (46%) and non-resolving cough in 9 (38%) children. Regardless of TM, asthma diagnosis was additionally established in 7 (29%) children in whom anti-asthmatic treatment was prescribed (inhaled corticosteroids in 4, montelukast in 3).

Prominent postinfectious cough (lasting less than 4 weeks) was reported by parents of 15 (63%) children in the first year after TM diagnosis and still reported in 12 (50%) in the last year preceding the survey (p = 0.38). Moreover, exertional dyspnea (exercise intolerance) was observed by parents in 10 (42%) children and post-exercise cough in 9 (38%). On the other hand, 7 (29%) children could manage strenuous physical activity without any disturbing respiratory symptoms.

In 22 (92%) children, parents described cough during respiratory infection as barking or unusual in sound. However, in 13 (54%), they reported the same characteristics of cough in periods outside of infections.

Conclusion:
Clinical symptoms of TM do not completely resolve with child’s age. And until early school age, the most common persistent symptom is prominent postinfectious cough, which is characterized as barking or unusual in sound. In over one third of children with TM, exercise intolerance due to cough is also present. Respiratory tract infections diminish in frequency and severity with child age. Primary care physician should be aware of the evolution of TM symptoms to avoid unnecessary treatment.

We need further investigations in children with TM history in the area of pulmonary function testing, including considering exercise challenge testing.

D64 – Late Sequelae of Foreign Body Aspiration in the Bronchial Tree.

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Tracheobronchial foreign body aspiration is a common cause of pulmonary complications especially in toddlers. The delay in diagnosis is associated with increased incidence of complications with significant morbidity and mortality in the affected children.

We present a 3-year-old girl with chronic symptoms of daily spasmodic cough preceded by protracted pneumonia. The girl was non-atopic and had normal neurological development with negative family history. The parents reported that the child consumed whole nuts but emphatically declined any choking episode. The symptoms started a year ago prior to the admission in our department with roentgenological and clinical signs of infiltrative pneumonia in the right lower lobe. The CT-scan confirmed the clinical diagnosis without any suspicions for complications or foreign body aspiration. The aggressive and long-lasting antibiotic treatment led to temporary improvement followed by a two-month asymptomatic period. In the last nine months, the child had daily morning paroxysm of dry cough with expectoration of a low amount viscous mucoid sputum which was difficult to clear. The child's daily morning paroxysm of dry cough with expectoration of a low amount viscous mucoid sputum which was difficult to clear. The child

D58 – Behind an "Uncontrolled Asthma" – Clinical Case of a Late Diagnosed Congenital Anomaly.

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According to WHO, asthma is the most common chronic disease among children. Therefore it is not surprising that if a child presents with a chronic respiratory symptoms to a physician, the latter’s first thought and probably therapeutic management would be about asthma.

We present a case of an 11-year-old girl referred to our clinic after being treated for asthma without success for more than 6 years and labeled as "difficult to treat, uncontrolled asthma". From the past medical history, the following findings were notable: breast-milk aspiration at the age of 1 day (confirmed hyperventilation in the left lung), esophageal stricture surgically corrected at the age of 1 month, recurrent wheezing since infancy, food allergy and pet allergy. From the family history: elder brother with confirmed CF (the girl was born after pre-natal screening for CF and she was tested as carrier) and elder sister with epilepsy. At admission the notable findings were difference in both circumferences of the thorax (the left was larger than the right), diminished lung sounds on the right with crackles and rales. From the tests, we found negative bronchodilatatory response with predominant restriction on spirometry, right lung smaller in size compared to the left on X-ray of the lungs. CAT confirmed our suspected diagnosis – lung hypoplasia. The therapy was modified according the confirmed diagnosis and the asthma control medications were discontinued. For the following 6 months, no significant medical problems were noted, as well as no "asthma exacerbations".

We present the case as an illustration that not all "difficult to treat asthma" patients are really stricken with asthma. The correct diagnosis requires a comprehensive investigation—including an in-depth history and physical examination, pulmonary function studies, X-rays, laboratory studies, endoscopy, and specialized studies (e.g. allergy testing, methacholine challenge, 24-hour pH probe)
demonstrated exacerbated chronic pneumonia in the middle and lower right lobe, zones of hypoventilation and atelectasis, bronchiectasis and visible foreign body in the right intermediary bronchus. Rigid and flexible bronchoscopy was performed and four small particles of whole sunflower seeds were extracted. After the foreign body extraction, complex conservative treatment for non-CF bronchiectasis and chronic wet cough was provided. The child is still being followed.

Tracheobronchial foreign-body aspiration in children is still considered as one of the most important diagnostic and therapeutic challenges for physicians. In cases without any history of choking incident, the early diagnosis is a state of art. The consumption of whole nuts in toddlers is one of the leading causes of foreign body aspirations in our geographical region and is often a missing clue pointing to the correct diagnosis. The delay in foreign body extraction could lead to non-reversible lung damage with chronic purulent inflammation.


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Background: Communicating bronchopulmonary foregut malformations (CBPFM) are congenital anomalies characterized by a patent communication between a portion of the lung and the esophagus or stomach. The spectrum ranges from esophageal atresia with a communication between distal esophagus and the sequestered lung (Type I), immature lung with a mass that is formed from the distal esophagus (Type II), a connection between the sequestered lung lobe and the esophagus or stomach (Type III), and a communication between the esophagus and the bronchial system (Type IV). CBPFM are rare and the majority of cases present with symptoms in infancy. We report a case of CBPFM with an unusual presentation of a pulmonary cavitary lesion in late childhood.

Case Report: A 9-year-old boy presented with hemoptysis for 3 days and prolonged cough for 3 months. There was no fever or constitutional symptoms such as loss of weight, loss of appetite or night sweats. There was no pulmonary tuberculosis contact.

Antenatal history was significant for maternal pre-eclampsia with severe fetal intrauterine growth retardation. He was born at 35 weeks of gestation, with birth weight of 1530 grams. There were no respiratory symptoms in the neonatal period.

This child also had a history of asthma and allergic rhinitis. His first wheezing episode was when he was a few months old, with subsequent wheezing episodes a few times a year. His wheezing episodes were preceded by fever and upper respiratory tract infection symptoms, and responsive to bronchodilators. He was asymptomatic in between the wheezing episodes. He was started on inhaled corticosteroids (ICS) from the age of 2 to 3 years old, after which he did not return for further review. He presented again after an admission for asthma exacerbation at 7 years old. Spirometry demonstrated mild bronchodilator response and he was restarted on ICS. Although non-adherent with his ICS, his wheezing episodes were infrequent. His grandfather has asthma and allergic rhinitis, and smokes at home.

Physical examination, including the respiratory system, was unremarkable. There was no digital clubbing, lymphadenopathy or abdominal organomegaly. Chest X-ray revealed a right upper lobe cavitary lesion, raising the concern of pulmonary tuberculosis. Blood and sputum investigations for bacterial, fungal and mycobacterial infections were negative. Mantoux test and human immunodeficiency virus screen were negative. Hypochromic, microcytic anemia (hemoglobin 7.3 g/DL) was noted, secondary to iron deficiency (low serum iron and ferritin, elevated serum transferrin). Occult blood was positive in his stools. Blood coagulation profile was normal.

He was treated empirically for cavitary pneumonia with a course of antibiotics. The follow-up chest X-ray showed persistence of the cavitary lesion. Computed tomography (CT) of the thorax revealed the lesion to be an area of consolidation with dilated air spaces. Of note, the medial end of the branching airways in the cavitary pneumonia did not show a connection with the trachea or right bronchus, but was instead directed towards the esophagus. The esophagus also showed a tubular out-pouching at its right lateral aspect, suspicious of a bronchopulmonary malformation with a communication to the esophagus. A water-soluble contrast swallow was performed, demonstrating the contrast opacifying a cranially angulated tubular branching structure arising from the right anterior aspect of the esophagus, consistent with a Type III CBPFM.

The child underwent resection of the CBPFM. Pre-operative flexible bronchoscopy showed absence of the right upper lobe bronchus. Esophagogastroduodenoscopy demonstrated an acutely angulated fistula on the right side of the mid esophagus. Purulent fluid was noted on entry into the esophagus. Open thoracotomy confirmed a Type III CBPFM with esophageal communication. The CBPFM was resected with no complications. Histology confirmed findings of CBPFM with presence of pneumonia, micro-abcess formation and bronchiectasis, and no signs of malignancy.

The child recovered well after the surgery, with resolution of the chronic cough.

Discussion: A wide spectrum of diseases ranging from infections, malignancies, chronic systemic diseases and congenital malformations such as CBPFM may cause cavitary lesions in the lung. This case highlights the pitfall of relying on “classical” chest X-ray finding and history in making the correct diagnosis. Pulmonary tuberculosis and malignancies would be the top differentials given the history of prolonged cough, hemoptysis and cavitary lesion on chest X-ray, but the cause turned out to be a rare condition.

Careful and unbiased history taking is important. A retrospective review of the case notes showed that the initial complaint was hematemesis at the Emergency Department triage. Retrospective clarification with the parents revealed that the prolonged cough was temporally related to feeding. These history findings would fit better with CBPFM.

While the chest X-ray suggested a cavitary lesion, the CT thorax revealed that it was severe bronchiectasis of the sequestered upper
Tuberculosis (TB) is a mycobacterial infectious disease that has a wide range of manifestations. Anemia is a commonly seen manifestation in patients with TB, however hemolytic anemia is a rare cause of tuberculosis-associated anemia. We report 4 cases of autoimmune hemolytic anemia (AIHA) in association with childhood disseminated tuberculosis.

Methods: Retrospective study including 4 cases of disseminated tuberculosis associated with autoimmune hemolytic anemia.

Results: A total of 4 cases of disseminated tuberculosis (DT) associated AIHA were hospitalized in our department during the year 2017. They were respectively aged 10, 8, 12 years, and 6 months. Two children had a history of DT (one child), and of lymph node TB (one child) one year before hospitalization. The initial presentation included fever, asthenia and pallor in all cases. The different localizations of TB were: pulmonary (3 patients), pericardial (3 patients), abdominal (3 patients), lymph nodes (4 patients) and meningitis (2 patients).

The initial laboratory tests showed hemoglobin levels between 6.6 and 8 g/dl, with direct Coombs test positive for IgG in all cases indicating warm AIHA. All children were transfused at least once, and two patients needed recurrent transfusions.

AIHA responded well to specific antibiotic treatment for two patients, and corticosteroid therapy was not necessary. For the two patients who had tubercular meningitis, they were started on anti-TB along with corticosteroids simultaneously, and AIHA responded well to this course of treatment. Direct Coombs test turned negative in all patients.

Conclusion: The association of AIHA with tuberculosis is extremely rare. Only 16 cases of AIHA in association with TB have been reported in the literature, 3 of which were pediatric cases. It is important to recognize this complication given its severe implications, and moreover, TB should be considered as a cause of AIHA, especially in areas where the disease is common.
Congenital lung anomalies comprise a group of anatomical abnormalities of the respiratory tree including congenital cystic malformations, bronchopulmonary sequestrations, bronchogenic cyst, bronchial atresia and congenital lobar emphysema. In this present study, we aimed to determine the types of congenital lung diseases (CLD) and each anomaly is discussed in terms of underlying etiology, clinical presentation, and imaging characterization with emphasis on the most up-to-date research and treatment in the pediatric patient group attended in our hospital. The obstetric and other patient groups were evaluated for CLD existence by various imaging techniques between 2003 – 2017. Patients with any type of CLD were evaluated retrospectively. In this 14-year time period, 23 patients were diagnosed with CLD. Seven patients were diagnosed with ultrasonography only, 2 patients with ultrasonography and magnetic resonance imaging in the prenatal period. Ten patients were diagnosed with computed tomography in the postnatal period. The early diagnosis and treatment of CLD is of most importance given its fatal progression in the prenatal and postnatal period.

Ten of the patients were operated, 3 were operated during the neonatal period, 4 during infancy, and 3 between 1 and 13 years of age. None of the patients developed any complications. Postoperative follow-up duration ranged between 1 month and 5 years of age. Only 5 patients had accompanying diseases, which were VSD, hemivertebra, pectus excavatus, PFO, IgA deficiency and milk allergy. These anomalies can be detected with increasing frequency by pre-natal sonography, but may also present for the first time with symptoms in childhood or later life. We believe intrauterine diagnosis and follow-up are important in these patients.

**D169 – Keutel Syndrome with Partial IgA Deficiency: An Unusual Case in a Family with Keutel Syndrome.**

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**Introduction:**
Keutel syndrome (KS) is an autosomal recessive hereditary syndrome caused by homozygous mutations in the MGP gene encoding the Matrix Gla protein. It is characterized by abnormal cartilage ossification/calciﬁcation, peripheral pulmonary stenoses (PPS), brachytelephalangia and inner ear deafness and patients generally have respiratory problems.

Partial IgA deficiency has not been reported with KS previously.

We report a case with classic KS who also had partial IgA deficiency born in a family with six individuals with KS.

**Case:** The index case was a 15-year-old boy admitted to our clinic with chronic cough. He had brachytelephalangism, pulmonary stenosis, hypertension, mid facial retraction, muffled voice and moderate hearing loss. Tracheobronchial calciﬁcations were observed in chest X-ray and thorax computerized tomography. His mother, father, brother, sister and uncle had the same clinical and radiological features. All of the six individuals were diagnosed with KS after genetic analysis. His sister, a 12-year-old girl, also had recurrent sinusitis, otitis and pneumonia. Her immunological evaluation revealed partial IgA deﬁciency while peripheral lymphocyte subset analysis and lymphocyte activation test were normal. She was put on antibiotic prophylaxis. The infectious episodes decreased.

**Conclusion:** Although abnormal tracheobronchial cartilage calciﬁcation in Keutel syndrome can often cause asthma-like disease, however, recurrent upper and lower respiratory problems are not common. Therefore immune work-up should be performed in patients with KS.

D170 – Comparison of Clinical Presentation and Outcomes after Surgical Repair in Children with Aortic Arch Anomalies.

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**Background:** Aortic arch anomalies represent uncommon reasons for chronic respiratory and gastroesophageal symptoms in infants and young children. We sought to review our experience in infants and children with anatomically complete vascular rings, and compare clinical presentation and outcomes with those with double aortic arch (DAA) and right aortic arch with left ligamentum (RAA).

**Patients and methods:** Children with severe chronic respiratory and gastroesophageal symptoms and the above two aortic arch anomalies, detected by flexible bronchoscopy and chest CT scan, were evaluated. Age at symptom onset, at diagnosis and at surgery and symptoms frequency at diagnosis and after surgical correction were evaluated and compared in the two patient groups.

**Results:** Out of 35 children, 18 had a double aortic arc and 17 had a right aortic arch, 8 with right aortic and associated Kommerell diverticulum. In the whole population, the median age at symptom onset, at diagnosis and at surgery was 3.0 (3.0–36.0), 10.0 (1.0–72.0), and 36.0 (7.5–84.0) months old, respectively. Time intervals between age at symptom onset and diagnosis, age at symptom onset and surgery, and diagnosis and surgery were significantly lower in the DAA group than in the RAA group (p < 0.005, each comparison). In the whole population, the most prevalent manifestations at diagnosis were chronic cough (74%), dyspnea (37%), LRT infections (37%) and dysphagia/regurgitation (34%). Only the prevalence of dysphagia/regurgitation was different in the two groups, being higher in the DAA than in the RAA group (p < 0.05). Because of the severity of symptoms and the lack of response to medical treatment, all patients underwent surgical repair: a) resection of the lesser of the 2 aortic arches in DAA, and b) vascular ring release in RAA, with resection of the Kommerell diverticulum, when present, followed by transposition of the left subclavian artery to the left carotid artery. In addition, anterior aortopexy was performed in 4 patients. No major complications were
reported after surgical treatment in both groups, and morbidity was chiefly related to tracheomalacia or bronchomalacia, prolonging postoperative stay. At the follow-up evaluation [median: 10 (9–13) months] after surgery, a resolution of the gastroesophageal symptoms and an improvement in respiratory symptoms, as well as in patients with residual airway malacia, were reported in both groups.

Conclusion: In children with DAA and RAA, surgical treatment can be accomplished with low morbidity and essentially no mortality and good clinical outcomes.

D186 – Inflammatory Pseudotumor in Children.

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Introduction: Inflammatory lung pseudotumor is a rare benign neoplasm that usually manifests itself as a solitary pulmonary nodule. Endobronchial presentation is infrequent. Histologically, it is composed of lymphocytes, histiocytes, plasmocytes and myofibroblasts. The treatment of choice remains conservative surgery and one should always seek to obtain free margins due to the possibility of local recurrence. The objective of this work is to report a case of inflammatory pseudotumor as a cause of persistent pulmonary images in children.

Case report: P.O.A, 9 years old, schoolboy, male, from RJ, Brazil, hospitalized at the Municipal Jesus Hospital, RJ, for investigation of persistent pulmonary imaging in HTE and recurrent pneumonia. The mother reported 10 days of fever and cough, with a treatment of amoxicillin given on an outpatient basis, with no improvement. The condition evolved with abdominal pain and vomiting. No weight loss or decline in general state of health was noted. He reported two previous hospitalizations for pneumonia, the first of which was 6 months ago, with left pleural effusion. Four months later, he presented a new pneumonia episode in the same location. All required immunizations had been given. There was a family history of tuberculosis (mother and maternal grandfather). He lives with his mother and grandfather in a home with good hygiene and sanitation.

Physical examination: eutrophic, eupneic (FR = 24irpm), good perfusion, acyanotic, hypocortical (+/- 4). Bronchial Murmur reduced in the left hemithorax, without adventitious noises. The remainder of the examination went without notable issues. Amoxicillin with clavulinate and symptomatic treatment was initiated. Complementary examinations demonstrated: anemia (ht = 28.8% and hb = 9.9g/dl), leukocytosis with left shunt 22000 (with 15 sticks and 65 segmented), HSV = 28 mm, PCR = 122 mg/l, normal biochemistry and two negative tuberculin tests. Image exams: chest X-ray with hypotransparency in 2/3 lower HTE and left posterior opacity. Negative results for sputum smear microscopy were recorded. Chest tomography with contrast showed a left lung volume reduction, with discrete deviation of mediastinal structures and consolidation of heterogeneous impregnation of the left inferior lobe, compatible with mucoceles. Bronchoscopy: fragile endobronchial vegetative lesion in segment 6 of the left lower lobe bronchus. Biopsy: spindle cell proliferation, with low mitotic index, associated with mild lymphoplasmacytic inflammatory infiltrate, compatible with Inflammatory Pseudotumor. Favorable evolution, awaiting surgery.

Conclusion: In the case described, it is important to draw attention to the differential diagnosis of recurrent pneumonia cases of the same location. In the present case, due to the family history of tuberculosis, a high prevalence of the disease in Brazil, tuberculosis was investigated. However, the investigation was negative. Bronchoscopy examination with biopsy was decisive for the diagnosis. In young patients, those with well circumscribed lung mass and non-specific respiratory symptoms, the diagnosis of inflammatory pseudotumor (IPT) should be considered.


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Introduction: Neuroendocrine cell hyperplasia of infancy (NEHI) is a rare form of childhood interstitial lung disease of undefined etiology. Infants affected tend to present with dyspnea, tachypnea, persistent cough, failure to thrive and hypoxemia. It is a poorly understood disease. Dermatofibrosarcoma protubersans (DFSP) is a rare low-grade skin malignancy with high probability of recurrence. Its origin is not well established. It presents as a firm lesion, on which nodes may arise. The disease prevails between the second and fifth decades of life, but there are reports of presentation in childhood and at birth. DFSP has surgical treatment.

Objective: To report a simultaneous occurrence of two rare diseases: NEHI and DFSP.

Case Report: Male patient, 5 years old, with hospitalization at 7 months of age with history of respiratory distress since birth, sporadic dry cough, failure to thrive and need for nocturnal supplemental oxygen for a short period. During evaluation in Pediatric Pulmonology at 8 months of age, physical examination revealed a weight lower than 3rd percentile of the standard growth chart, absence of toxemia, increased anteroposterior diameter of the chest and pectus carinatum, tachyypnea at rest, with normal oxygen saturation in room air, and bibasilar crackles. Chest radiography showed lung hyperinflation. Chest HRCT scans showed ground-glass opacification in central regions of the middle lobe, the lingula, the lower lobes and upper lobes, and air trapping in the lower lobes and upper lobes (Images A and B). NEHI was confirmed based on clinical and tomographic findings.
During his follow-up, the child was referred to Dermatology to assess an abdominal macula with palpable subcutaneous nodules. His mother had noticed the lesion since birth. Histopathological and immunohistochemical examination with CD-34 antibody were consistent with DFSP (Images C and D). A tumor resection was performed. CT scans performed preoperatively did not show any metastases. Inguinal lymph node biopsy showed no signs of metastasis.

Discussion: It is important to report this case with an association of two rare pathologies to alert the possibility of a relationship between NEHI and the development of malignancy. A genetic basis is probably involved in these diseases due to the fact that both revealed clinical manifestations from birth.

**5. FETAL AND NEONATAL RESPIRATORY DISORDERS**

**E4 – Case Description of Development of Diaphragm Eventration in a Three-Month-Old Infant with Goldenhar Syndrome Associated with a Severe Laryngomalacia.**

**P-Y Chiu**

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**Introduction:**

Eventration of diaphragm is a congenital disorder in which all or part of the diaphragmatic muscle is replaced by fibroelastic tissue. The weakened diaphragm may be displaced into the thorax and compromise the patient’s breathing. Complete eventration almost invariably occurs on the left side and is rarely on the right side. We present a premature female infant whose right-side diaphragm eventration was first noted at one month of age, although the previous CXR films showed normal bilateral diaphragmatic levels.

**Case report:**

The 3-month-old female infant, with a history of symmetric SGA (birth weight 2400 g at 39 + 4 weeks of gestation) and multiple congenital anomalies, was referred to our hospital due to a deterioration of respiratory distress. She suffered from remarkable chest retractions at admission with a loud and high-pitch stridor sound. CXR showed increase infiltrations in bilateral lung field and a round-shape patch in the RLL area. Clinically, we provided support with nasal CPAP and chest physiotherapy, but the respiratory distress, stridor sound, and RLL patch persisted. Therefore, we arranged a bronchoscope study and noted a severe degree of laryngomalacia. We also examined the diaphragm movements with a fluoroscope, and found a remarkable eventration deformity of the right-side diaphragm at its posterior aspect by 3 rib spaces. (No paradoxical movement of the right diaphragm, and no herniation of abdominal contents into the thoracic cavity). Laser therapy to reconstruct the severe laryngomalacia and right diaphragm plication via abdominal approach to pull down the elevated diaphragm were undertaken. She improved in breathing and feeding and began to gain weight afterwards, and was discharged smoothly.

**Discussion:**

Although diaphragm eventration is a congenital defect, the case we present display a late development of right diaphragm eventration at one month of age. We suspect this to be a combination effect of both diaphragm muscle weakness of the right side and a high negative pleural pressure associated with the severe laryngomalacia. To date, we have not found any literature report mentioning this type of “late development of diaphragm eventration”.

**E12 – Few Symptoms, Almost Normal Lung Function and Good Exercise Capacity in Adolescents Born Moderately Preterm: Findings from a Community-Based Cohort**

*Vrijlandt E.1, Reijneveld S.2, Aris-Meijer J.3, Bos A.4*
Introduction:
Pulmonary outcomes of moderately-preterm children (MP) in adolescence are unknown. The aim of this study was to determine the long-term effects of moderately preterm birth on respiratory health: that is, respiratory symptoms, allergic symptoms, lung function and exercise capacity. This is the first study on this topic.

Methods: This was a prospective cohort study. Outcome variables were prevalence of respiratory symptoms determined by ISAAC Questionnaires, Lung function parameters such as FEV1, FVC, LCI and exercise test parameters such as maximal workload, maximal VO2, breathing frequency, ventilatory reserve, and BORG score.

Results: 71 children participated in the measurements: 37 MP and 34 full-term (FT). Both groups were comparable in age, height, weight and exercise activities, but differed in gestational age (MP 34 ± 1 weeks, FT 39 ± 0.9 weeks) and birth weight (MP 2442 ± 539 g, FT 3693 ± 393 g). Participants did not report many symptoms, but MP adolescents reported more (dry) cough (MP 22% vs. FT 3%, p = 0.016) and hayfever (MP 32% vs. FT 9%, p = 0.015) than FT. MP did not report more wheeze, dyspnea, asthma or eczema during the last twelve months. Most lung function measurements including LCI were within the normal range for both groups, except PEF (MP 86% pred vs. FT 93% pred, p = 0.05) and MEF75, (MP 86% vs. FT 96%, p = 0.06) which were at the lower limit of normal in MP. We observed no differences between the groups in maximal workload, maximal VO2, breathing frequency, ventilatory reserve, and BORG score. (See also table 1).

Conclusion: Moderate preterm birth has little impact on respiratory health in adolescence. Adolescents born MP report few symptoms (but more than FTs), have only mild lung function abnormalities compared to FTs and do not differ in the maximal exercise test and in physical activity level.

Table 1: patient characteristics, results of symptoms mentioned in questionnaire, main lung function and exercise test parameters. *No results are shown if participants did not answer a specific question.

<table>
<thead>
<tr>
<th></th>
<th>Preterm Born</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>37</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td><strong>Male/female</strong></td>
<td>21/16</td>
<td>18/16</td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight (gram) sd (range)</strong></td>
<td>2442 ± 539 (1345-3900)</td>
<td>3693 ± 393 (3070-4390)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gestational age (weeks) sd (range)</strong></td>
<td>34 ± 1 (32-35)</td>
<td>39 ± 0.9 (38-41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age (years) sd (range)</strong></td>
<td>13.6 ± 0.6 (12-14)</td>
<td>13.5 ± 0.5 (12-14)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Height (cm) sd (range)</strong></td>
<td>166.7 ± 7.6 (153-183)</td>
<td>167.7 ± 7.2 (152-182)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Weight (kg) sd (range)</strong></td>
<td>54.4 ± 12.4 (35-90)</td>
<td>54.9 ± 9.2 (38-72)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Current wheeze (%) Yes/ No</strong></td>
<td>3 (8)/30 (81)</td>
<td>2 (6)/30 (88)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Current asthma (%) Yes/ No</strong></td>
<td>5 (14)/31 (84)</td>
<td>1 (3)/27 (79)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Dry cough (%) Yes/ No</strong></td>
<td>8 (22)/24 (65)</td>
<td>1 (3)/29 (85)</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Current hayfever (%) Yes/ No</strong></td>
<td>12 (32)/23 (62)</td>
<td>3 (9)/29 (85)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>FVC % pred</strong></td>
<td>91 ± 12</td>
<td>94 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td><strong>FEV1 % pred</strong></td>
<td>92 ± 12</td>
<td>97 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td><strong>PEF % pred</strong></td>
<td>86 ± 14</td>
<td>93 ± 14</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>MEF 75 % pred</strong></td>
<td>86 ± 19</td>
<td>96 ± 18</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Heart rate max</strong></td>
<td>193 ± 9</td>
<td>192 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Load max (Watt)</strong></td>
<td>192 ± 34</td>
<td>200 ± 34</td>
<td>ns</td>
</tr>
<tr>
<td><strong>VE max (l/min)</strong></td>
<td>79 ± 22</td>
<td>85 ± 20</td>
<td>ns</td>
</tr>
<tr>
<td><strong>VO2 peak (ml/min/kg)</strong></td>
<td>43 ± 9</td>
<td>45 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td><strong>VO2 peak (ml/min)</strong></td>
<td>2317 ± 436</td>
<td>2401 ± 384</td>
<td>ns</td>
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</tbody>
</table>
Background: The increased and earlier use of prenatal ultrasound has facilitated the detection of congenital thoracic malformations (CTMs). Our Pediatric Pulmonology Institute follows an increasing number of patients with CTMs. We sought to examine if the increased number of CTM reflects true higher incidence or the result of an increased early use of prenatal ultrasound.

Objectives: To evaluate prenatal sonography detection rates of CTM, and to estimate changes in detection rates over a period of 16 years.


Results: A total of 34,716 prenatal US were performed at a median (range) gestational age of 15.4 (11.6–23.9) and 15.7 (12–33.6) weeks in 2001–2007 and 2007–2017, respectively. In 2001–2007, 12,016 prenatal ultrasound tests detected 19 CTMs, compared to 30 CTMs out of 22,700 tests in 2007–2017. Twenty CTMs, mainly congenital diaphragmatic hernia (CDH) and congenital pleural effusion (CPE), were associated with other fetal lesions. Thirteen congenital pulmonary airway malformations (CPAM) were detected; none of the latter was associated with other malformations. Detection rates did not change (1.58/1000 in 2001–2007 vs. 1.32/1000 in 2007–2017, p = 0.64).

Conclusions: CTMs were diagnosed earlier than previously reported. CDH and CPE tend to appear with multiple lesions and warrant further attention. The incidence rates remained stable when comparing the last decade to previous years. Thus, the increased referral of CTM can be attributed to an increase in prenatal screening studies performed, rather than a change in detection rates.

6. CYSTIC FIBROSIS

F94 – Trends in Early Lung Disease in Infants and Children with Cystic Fibrosis.

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Improvements in survival are continuously accruing in people with cystic fibrosis (CF) and appear to be evident in sequential birth cohorts [1]. As accumulating evidence points to the importance of early lung disease in CF, we hypothesized whether such improvements are also reflected in early lung disease outcomes of pulmonary inflammation, lung function and lung structure in infants and preschool children with CF.

Pulmonary inflammation and infection, lung function, lung structure and hospital admissions were retrospectively assessed in infants and preschool children with CF from 0 to 3 years old included in the AREST-CF early surveillance program. Details about this program and its protocols have been published previously [2–4]. In our cross-sectional analysis, we compared patients treated between 2006 and 2010 (cohort 1) with patients treated between 2011 and 2015 (cohort 2). We analyzed patients at time of routine annual BAL, which was: 3 months, 1 year and 3 years. We included a control non-CF group which had BAL-samples and inflammation data available from 2006–2015. In our longitudinal analysis, we tested all early lung disease outcomes and used multivariate mixed effects models with random intercepts to account for repeat visits. All models were adjusted for age and test center.

Infants and preschool children had similar age, gender and genotype between cohort 1 and 2 for the analyzed age-groups. The proportion of patients with detectable neutrophil elastase (NE) in BAL fluid was significantly lower in our most recent cohort: 15.5% (95% confidence interval [CI], 4.7% – 26.3%; p = 0.005) difference for patients aged 3 months (n = 176), 15.3% (95% CI 6.1% – 24.5%; p = 0.001) for patients aged 1 year (n = 229) and 13.9% (95% CI 1.2% – 26.6%; p = 0.034) for patients aged 3 years (n = 191). The proportion of patients with detectable NE in our control non-CF group showed no significant difference between the cohorts: 10% vs. 0% (95% CI –8.5% – 28.6%; p = 0.184) for cohort 1 and 2 respectively in 1-year-olds (n = 27) and 16.7% vs. 11.1% (95% CI –30.6% – 41.7%; p = 0.756) in 3-year-olds (n = 15). Lung structure and lung function outcomes showed no significant changes for the two CF cohorts. The results from the longitudinal analysis were similar to those reported for the cross-sectional inflammation data, showing reduced inflammation outcomes in cohort 2. Being in the second cohort was associated with lower proportions of NE for all ages combined, with an odds-ratio (OR) of 0.44.

This is the first study to identify secular changes in early pulmonary inflammation during the first years of life in CF. This finding suggests that enhanced focus and surveillance of early lung disease over the past decade manifests as improvements in early disease outcomes. Alternatively, these trends may be arising due to improvements in treatment following diagnosis occurring generally and unrelated to increased surveillance. The finding of reduced inflammation has the potential to be associated with longer-term improvements and even enhanced survival. We report that the development of early CT-identified bronchiectasis has not yet shown a significant downward trend and it is therefore necessary to further evaluate the potential for reducing inflammation early in life and the subsequent development of bronchiectasis later in life.

References:
3. Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C. Air trapping on chest CT is associated with worse ventilation distribution


**F148 – Relationship between the First Isolation of Pseudomonas Aeruginosa and the Preceding Viral Infection in Children with Cystic Fibrosis.**

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**Purpose of the study:** Identifying a pattern between the first isolation of Pseudomonas aeruginosa (PA) from oropharyngeal swabs and the preceding viral infection in children with Cystic Fibrosis (CF). Children in the first five years of life acquire several episodes of viral upper and lower respiratory tract infections and can end up presenting to hospital for supportive treatment.

**Methods:** This was a retrospective study at the Royal Manchester Children’s Hospital, a tertiary center for cystic fibrosis. Children with CF up to the age of 5 years were included in the study. Data was collected using an electronic database from January 2012 until December 2016. A diagnosis of a first PA isolation was confirmed with cough / oropharyngeal swabs. A diagnosis of a viral infection was confirmed with viral PCR on the nasopharyngeal aspirate.

**Results:** 56 children were included in the study, out of which 24 acquired an initial PA infection in the first 5 years of life. 8 out of these 24 children had a preceding viral infection in the last 8 months. 1 child had a preceding viral infection in the last 2 years. This might be due to undiagnosed viral infections that occurred closer to the initial PA infection date. The length of time from the last viral infection to the first acquisition of PA infection varied from a few days to a few months. No temporal relationship was established between both variables. Common viral isolates were Rhino virus and RSV.

**Conclusions:** 9/24 is a significant number (p < 0.05) of preceding positive viral infections before first PA isolations. Nevertheless, it is difficult to find a causal correlation between viral infections and the initial acquisition of PA in the early years of CF patients. The earlier the acquisition of PA infection, the more severe the CF-associated lung disease and the worse the prognosis. Small numbers in this study made it difficult to identify a particular viral infection leading to increased likelihood of PA acquisition.

**Discussion:** Antibody titers against certain PA antigens can diagnose PA pulmonary infections 6–12 months before the organism is isolated from oropharyngeal cultures. Therefore, performing such titers after every viral infection, may better demonstrate a correlation between viral infections and the initial PA acquisition. In addition, it might provide information on the type of virus that is most likely paving the way for PA colonization and lung damage before respiratory symptoms appear. There might be a role of vaccines against some of these viruses in children with cystic fibrosis.

**F160 – Galectin 9 Correlates with Lung Function Decline during Pulmonary Exacerbation in Cystic Fibrosis Pediatric Patients.**

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Galectin 9 belongs to the family of glycoproteins interacting with glycoconjugates present at the cell surface that regulate proliferation and apoptosis. In the previous studies, enhanced galectin 9 breakdown by neutrophil elastase was observed during neutrophilic inflammation of the airways. We hypothesized that galectin 9 expression in the airways and in peripheral blood may be altered upon pulmonary exacerbation in cystic fibrosis.

We analyzed 31 CF patients and 20 healthy controls aged 6–18 years. Patients were assessed twice: during pulmonary exacerbation (PE) and during stable period. In all patients, we assessed lung function with several tests (FEV1, FVC, TLC, RV, R5, X5, Rf, AX), CBC, CRP, microbiological analysis of sputum culture and radiological analysis. Severity of symptoms was assessed using Shwachman – Kulczycki score. Galectin 9 mRNA expression was analyzed using real-time PCR method and protein concentration in serum and sputum supernatants was measured using ELISA kit.

We observed that Galectin 9 protein concentration was significantly higher in CF patients during exacerbation (9.74 ng/ul) and stable period (9.57 ng/ul) than in healthy control subjects (6.55 ng/ul) (both p values below 0.001). Concentration of Gal-9 was significantly higher in sputum than in blood (p < 0.0001). No significant correlation was observed between Gal-9 concentration and disease severity (SK score). Gal-9 level correlated with disease progression (exacerbation within 3 months from inclusion in the study, changes in radiological picture, lung function); we observed a significant correlation with FVC decline (p = 0.025), but not with the other analyzed progression markers.

Galectin 9 seems to be related to airway inflammation in CF and may be a marker of lung function decline, mainly vital capacity reduction, and a marker of future exacerbations.

The work was supported by National Science Center, Poland, grant no. 2016/22/E/NZ5/00383.

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


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Introduction:
Hypophosphatasia is a rare genetic condition causing abnormal development of bones and teeth due to mutations in tissue non-specific alkaline phosphatase (ALP) gene leading to low activity of the enzyme. There are six main forms with varying severity. The most severe form is perinatal (autosomal recessive) causing markedly impaired bone mineralization, skeletal malformation, nephrocalcinosis, cranial synostosis, chest wall deformities, underdeveloped lungs and airway malacia.

This is a potentially fatal condition for which termination was often previously offered. However there have been significant developments of new enzyme therapies along with the introduction of airway support which means these children can now survive.

Method and Results:
We present four cases treated by the endocrine department with enzyme replacement therapy (ERT) in the form of asfotase alpha in conjunction with the Respiratory, ENT and Intensive care teams. These additional teams facilitated tracheostomy and long-term ventilation in order to support their underdeveloped lungs and malacic airways in the initial phases of treatment. The children were recruited as part of a clinical trial for the ERT with one of the patients administered the treatment on compassionate grounds. In three patients, the malacia completely resolved in the first 24 months of life and airway support has been discontinued. One child continues on long term ventilation due to other comorbidities. Asfotase alpha has been shown to improve skeletal mineralization and may have a direct impact on airway malacia although this has not been fully investigated. We do know that it at least indirectly aids by supporting growth of the child and therefore the airway caliber and cartilage rigidity also improves with age.

Conclusion:
As demonstrated, our case series shows that these children now have a good prognosis. With timely, sometimes antenatal diagnosis and a multidisciplinary approach, novel therapies and airway support via long term ventilation mean that these children have been able to survive infancy and have their respiratory support removed as they have grown.


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Objective: The purpose of this case report is to summarize the clinical characteristics, diagnostic workup and outcome of a patient affected by ROHHAD syndrome.

Method: We retrospectively reviewed the patient’s clinical history.

Introduction:
Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome is an infrequent but known clinical entity, and a possible cause of consulting to the pediatric pulmonology clinic as a sleep-related disorder. It is considered one of the nocturnal hypoventilation differentials; it might also present as a chronic progressive entity, such as the case present herein, highlighting the diagnostic challenge of this uncommon disease.

Case report: A 4-year-old boy was admitted to our clinic, due to mental status obtundation and acute respiratory failure, both hypercapnic and hypoxic, in the context of an acute pneumonia. He required noninvasive ventilatory support, and finally he was intubated and ventilated.

The patient is the child of non-consanguineous parents. No neurological or respiratory disease was previously reported in the family.

Early medical history was remarkable for early developmental motor delay and hypotonia. Febrile seizures and poor exercise tolerance were also reported. Due to central obesity and short stature with delayed bone age –2.5 SD, he has been followed by an endocrinologist.

On physical examination, the patient presented generalized hypotonia with shallow respiratory effort and weakness. General hyperreflexia, bilateral mydriasis, strabismus, and palpebral ptosis were also observed.

Brain and spinal cord MRI were normal. Nerve conduction velocities were normal (including phrenic nerve stimulation and pyridostigmine test). Central nervous system infection was ruled out, toxics in urine were excluded and autoimmunity screening was negative. Heart function was normal.

To remark, a hypernatremia and polyuria were found, which spontaneously resolved, with non-fulfilled criteria for diabetes insipidus. The patient’s respiratory failure improved by day 12, being extubated to non-invasive ventilation (NIV) at day 13, and finally weaned on day 17. During hospital admission, he presented again with mixed respiratory failure and was reintubated. He had to be weaned to NIV because of persistent hypoventilation with hypercapnia. Significant dysautonomia was noted with episodes of hypothermia, bilateral mydriasis, and cold sweating, but no heart rate abnormalities (Holter and echocardiogram were normal).

Lactate was mildly elevated (in the context of respiratory acidosis), and vitamin supplements were prescribed for suspected mitochondrial chain disorder. Subsequent studies (mitochondrial respiratory chain enzymatic activity and genetic analysis of mitochondrial DNA) were normal.

He was discharged two months later with home bilevel NIV. He presented serial episodes of acute respiratory decompensation 7, 12 and 13 months after first admission, with short inpatient stays.

At routine follow-up blood test at 7 years-old, a hypernatremia (159 mmol/l) was detected, without diabetes insipidus criteria, which resolved spontaneously. Holter monitoring was normal.
At age 9 he moved to Italy. He presented another respiratory failure associated with respiratory infection, needing higher levels of NIV support. Thermal dysregulation and abnormal sweating were noted, believed to be of central origin. A polysomnography was performed in the absence of NIV: it showed normal sleep architecture, without sleep disordered breathing, AHI of 3.2 and 5.2 in supine position, mean oxygen saturation 92%, lowest 86% only briefly. CO2 was not measured, sporadic central events (hypopneas and one apnea). Late onset congenital hypoventilation syndrome was suspected but PHOX2B gene mutation was negative. At this time, he was started on growth hormone (GH) because of GH deficiency and negative stimulation test. On follow-up, hypernatremia with elevated plasma osmolality and elevated urine osmolality was noted, responding to fluid intake, but causing nocturnal enuresis which was distressing for the patient. Further hormone studies revealed central hypothryroidism, lower limit cortisol that responded to ACTH stimulation, and hyperprolactinemia. Hypothalamic dysfunction was diagnosed. A control brain and spinal cord MRI were performed and resulted normal. He was therefore treated with hormone replacement therapy: somatropin (GH), desmopressin, levothyroxine, and hydrocortisone in stress situations.

At age 10, he returned to Barcelona. A polysomnography showed a rapid (within one hour) and marked oxygen desaturation, mean 89% and lowest 78% following an obstructive respiratory event, peak CO2 was 59 mmHg, the study was deemed positive for severe hypoxemia with hypercarbia and he continued on NIV with normalization on usual home pressures (IPAP 21, EPAP 8).

At age 12, he moved to Germany. He presented another hypercapnic respiratory failure in the context of pneumonia which required intubation for two weeks. During that episode, he presented severe central and obstructive apneas that resulted in severe bradycardia with AV nodal escape rhythm and asystolia. An abnormally low heart rate was detected and a Holter study showed alternating sinus rhythm with low auricular rhythm, compatible with dysautonomia.

Nowadays, at age 14, he is being followed in our clinic again. He keeps presenting episodes of daytime sleepiness, fatigue, speech problems, and crises of palpebral pseudoptosis. His spirometry is normal (FEV1 84%, FVC 80%, FEV1/FVC 90, MEF 130%), and he keeps using home NIV for daytime naps and nocturnal sleep time. Holter monitoring shows normal sinus rhythm alternating with low auricular rhythm. Since atypical narcolepsy with low hypocretin levels in cerebrospinal fluid have been described, a lumbar puncture was performed but hypocretin levels were normal. An oncology screening protocol for neural cell tumors was negative. His stature is 155 cm (p21), weight 58.3 kg (p78), body mass index is 24.2 (p98), Bone age corresponds with chronological age, Tanner puberty stage P1G1, with both testes being 3 ml. Since puberty is delayed, he is started on testosterone. He is on hormone replacement therapy with GH, hydrocortisone, desmopressin, and levothyroxine. Neuropsychological study reveals normal intelligence quotient, but difficulties in planning, immediate visual memory, holding attention, orthography, and affective symptoms with difficulties establishing relationships.

Conclusion: ROHHAAD syndrome is a clinical diagnosis, and lacks a known specific gene marker. It should be included in the differential diagnosis of hypoventilation syndromes (Congenital Central Hypoventilation Syndrome, Ondine’s syndrome, Prader Willi syndrome, neuromuscular diseases, structural or metabolic disorders) and especially suspected in patients with rapid-onset obesity or hypothalamic disorders. As has been published, not all the signs and symptoms appear at the same time and sleep-related breathing disorder can be the last one, hence endocrinologists should be aware of this feature and request sleep night studies regularly if ROHAAD syndrome is being suspected.

G159 – Non-Resolving Pneumonia: A Clinical Presentation of CVID.

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Introduction: Normal resolution of pneumonia is not easily defined and may vary depending upon the underlying cause and host response to pathogen. If clinical and radiographic indices are considered, it can be defined as slow resolution of radiographic infiltrates or clinical symptoms despite adequate antibiotic therapy. There are several components to successful resolution, including clinical improvement, radiographic resolution, and microbiological eradication. Improvement in vital parameters usually occurs in 2–3 days, and most patients note subjective improvement within 3–5 days of treatment. Radiographic resolution of pneumonia is estimated at 3–4 weeks and microbiological eradication is very variable and dependent on the infectious agent. If resolution of pneumonia is not appropriate, additional evaluation should be done. Considering the fact that non-resolving pneumonia is not a common condition, comorbid diseases and other host factors that can be associated with slower resolution of infiltrates should be investigated.

Case report: A 3.5-year-old boy was admitted to our hospital for diagnostic evaluation of recurrent pneumonias and bronchitis. Until the age of 3, he was already treated for 4 radiologically and clinically confirmed pneumonias, 3 of which were treated inpatient. By the time he was admitted for planned additional diagnostics, he had already had an adenoidectomy because of previously found adenoid hypertrophy. Allergy tests were conducted as well as 24-hour pH-metry of the esophagus with impedance and cardiac evaluation, which were all normal. Chest X-ray repeatedly showed bilateral infiltrations. Flexible bronchoscopy showed diffusely edematous bronchial mucosa with abundant turbid secretion, without any anatomical abnormalities or foreign bodies. Immunoelectrophoresis showed decreased levels of IgG (4.6 g/L) and IgM (0.3 g/L) with normal levels of IgA (0.7 g/L). Consequently, further immunological evaluation was performed. Lymphocyte flow cytometry immunophenotyping showed a decreased absolute number of CD4 + CD8+ (T helper cells), while other subtypes...
were in normal range. Flow cytometry immunophenotyping of B lymphocyte subpopulations showed a decreased level of plasmablasts and double negative B lymphocytes. By assessing antibodies to hepatitis B surface antigen (antiHbs) titer, which were undetectable, inadequate antibody response to vaccines was confirmed. Considering the results of the diagnostic evaluation, the diagnosis of common variable immunodeficiency (CVID) was made and intravenous immunoglobulin replacement therapy was started. Since then, the boy has been receiving his therapy in monthly intervals and no new pneumonias were verified.

**Conclusion:** We present CVID in a boy who was initially diagnosed with non-resolving pneumonia. In children with non-resolving pneumonia, detailed immunological evaluation should be performed.

**Key words:** CVID, non-resolving pneumonia, children

G162 – Immunodeficiency and Respiratory Papillomatosis Coexistence.

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We report on an association of immunodeficiency and juvenile laryngeal papillomatosis (JLP) in a pediatric-aged patient. A five-year-old female patient was referred from another center with suspicion of bronchiectasis. Her tomography was reported as fibrotic changes due to necrotic pneumonia. She had an atypical facial appearance, bilateral rales and rhonchi on her physical examination. It was learned that she had recurrent upper respiratory infection frequently. Because of the medical history of recurrent lung infections, immunological investigations and flexible bronchoscopy under general anesthesia were performed, showing vocal cords and upper 1/3 trachea were normal. Papillovesicular lesions were extending from the trachea towards the right main bronchus. Part of the lesions was bundle. Swab sample and lavage were tested for HPV-6 and HPV-11. In immunological tests, there was a decrease in the number of CD16 (+) and CD56 (+) T lymphocytes in peripheral blood lymphocytes (CD16/56: 2), as well as in immunoglobulins, particularly IgG3 (11 mg/dl). Intravenous immunoglobulin therapy was initiated and she has been investigated for immunodeficiency and genetics.

Juvenile Laryngeal Papillomatosis may present with cough, stridor, hoarseness or dysphagia, as well as pneumonia. Laryngeal papillomatosis is the most common benign laryngeal tumor in children. It is generally diagnosed before five years of age. It is thought to be caused by acquisition of the human papillomavirus (HPV) vertically during labor of an infected mother. Genetic variability related to the immune system may represent one of the most effective factors in the development of caused HPV. Due to localization and detection of immunodeficiency, we found this of interest.


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**Background:** In children with gastroesophageal reflux (GER), both acidic refluxes (AR) and weakly acidic refluxes (WAR) can induce respiratory symptoms (RS).

**Methods:** In order to characterize the airway inflammation in children with more prevalent WAR or AR (defined according to a ROC curve analysis), we performed a 3-year retrospective review of the medical records of patients who underwent fiberoptic bronchoscopy for difficult-to-treat chronic/recurrent respiratory symptoms and who had a positive multiple intraluminal esophageal impedance (pH/MII) monitoring.

**Results:** In the 13 WAR and 11 AR children, the number of cells recovered by bronchoalveolar lavage (BAL) was similar [0.78 (0.29–1.28) x 10^6 cells, and 1.05 (0.68–1.64) x 10^6 cells, respectively] (P = 0.22). A neutrophilic alveolitis and an elevated lipid-laden-macrophage (LLM) index were detected in both groups: no differences were found in neutrophils and lymphocyte percentages or in LLM index between WAR and AR children. In contrast, higher BAL epithelial cell proportions were seen in WAR [10.4 (7.25–23.45)], as compared to AR [2.5 (1.25–7.25)] children (P = 0.0045), suggesting greater airway damage in the former. In the whole patient population, a significant correlation was found between the proportions of BAL epithelial cells and the number of WAR events (r = 0.43; P < 0.037). Finally, elevated BAL concentrations of substance P and of pepsin were observed, not statistically different in the WAR and AR groups.

**Conclusions:** In this patient population, WAR events can be associated with a significant airway inflammation and injury that, because of the biochemical mechanisms involved, are likely not completely preventable and/or counteracted by anti-acid treatments.

G175 – Tracheal Stenosis in Patients with Mucopolysaccharidoses: A Case Report and Literature Review.

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**Introduction:** Mucopolysaccharidoses (MPS) are comprised of hereditary disorders of different lysosomal storage disorders, joined by errant degradation of glycosaminoglycans (GAGs). The main accumulated storage products include GAGs containing heparan, keratan, dermatan, and chondroitin sulfates. These substances are ubiquitous in connective tissues, hence the manifestations are broad and challenging, including upper and lower airways.
Case Description: A 5-year-old boy, with a history of MPS, indirect inguinal hernia, umbilical hernia. Four months before, he was admitted in a county hospital for surgery for indirect inguinal hernia repair. During anesthesia, asphyxia appeared. After emergency treatment, he recovered. The surgery was cancelled. He presented to the clinic department with a chief complaint of slight cough for 1-month history and fever for 2 days with no treatment. A chest X-ray film was obtained showing pneumonia. He was admitted to the pediatric pulmonology department. Physical examination revealed a short neck, growth delay and an abnormal facies. The three-dimensional reconstruction derived from the chest CT scans was performed, showing laryngotracheal stenosis. An electronic bronchofibroscopy was suggested for comprehensive evaluation of upper and lower airways and safe airway management. However, his parents rejected. Simultaneously, considering the risk of anesthesia, surgery was also rejected. Telephone follow-up was conducted every month. His parents noted that he had been in his usual state of health except for intermittent cough with difficult recovery.

Discussion: MPS, mainly MPS type I, II, and VI, are complicated by severe obstruction of the upper airways, tracheobronchial malacia, and/or stenosis of the lower airways resulting from the abnormal degradation of glycosaminoglycans which can result in severe, potentially fatal, difficulties during anesthetic procedures. Significant, multi-factorial airway compromise may occur already in early childhood. Airway obstructions may be localized in any of the physiological airways, from the nose to the peripheral bronchia. Insufficient understanding or insufficient emphasis will result in serious consequences, especially in grass-roots hospitals. Safe airway management necessitates a multidisciplinary approach and combined surgeries. 3D CT and bronchoscopy provide quantitative and morphological evaluation of airway stenosis, which is favorable to airway management in MPS children.

G195 – Diffuse Interstitial Lung Disease in an Infant with Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset in Infancy (SAVI).

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Introduction: Hereditary autoinflammatory disorders are an exceptionally rare cause of diffuse lung disease in children. This case report shows an infant with Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset in Infancy (SAVI), whose main features are systemic inflammation, cutaneous vasculopathy and pulmonary disease.

Objectives: To review the management and differential diagnosis of early-onset pulmonary disease, especially when associated with vasculitic skin rash and persistently high systemic inflammatory markers.

Case Report: A 6-month-old boy was admitted to evaluate failure to thrive after starting cow’s milk feeding at 4 months of age. On examination, he had tachypnea (75 breaths/min) and chest X-ray was abnormal with a diffuse interstitial pattern.

He was a full term newborn with no other previous history of interest apart from some choking on feedings and cough and cyanosis while crying. His mother, sister and grandmother were celiac. His mother suffered from diabetes and hypothyroidism.

He was then studied for sweat test, tuberculin skin test, echocardiography, abdominal ultrasound; all were normal. Erythrocyte sedimentation rate (ESR) was 71 mm/h, IgG was elevated (2100 mg/dl), and his chest CT showed diffuse ground-glass opacities and septal thickening. At bronchoalveolar lavage (BAL), 40% of lymphocytes and 20% of neutrophils were found. A 24-hour esophageal pH-metry showed severe gastroesophageal reflux, thus omeprazole was started.

A pulmonary biopsy at 8 months of age revealed septal widening with lymphocytic T and B aggregates in the interstitium and the airways.

Serum precipitating IgG antibodies to cow’s milk proteins were positive, and an initial tentative diagnosis of milk-induced hypersensitivity pulmonary disease was made. A cow’s milk-free diet was initiated, with an improvement in growth.

He was administered several boluses of high-dose steroids but no significant respiratory improvement was observed.

At the age of 14 months, he started having a macular rash on the cheeks and ear nodules that worsened with cold. During the following months, this rash extended and became purpuric-necrotic. A skin biopsy showed leukocytoclastic vasculitis and interface dermatitis. ESR was again high (64 mm/h) and transaminases were also increased (AST 110 IU/L, ALT 85 IU/L). Subsequent studies showed that some autoantibodies were positive: ANA (1/640), SMA (1/160), anticyrtric acid phosphatase, anti-β2-glycoprotein G 131 U/ml. A suspicion of systemic lupus erythematosus was made.

Different treatments were tried with partial improvement of cutaneous lesions and transaminases: azathioprine, anakinra, hydroxychloroquine, mycophenolate, tacrolimus, and monthly administration of immunoglobulins.

During the first 3 years, he had mild tachypnea that subsequently resolved, with normal SaO2 and normal auscultation. Digital clubbing appeared. Respiratory auscultation and SaO2 were always normal and he never needed oxygen supplementation.

When he was 5 years old, Tocilizumab was started. There was a clear improvement both clinically and blood test-wise, nonetheless this treatment had to be stopped due to muscular toxicity after 4 months.

At six years of age in 2014 (after publication of this new entity: N Engl J Med 2014;371:507–18), this patient was found to have a mutation at the TMEM173 gen and SAVI syndrome was diagnosed.

Since the age of 3, he has been asymptomatic from the respiratory standpoint having only some dyspnea on heavy exercise. Currently he...
is 9 years old and has been following treatment with Ruxolitinib for two years now. There seems to be a good clinical response but ESR is still increased (112 mm/h). Interstitial disease on chest X-rays and CT has persisted. Spirometry shows an alteration compatible with mild restriction [FVC 0.67L (69.49%), FEV1 0.65L/s (75.79%), FEV1/FVC 113%, MMEF 1.78L/s (154%)].

**Conclusion:** SAVI syndrome is an autoinflammatory disease caused by gain-of-function mutations in TMEM173. It provokes interferon dysregulation that leads to persistent systemic inflammation and signs of peripheral vascular inflammation that starts in the first months of life. We describe the pulmonary anatomo-pathological features in a child with this disease.

It is important to include interferonopathies such as SAVI syndrome in the differential diagnosis of a child with interstitial lung disease, especially when associated with persistently increased acute-phase reactant levels and progressive skin damage.

**8. NEUROMUSCULAR AND CHEST WALL DISEASES (INCLUDING SIDS)**

**H23 – Daily and Nocturnal Respiratory Monitoring in Patients with Duchenne Muscular Dystrophy and Left Ventricular Assistance Device.**


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**Background:** Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder, characterized by progressive skeletal muscle weakness, loss of ambulation, and death secondary to cardiac or respiratory failure. Forced vital capacity (FVC) is an effective marker of respiratory failure evolution. FVC peaks between ages 9 and 16 and then decreases by 5–10% per year until ventilatory support is required for survival. Noninvasive ventilation (NIV) is an effective treatment for respiratory failure. End-stage dilated cardiomyopathy (DCM) is a frequent finding in DMD patients, but they are rarely candidates for cardiac transplantation, thus left ventricular assist devices (LVAD) can be used as a bridge-to-transplantation or as a destination therapy. The aim of our study was to analyze the diurnal and nocturnal respiratory assessment, survival, death rate and causes of death in DMD patients with LVAD.

**Methods:** FVC, polysomnography (PSG), nocturnal pulsoximetry, mean transcutaneous carbon dioxide (tcCO2) pre- and post-LVAD, survival and causes of death were recorded.

**Results:** Six DMD patients aged 15 years ± 0.5 at LVAD placement were enrolled. Mean FVC pre-LVAD, calculated on 5 patients at 14 ± 0.4 years, was 41.5% of predicted values. 3 patients had PSG pre-LVAD with normal outcome. Pulsoximetry and tcCO2 pre-LVAD performed in 4 patients showed normal range. After 2 years, the mean FVC of all 6 patients was 18.6% (minimum 6% and maximum 44%). 4 patients were treated with nocturnal NIV, introduced 4 months after LVAD, 1 patient did not need ventilation support (FVC 44%). All ventilated patients showed normal PSG, nocturnal pulsoximetry and tcCO2. Three patients died at 18 ± 0.2 years, at an average distance of 2 ± 0.5 years since LVAD placement. Causes of death were respectively brain hemorrhage during anticoagulant treatment, septic shock from lung infection and iatrogenic tracheal rupture in another hospital. Three patients are alive at 2 ± 0.3 years after surgery.

**Conclusion:** LVAD does not affect the natural decline of respiratory function in DMD patients, whom require NIV to treat the ventilatory failure and to ensure their survival.

**H83 – An Unusual Cause of Atelectasis and Chronic Inflammation in the Lung.**

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**Case report:** A 4-year-old girl presented with fever and pneumonia of the right middle lobe (RML). She was treated with antibiotics (cefuroxim) with a rapid clinical improvement, but with a persistent atelectasis of the RML, despite physiotherapy.

A few weeks later, fever relapsed, demonstrating again pneumonia in the RML. A bronchoscopy was performed, showing mucus plugging in the RML, which was subsequently removed. No anatomical abnormalities were seen. Intrapulmonary percussion ventilation physiotherapy was started. However, a third episode of cough, wheezing and fever was seen after 2 weeks, showing again the same radiographic abnormalities. Biochemical markers of inflammation were low.

A second bronchoscopy showed inflamed mucosa with purulent secretions in the right bronchial tree, especially the right middle and upper lobe. A broncho-alveolar lavage revealed *H. influenzae* and *M. catarrhalis*. A CT scan was performed to exclude bronchiectasis. Instead, an important exostosis of the costal side of the anterolateral arch of the fourth right rib was observed, compressing a part of the RML. A 3D-reconstruction of the CT-images could precisely demonstrate the aspect of this shortened
and deformed rib. There was no history of thoracic trauma, suggesting this was a congenital rib malformation. To avoid further complications, endoscopic surgery for partial rib removal is planned in the near future.

**Conclusion:** Congenital rib malformations are a rare cause of compression atelectasis and subsequent chronic inflammation of the lung. This case emphasizes the importance of also considering extrapulmonary anatomical anomalies in cases of relapsing lung problems in the same lobe.


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**Introduction:** Patients with pectus excavatum (PE) frequently experience shortness of breath and aerobic capacity limitation. However, it is unclear whether there is an objective limitation of the cardiorespiratory system. In the 1990’s, a minimally invasive procedure for PE repair (Nuss procedure) was introduced. The aims of the study were to assess whether there are cardiorespiratory limitations in these children at rest or during exercise.

**Methods:** A retrospective study. Demographic parameters, clinical symptoms and PE severity of all children assessed for PE at the Schneider Children’s Medical Center of Israel were extracted and evaluated. Baseline pulmonary functions including volumes (total lung capacity-TLC, forced vital capacity-FVC and residual volume -RV, tidal volume-TV), flows (forced expiratory volume in one second-FEV1), maximal voluntary ventilation (MVV) and cardiopulmonary exercise testing were performed in all children.

**Results:** 140 children (111 boys, mean age 14.3 ± 3.6y) with PE were assessed in 2004 – 2015. Lung volumes at rest and flows were found to be normal with no difference between children with chest pain or exercise intolerance and asymptomatic patients. However, severe PE was associated with lower lung volumes and lower tidal volume at rest. Dead space volume (VD) at rest was found to be higher in the moderate-severe group (VD/VT- 42 ± 7% vs. 37 ± 4%; p = 0.004).

VO2max (O2 consumption at maximal exercise) was within normal range with large variability (94 + 24% predicted). The maximal load achieved was 85 ± 16% predicted and the ventilatory anaerobic threshold appeared earlier than expected (< 40% VO2max) in 53% of cases. Ventilatory breathing reserve was normal in most children (VE/ MVV- 66 ± 16%). O2 pulse was within normal range, but with large variability (O2 pulse- 86 ± 21% predicted). No significant heart rhythm abnormalities were observed.

VD/VT at maximal exercise was 31 ± 5% and tidal volume at maximal exercise was increased to 0.44 ± 0.09xvital capacity, both suggesting less efficient ventilation.

PE patients tended to be tachypneic at maximal exercise (respiratory rate- 118 ± 29% predicted).

Pulmonary equivalents at maximal exercise were elevated, suggesting less effective gas exchange in these patients.

Severe PE was associated with lower maximal load, with no difference in VO2 max and other ventilatory measurements.

Respiratory symptoms were associated with lower VO2max and higher respiratory equivalents compared to asymptomatic patients.

**Conclusions:** Children with PE have normal pulmonary functions at rest. However, they show maladaptation to exercise, suggesting compromised chest wall mechanics. These changes might have a role in the discomfort PE patients experience while exercising.

**H115 – Sleep Disordered Breathing in Children with Congenital Myasthenic Syndrome: Clinical Presentation and Management.**

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**Background:** Congenital myasthenic syndromes (CMS) are a heterogeneous group of inherited disorders affecting neuromuscular transmission, characterized by fatigable weakness that varies in severity, including respiratory failure. The presence and severity of sleep-disordered breathing (SDB) is poorly documented in this population.

**Objectives:** To describe the clinical presentation and the role of cardiorespiratory polygraphy (CRP), including capnography, in determining the presence of SDB and need for respiratory intervention, including ventilatory support.

**Methods:** Review of medical records and CRPs performed (Embla S4500; Software REMlogic ver 2) in all children with CMS referred to the Sleep Unit at Great Ormond Street Hospital (GOSH) 2003–2017.

**Results:** We identified 23 cases (15 girls) of CMS referred by neurologists to exclude SDB and/or hypoventilation. 4/23 children were established on ventilatory support before the referral and the CRP was performed on it. The median age at the first CRP was 8.3 years (range 0.3–16.8 years). The CRP was abnormal in 9/23 cases (39%). It showed six cases of SDB (five of them with hypventilation) with three of these showing symptoms of obstructive SDB at the time of referral. The other three cases had hypventilation without obstruction (all of whom were on Bi-Level pressure ventilation at the time on the study). We started positive pressure ventilatory support in 4 cases and optimized it in 4 patients (all of whom already established on ventilation).

**Conclusions:** The CRP with capnography has been useful in our study in order to determine the most appropriate time to commence long term ventilation or to optimize ventilation settings in patients already established on ventilatory support.
Although CRP may not predict a respiratory crisis in CMS, it is useful in the diagnosis of SDB even when there is a negative clinical history.

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

I29 – Are Pediatric Pulmonologists Adhering to Tobacco Prevention, Control, and Treatment Guidelines?

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Background: Tobacco use is the world’s leading preventable cause of death. Children exposed to second (SHSe) and third hand smoke (THSe) are at risk for smoke-related morbidity and have limited options for avoiding exposure. Tobacco smoke exposure increases the risk for sudden infant death syndrome, lower respiratory tract infections, middle ear disease, severe asthma, and slowed lung growth.1,2 Every possible effort should be made to decrease the burden of tobacco-related diseases.

The American Academy of Pediatrics (AAP)3, the American College of Chest Physicians (ACCP)4, and many international organizations have published guidelines to assist physicians in tobacco prevention, control, and treatment. The AAP recommends that pediatricians screen for tobacco smoke exposure at every visit and offer smoking parents counseling, treatment, and referral to quit lines5,6.

Unfortunately, pediatricians’ adherence to the guidelines remains low7,8,9. This may be attributed to lack of physician awareness and familiarity with published guidelines, as well as a lack of knowledge regarding available tools. It is essential that pediatric pulmonologists, who manage primarily diseases that are directly affected by SHSe, adhere to published guidelines.

Purpose of Study: Data regarding whether pediatric pulmonologists adhere to guidelines is lacking. We conducted a survey to assess pediatric pulmonologists’ practices with respect to SHSe screening, counseling, treatment, and referral to cessation services.

Methods: Survey questions included whether respondents used either the AAP Julius B. Richmond Center of Excellence Clinical Efforts Against Second Hand Smoke Exposure (CEASE) toolkit10 or the ACCP Smoking toolkit4. Participants were then queried whether they screened, counseled, treated, and referred caregivers to cessation services some of the time, always, or never. Confidence in smoking cessation promotion and willingness to attend a course if offered at a national meeting was asked. The questionnaire was posted on the pediatric pulmonology list server PedLung. PedLung reaches pediatric respiratory physicians around the globe. Survey Monkey was used to design and administer the questionnaire. Responses were anonymous. Results were compared with our previous data of general pediatricians7.

Results: Eighty responses were obtained. Only 1% stated they always use the AAP and ACCP clinical practice guidelines. Although respondents reported always screening (93%) and counseling (77%), only 27% referred caregivers. Zero percent responded to always prescribing nicotine replacement therapy (NRT), bupropion, and varenicline. Over 55% of respondents did not feel comfortable treating tobacco dependence in caregivers but only 41% responded that they would attend a cessation training course if offered at a national meeting.

Conclusion and Discussion: Compared to our cohort of general pediatricians, the rate of screening and counseling of the respondents was higher but the rate of treatment and referral was similar7. Despite the morbidity of SHSe in common pulmonary diseases like broncho-pulmonary dysplasia11, cystic fibrosis12, and asthma13, pediatric pulmonologists are not using available tools to assist smoking caregivers. It is imperative that physicians who treat children with respiratory disorders feel confident in treating caregivers’ tobacco dependence. A revision of pediatric pulmonary training programs’ curriculum is needed and should include tobacco cessation training to assure graduates are able to be actively involved and at the forefront of treating the tobacco epidemic.

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I57 - A Randomized Placebo-Controlled Trial on the Use of Arginine Supplementation for the Prevention of Nosocomial Infection in Critically Ill Patients.

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Introduction:

A. Rationale – Healthcare costs have increased through the years. Nosocomial infections increase morbidity, mortality, and cost and length of stay far beyond what is expected based on the underlying disease state. Hospital-acquired infections generate substantial economic burdens not just for the patient but for the hospital resources as well. It is important that we find other ways to prevent nosocomial infection from occurring in the first place.

B. Objective – The main objective of this study is to determine if supplementation with arginine will have an effect on nosocomial infection rate versus placebo in critically ill pediatric patients.

C. Significance of the Study – The efficacy of arginine supplementation to prevent nosocomial infection among critically ill children has not been well established. Various studies have yielded contradictory conclusions and are mostly among adults.

Methodology:

A. Study design – Randomized, double blind, placebo-controlled clinical study.

B. Study setting – This research was conducted in the UP Philippine General Hospital Pediatric Emergency Room, Pediatric wards and Pediatric Intensive Care Unit.

C. Study participants – Eligible patients aged 1-17 years old who are critically ill and necessitate ICU admission were enrolled in the study with the following inclusion criteria: critically ill patients who necessitate ICU admission who will be admitted for at least 3 days, able to tolerate oral feeding, no malabsorption diseases, have no immunodeficiency, have no congestive heart failure, are well nourished or are not severely malnourished, have no severe burns, have no nosocomial infection during 1st day of admission from other institution and are not allergic to arginine.

D. Statistical Analysis – Sample size was calculated using the Epi Info software Version 7 based on the assumption that the use of arginine will result in a 20% reduction in the occurrence of nosocomial infection. It was estimated using a nosocomial infection rate of 44% and a confidence interval of 90% with 80% power, we needed 22 children per group to show a 20% difference. To allow for study withdrawal, a total of 50 patients were recruited, 25 patients per arm. Data were analyzed using Epi Info Version 7 software. A T-test was performed comparing the difference between the means of 2 independent samples. In comparing the distribution of discrete variables between two groups, the chi-square test or Fisher’s exact test, when appropriate, was performed. Bartlett’s test for homogeneity was used to determine if 2 groups were the same or not. All tests were performed at a significance level at P < 0.05.

Results:

A total of 48 patients out of 50 predicted sample size of critically ill patients were recruited for the study. Of the 50 patients recruited, 48 were discharged. 1 was withdrawn from the control group from the study due to mortality and another was also withdrawn from the arginine group due to mortality. Both patients died from their primary disease of Pediatric Community Acquired Pneumonia D less than 48 hours after admission.

Baseline characteristics of both groups were not significantly different from each other. Age, height, weight, sex, chief complaint and primary diagnosis were statistically the same in both groups.

With regard to primary outcome of this research, it is interesting to note that none of the patients in the arginine group developed nosocomial infection as compared to the placebo group wherein 3 out of the 24 patients developed nosocomial infection, particularly a nosocomial pneumonia. This showed a Relative Risk Reduction of 100% and an Absolute Risk Reduction of 12.5% with number needed to treat at 8 patients. These are promising, however a result of 0.234 by Fisher’s Test means that there was no statistical difference between the two groups.

Statistical analysis also showed that there was no statistical difference in arginine levels between arginine group and the placebo group, before and after supplementation, using the Bartlett’s Test, P value 0.120 and 0.074 respectively and degrees of freedom 1. The lack of statistical significance may be attributed to the dose given to our patients. This was estimated using a nosocomial infection rate of 44% and a confidence interval of 90% with 80% power, we needed 22 children per group to show a 20% difference. To allow for study withdrawal, a total of 50 patients were recruited, 25 patients per arm. Data were analyzed using Epi Info Version 7 software. A T-test was performed comparing the difference between the means of 2 independent samples. In comparing the distribution of discrete variables between two groups, the chi-square test or Fisher’s exact test, when appropriate, was performed. Bartlett’s test for homogeneity was used to determine if 2 groups were the same or not. All tests were performed at a significance level at P < 0.05.

E. Conclusion/ Recommendation:

Arginine supplementation has no effect in the prevention of occurrence of nosocomial infection in patients that are critically ill.
However, further studies are highly recommended and use of a higher dose of arginine supplementation at 3000 grams –8000 grams is encouraged.

**Reflections:**
Even with the low dose of arginine that was used in this study, the results are promising. It is imperative that we perform further investigation using a high dose of arginine. Maybe with higher doses, the positive effect will be better demonstrated and a statistical difference will be achieved in the prevention of nosocomial infection.

### I85 – Exposure to Radiation by Imaging in Severe Asthmatic Children, Hospital Concepcion, Chile

**Soto Lavín S.1, Niklitschek Soto S.2, Fuentes G.3, Fuentes C.3, Cea R.4, Sepulveda J.4, Toledo C.4**

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**Introduction:** The effects of ionizing radiation occur up to a certain dose, the latter being measured in mSv. It can be instantaneous or occur over decades. Cancer has been identified as a possible manifestation years later. Human beings are exposed to ionization stemming from food, solar waves and certain equipment at home. It is measured as 3 mSv per year. This amount can increase with exposure to X-rays or computed tomography (CT). The age and type of irradiated tissue are important. Children are more sensitive and their life expectancy increases the possible long-term effects. Therefore, it is of vital importance to have the correct justification and optimization of these exams for diagnostic purposes in pediatrics.

**Material and Method:** 101 of 129 severe asthmatic children were included. They had been hospitalized in the Pediatric Service between October 2013 and July 2016. They were chosen because they were a well-identified group. Twenty-eight children were excluded due to incomplete data. Each child had a digital file in a program called Synapse. All files were reviewed with standard information on mSv from all X-rays and CT scans as a result of their complete medical files. All data were consolidated in Excel and statistical analysis with R-Project was performed.

**Results:** The age of patients varied between 5 and 14 years with a median of 6.2 years. \((Q_1 = 4.94, Q_3 = 8.4)\). A total of 430 radiological examinations were performed in the 101 patients corresponding to 95.8% for X-rays and 4.2% for CT scans. The most frequently irradiated areas were: 71.6% thorax, 12.5% limbs and 10% brain (skull). The standardized radiation received by patients in the period had a median of 0.56 mSv \((Q_1 = 0.28, Q_3 = 2.31)\). Eight patients exceeded 10 mSv. One of them reached the value of 29.55 mSv.

**Conclusions:** Severe asthmatic children who have been hospitalized in Concepcion registered in their medical history that they have received a quantity of radiation stemming mainly from chest X-rays for which the median is equal to 17% of annual base radiation. Some patients must be followed over time in order to look for certain secondary effects of radiation exposure.

### I96–Clinical Epidemiology Study on 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. It is one of the most common causes of community-acquired pneumonia (CAP). In recent years, epidemiological characteristics of *M. pneumoniae* infection have changed; in the last a few years macrolide-resistance *M. pneumoniae* strains have also become common. Further epidemiological studies are needed to find answers to this phenomenon.

**Methods**

1. Study population: patients seen at 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: after acquisition of pharyngeal throat swabs from subjects, we detected *M. pneumoniae*-DNA by real-time PCR method. For some objects, 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* strains: throat swab was inoculated to *M. pneumoniae* solid medium, and the isolation, liquid culture and PCR validation were carried out.
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 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, with 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 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 different parts 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 an isolation rate of 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. Thus, *M. pneumoniae* is an important pathogen of CAP. Age, severity of disease and multiple siblings were risk factors of *M. pneumoniae* infection. Macrolide-resistant strains were predominant at present. MLVA genotyping may be a molecular epidemiological method of predicting macrolide-resistant strains of *M. pneumoniae* infection.

**[Key words]** Mycoplasma pneumoniae; surveillance; PCR real-time; outbreak; MLVA; genotyping

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**I98 – Problematic Asthma: Risk Factors for the Persistence of Symptoms and Assessment of Features Distinguishing Difficult-to-Treat from Severe Asthma**

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**Introduction:** Problematic Asthma (PA) is characterized by an apparent resistance to therapy with high-dose inhaled corticosteroids (ICS) and other controllers. Although PA represents a small percentage of cases of asthma, the severity of its clinical manifestations affects the quality of life and has an economic impact on health care costs. In addition to confirming the diagnosis of asthma and excluding rare cases of steroid-resistant asthma, difficult-to-treat asthma (DA) must be distinguished from severe asthma (SA).

DA is the term that characterizes asthmatic patients with a poor control of symptoms depending on different factors: poor compliance, environmental triggers, presence of comorbidity.

SA is instead present when adequate control of asthma cannot be achieved by high-dose ICS and additional controllers (long-acting inhaled beta 2 agonists, montelukast and/or theophylline) or by oral corticosteroid treatment or is lost when the treatment is reduced.

The 2014 ATS / ERS Guidelines on SA underline the importance of discriminating the two entities for which the diagnostic and therapeutic approaches are different. During the first clinical evaluation, it is therefore important to identify severity markers that can suggest the diagnostic procedure to be undertaken.

**Methods:** We compared a group of patients with PA (n = 51) that were referred to our Broncopneumology clinic between November 2013 and October 2014 with a group of patients with well-controlled asthma (n = 62) that were referred in our clinic in 2015.

**Aim:** The aim of the study was to analyze the presence of risk factors determining the persistence of respiratory symptoms and identify anamnestic and instrumental data that allow an early identification of DA and SA, in order to optimize the therapy and direct more in-depth investigations only to those who warrant it.

**Results:** The PA group showed a significantly higher number of hospital admissions (p = 0.03), the presence of smoking parents (p = 0.03) and a compliance index in performing therapy statistically lower (p = 0.001).

The analysis of a subgroup of patients suffering from SA (n = 14) compared with the DA group (n = 37), showed that in the first group there was a higher frequency of hospital admissions (p = 0.04), the presence of food allergies from the first months of life (p = 0.0001) and a reduction in respiratory function, expressed by reduced values of Forced Expiratory Volume in 1 second (FEV1), at the limit of statistical significance (p = 0.06).

**Conclusions:** The identification of environmental, instrumental and anamnestic risk factors can reduce the number of more in-depth investigations that should be addressed to those cases that are warranted. By facilitating an early distinction between patients with DA and SA, therapy will be optimized, reducing the severity and recurrence of respiratory symptoms and consequently the need for additional medical care.

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**I193 – Subgroups of Children with Severe Asthma: Clustering Data Mining Analysis.**

**Soto Lavin S.1, Niklitschek Soto S.2, Pizarro J.3, Meza F.4, Silva N.4**

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**Introduction:** Asthma is a chronic respiratory manifestation including symptoms, genetic aspects, different response to treatment guidelines and is underdiagnosed in childhood. It produces missing days at school and a very expensive cost when it is undercontrolled. The prevalence is 15 to 18% and 4% will have severe asthma with a high risk of requiring emergency management and hospitalization. **Method:** Included were all children between 5 and 15 years old, hospitalized in the Pediatric Service at Hospital Regional Concepcion in Chile (HCRC) because of asthmatic crisis from October 2013 to July 2016. There were 129 children in this situation and their files were reviewed. Statistical analysis was made with clustering data mining. **Results:** The median value for age was 6 years old (5-15), with no differences regarding gender, cough 1 to 10 days (mean 2 days), fever 1 day or less (>38°C) (mean 1 day), 98% respiratory distress, initial O2 saturation 79 to 97% with digital equipment (mean 91%), white cell count from 7300 to 21790 (mean 13015), neutrophils from 46 to 96% (mean 88%), C-Reactive Protein (PCR) from 0.2 to 64 (normal < 10) (mean 11.35), days in pediatric service at hospital from 1 to 14 days (mean 3 days), oxygen requirement < 1 to 12 days (mean 2 days). The analysis separated all of these patients into 4 subgroups. Their characteristics were:
Subgroup I: This group was characterized by age 8 (Q1 = 6, Q3 = 10), urban address, without medical control, oxygen saturation 94% (Q1 = 92.25, Q3 = 95%) 3 days of cough, no fever, wheezing ++, no virus detectable with indirect immunofluorescence (Adenovirus, Influenzae, Respiratory syncytial virus, parainfluenzae, metapneumovirus), Polymerase Chain Reaction for mycoplasma negative, white cell count 28,000 (Q1 = 14500, Q3 = 39000), with 51% neutrophils (Q1 = 40.5, Q3 = 60), C-Reactive Protein (PCR) 21 (normal < 8) (Q1 = 4.1, Q3 = 38.15), need for oxygen 2 days (Q1 = 2, Q3 = 3), 4 days at hospital (Q1 = 3, Q3 = 5), chest X-rays without pneumonia or atelectasis, pleural reaction 4.75 (Q1 = 33.75, Q3 = 66.75), 25% used clarithromycin.

Subgroup II: This group came from different areas, mean age 6.5 years (Q1 = 6, Q3 = 8.75), most of them under medical supervision, cough 6 days (Q1 = 3, Q3 = 8), fever < than 1 day (Q1 = 0, Q3 = 1), respiratory distress, wheezing ++, white cell count 23500 (Q1 = 18500, Q3 = 51750), neutrophils 48% (Q1 = 32.75, Q3 = 63), PCR 19.6 (Q1 = 15.32, Q3 = 24.5), oxygen supply 3 days (Q1 = 2, Q3 = 5), 6 days at hospital, chest X-rays with hyperinsufflation.

Subgroup III: mean age 6 years (Q1 = 5, Q3 = 8), cough 6 days (Q1 = 3, Q3 = 6), without fever, with respiratory distress ++, wheezing ++, mean of oxygen saturation 92% (Q1 = 91, Q3 = 95), virus (–), mycoplasma (–), mean PCR 9.8 (Q1 = 3.7, Q3 = 17.8), oxygen supply 2 days (Q1 = 1, Q3 = 3), 4 days at hospital, without any abnormality at chest X-ray, mean of neutrophils 20%, mean of eosinophils 1440 (Q1 = 930, Q3 = 2560).

Subgroup IV: they came mainly from one area Chiguayante, age did not vary, most were under medical supervision with their family doctor, cough 4.5 days (Q1 = 3, Q3 = 6), without fever, without respiratory distress, oxygen saturation 92% (Q1 = 90, Q3 = 95), virus (–), mycoplasma (–), mean for neutrophils 52.5% (Q1 = 26.75, Q3 = 67.75), PCR 17.25 (Q1 = 7.3, Q3 = 32.33), oxygen supply 2 days (Q1 = 2, Q3 = 3), 4 days at hospital, azithromycin 40%, clarithromycin 30%, chest X-ray without pneumonia only inflammation signs, eosinophils 685 (Q1 = 495, Q3 = 1400).

Conclusion: Pediatric patients with severe asthma in crisis, hospitalized in Hospital de Concepcion from 2013 to 2016, presented different characteristics forming 4 subgroups according to clustering data mining analysis.

10. INVESTIGATION AND DIAGNOSTIC TESTS

J14 – Polysomnography is an Important Method for Diagnosing the Pediatric Sleep Problem: Experience of One Children’s Hospital

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Background: Sleep problems in children are relatively fewer than in adults, but cannot be overlooked. Polysomnography (PSG) is an important method to diagnose sleep problems in adults, which could also be used for children. Here we collect the PSG data, analyze and share the experiences of PSG in children.

Methods: The results of a PSG study in children (< 18 years old) with sleep problems from April 2015 to May 2017 at the China Medical University Children’s Hospital were collected and analyzed retrospectively.

Results: A total of 310 patients (209 males and 101 females) undergoing PSG were collected. The apnea & hypopnea index (AHI) of these 310 patients was as follows: the AHI was 0–5 in 221 patients, 5.1–10 in 45 patients; and over 10.1 in 43 patients.

The final diagnoses in 209 male patients were as follows: 109 obstructive (52.2%), 65 snoring (31.1 %), 34 limb movement sleep disorder (16.3%), 11 insomnias (5.2 %), 9 parasomnias (4.3%), 8 hypersomnias (3.8%), 7 other sleep-related breathing disorder (3.3%), 6 central (2.9%), 3 narcolepsy (1.4%), 3 sleep terrors (1.4%) and 1 sleep seizure 0.5%.

The final diagnoses in 101 female patients were as follows: 45 obstructive (44.6 %), 31 snoring (30.7%), 17 limb movement sleep disorder (16.8%), 13 other sleep-related breathing disorder (12.9%), 11 insomnias (5.3%), 7 central (3.3%), 7 parasomnias (3.3%), 4 hypersomnias (4.0%), 2 sleep seizure (0.9%) and 2 sleep terrors (0.9%).

Management of 270 patients (40 patients did not return to OPD for follow-up) was as follows: surgery with adenoidectomy and tonsillectomy in 19 patents (7.0%), continuous positive airway pressure (CPAP) in 2 patients (0.7%), and medical treatment or observation in 249 patients (92.2%).

Conclusion: The majority cause in children with sleep problems was obstructive sleep apnea syndrome (OSAS) (49.6%), while only 12.3% of pediatric OSAS underwent surgery in our study, which is underestimated since some children with OSAS underwent surgery without performing PSG. PSG may help detect significant sleep-related problems and application of PSG results is useful for therapeutic decisions in children; we suggest that children with sleep problems should accept a PSG study.

J19 – An Emerging Diagnostic and Therapeutic Procedure when Facing Lung Collapse in a Fontan Patient.

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A 10 y old female with a history of complex congenital heart disease and Fontan physiology, presented to our institution with severe respiratory distress. She was diagnosed with plastic bronchitis and was treated with manual casts removal by rigid bronchoscopy. Due to her unstable condition, she was subsequently treated with high pressure ventilation, nitric oxide and inotropes. To facilitate potential cast resolution, she was also treated with tracheal installation of TPA as well as Alteplase and budesonide inhalations; however, her condition did not improve. A wide variety of imaging including chest X-ray, echocardiogram and cardiac catheterization failed to identify the etiology of her presentation.
Plastic bronchitis (PB) is a rare clinical disease, characterized by formation of casts that obstruct the airways and lead to asphyxia [Itkin MG et al.]. Plastic bronchitis can be associated with many conditions such as Congenital Heart Disease with Fontan physiology, lymphatic abnormalities, Allergy, Asthma, Cystic Fibrosis, Allergic Bronchopulmonary Aspergillosis, Tuberculosis, Influenza A virus infection, pneumonia, Sickle Cell Disease, neoplastic infiltrates and Rheumatoid Arthritis. Many cases are still labeled as idiopathic [Rubin BK]. A new recent diagnostic technique, DCMRL—Dynamic Contrast Magnetic Resonance Lymphangiography, has identified abnormal anatomic lymphatic variants as the cause for cast formation in many previous idiopathic cases [Dori Y]. This diagnostic technique improved our understanding of PB and enabled a new optimal therapeutic approach. The reasons why this new procedure has become our first-choice imaging technique are summarized in table 1.

Our patient's DCMRL showed markedly abnormal intrathoracic lymphatics. The thoracic duct (TD) was dilated and tortuous, coursing towards the innominate vein on the left. In addition, there was abnormal perfusion affecting mostly the right lung with largely sparing of the left lung. There was also an additional left-sided accessory thoracic duct supplying retrograde flow to the lungs. Last, there was flow into a large left-sided supraclavicular and axillary network. Following the diagnostic procedure, selective embolization of the lymphatic collaterals from distal TD and selective embolization of the left sided duct were performed. After the procedures her symptoms resolved, and she was able to wean from her medications.

Figure 3 DCMRL showing bilateral ducts (arrows) and bilateral abnormal pulmonary and mediastinal perfusion (arrow heads).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>MRI</td>
<td>1) Good spatial and temporal resolution</td>
<td>Cannot be performed in patients with certain metal implants</td>
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<tr>
<td>Lymphangiography</td>
<td>2) Minimally invasive</td>
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<td></td>
<td>3) Water-soluble contrast agent</td>
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<td>4) Does not use ionizing radiation</td>
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<tr>
<td>Conventional Lymphangiography</td>
<td>1) High spatial resolution</td>
<td>1) Invasive</td>
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<tr>
<td></td>
<td>2) High temporal resolution</td>
<td>2) Require radiation</td>
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<td></td>
<td>3) uses oil contrast agent</td>
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<tr>
<td>Lymphoscintigraphy</td>
<td>1) Minimally invasive</td>
<td>Poor spatial resolution</td>
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<td>2) Good temporal resolutions</td>
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This case highlights the new approach to PB based on the role of lymphatic abnormalities in its etiology. DCMRL is a new technique to detect abnormal pulmonary lymphatics, and intervention radiology is a new way to treat it safely and successfully.

**J41 – Correlations of Six-minute Walk, Lung Clearance Index, and Quality of Life in Patients with Bronchiolitis Obliterans and Cystic Fibrosis.**

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**Background:** Lung Clearance Index (LCI) is a global measurement of ventilation inhomogeneity, and it was recently suggested as an outcome measure for clinical trials in Cystic Fibrosis (CF). However, the test requires expensive equipment and expertise. Six-minute walk test (6MWT) is a simple non-invasive and inexpensive tool to predict outcome in pulmonary hypertension. Recently it has been used in CF to evaluate candidates for lung transplantation and to predict exacerbations. Both LCI and 6MWT were found as useful markers in Bronchiolitis Obliterans (BO). In BO, 6MWT was found to have an important prognostic value and demonstrated a significant correlation with clinical scores and pulmonary function tests.

There are no studies in CF and post-infectious BO evaluating the correlation between the 6MWT results, LCI and Quality of Life (QOL). Such correlation may enable easy and non-expensive tests when resources are limited.

**Objective:** To evaluate the correlations between 6MWT, LCI, and quality of life in patients with BO and CF patients.

**Methods:** This is a prospective study including patients with BO and CF. Patients performed 6MWT, LCI test, spirometry, whole body plethysmography, MVV (minute ventilatory ventilation), and Quality of Life questionnaire – SF-36.

The primary outcome parameters were defined as 6MWT in both groups. Correlation of 6MWT to LCI, pulmonary function tests and
QOL questionnaires were sought. Demographics of the two groups were compared by unpaired t-test. Fisher’s exact test, Pearson, ch square test, and correlation were performed as needed.

Results: 19 CF (58% male, mean age 17.6 ± 11.2 years) and 17 BO patients (59% mean age 14.7 ± 5.9 years) were recruited. No statistically significant differences were found between CF and BO patients in pulmonary function tests, LCI, and SF-36 QOL questionnaire score.

The mean 6MWT score was similar in both groups, 461.8 ± 67.2 m compared to 502.6 ± 70 m in CF and BO patients respectively (p = 0.083).

While in CF patients, the 6-MWT score correlated negatively with percent predicted LCI (r = -0.519, p = 0.047), in our small BO group no such correlation was found.

No correlation was found between 6MWT scores and SF-36 QOL questionnaire score in both CF and BO patients.

Conclusion: 6MWT correlates with percent predicted LCI in CF patients, and may be helpful in evaluating CF patients in countries with limited resources and no available LCI. Further larger studies are needed to evaluate its role in other chronic diseases such as BO.

J46 – Lung Ultrasound in Bronchiolitis- Is it a Reliable Method?

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Background: Bronchiolitis is a diagnosis that is based on clinical criteria. The aim of the study is to evaluate the feasibility of ultrasound in the diagnosis of bronchiolitis.

Material and Methods: This was an observational study of 43 infants, 1 to 23 mo of age (average age 8.34), hospitalized in the “Alexandrovska” pediatric clinic with bronchiolitis for the period December 2016-March 2017. Ultrasound scans were performed in all patients in the first 24 hours of admission (linear transducer 5.3–11 MHz, with portable ultrasound) and chest X-ray in 35 children. Tests for respiratory viruses (PCR method) were undertaken in 32 patients.

Results: Lung ultrasound findings did not depend on the etiological agent, p = 0.5. Children without chest X-ray changes had normal ultrasound findings in 85% (11/13) of cases. In all patients with severe bronchiolitis, on oxygen treatment (8/8), ultrasonographic changes were recorded, p = 0.001. There was a correlation between the length of hospital stay and degree of ultrasound changes (p = 0.02). Lung ultrasound enabled the identification of infants with underlying radiological changes with a specificity of 84.6% (95% CI: 54.5–98.3%) and sensitivity of 80% (95% CI: 59.3–93, 1%), a positive predictive value of 90.9% (95% CI: 72.2–97.1%) and a negative predictive value of 68.7 (95% CI: 49.2–83.3%).

Conclusions: Thoracic ultrasonography is a reliable tool and alternative to chest X-ray for infants with bronchiolitis, with some advantages: no risk of irradiation and the possibility of dynamic follow-up.

Keywords: lung ultrasound, bronchiolitis, infants.


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Background: Pulmonary hypertension (PH) is a progressive pulmonary vascular disorder characterized by increased pulmonary vascular resistance and pulmonary arteriolar remodeling. Wnt signaling controls cellular functions during embryonic development and the injury of acquired tissues. β-catenin is a central mediator of the Wnt signaling pathway and controls the transcription of genes during both normal and malignant development. Recently, a gene expression analysis of pulmonary arterial resistance vessels revealed differentially regulated canonical and noncanonical WNT genes in PAH.

Aim: In this study, we attempted to investigate the altered expression of Wnt and Wnt-related proteins of lungs of rats with PH secondary to left ventricular dysfunction by aortic banding, so-called group II PH.

Materials and methods: Utilizing the PH rat model created by ascending aortic banding for 42 days (6 weeks), we studied altered expressions of β-catenin, mRNA and protein expression of canonical Wnt ligands (Wnt3a, Wnt 7a) and non-canonical Wnt ligands (Wnt5a and Wnt11) in lungs of 6 week-aorta-banded rats compared to sham-operated rats. In addition, the immunohistological staining of β-catenin of lungs was also performed in both groups.

Results: In lungs of aorta-banded rats, there were significantly increased protein expressions of Wnt5a, Wnt11 and Wnt5a, and significantly decreased protein expression of β-catenin. In contrast, there were increased mRNA expressions of Wnt2, FZD5 and Ltb, and decreased mRNA expressions of Wnt3a, Wnt7a, Wif, sFRP1, sFRP2. Very interestingly, there was decreased β-catenin staining of endothelium in lungs of aorta-banded rats.

Discussion: In group II PH secondary to left ventricular dysfunction, the development of PH is closely related to the non-canonical Wnt pathway predominantly, rather than the canonical Wnt pathway. The results are compatible with the up-regulated Rho expression of lungs of aorta-banded rats in our previous study.

J114 – Is It Possible to Predict Airway Basement Membrane Thickness by Non-invasive Parameters?

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Airway remodeling occurs in various chronic respiratory diseases. Basement membrane (BM) thickening is one of the most apparent signs of such changes. It can be found in different forms of chronic bronchitis and can be easily and objectively quantified. This makes it a convenient surrogate parameter of airway wall remodeling. However its clinical
use is hampered by an invasive procedure required to obtain a sample of endobronchial biopsy. Consequently the possibility to predict remodeling by non-invasive parameters would be of a great clinical value in the management of patients with chronic respiratory disease. In our work, we aimed to study the relationship between BM thickness and anthropometrical and/or functional parameters.

Between January 2014 and December 2016, we prospectively enrolled 47 patients with chronic bronchitis (CB group) including those with cystic fibrosis, primary ciliary dyskinesia and other forms of chronic bronchitis (e.g. related to primary immunodeficiency), who underwent clinically indicated flexible bronchoscopy. Additionally 20 controls (Co group) – that is, patients with bronchoscopy for acute non-inflammatory conditions (foreign body aspiration, stridor) and no chronic respiratory pathology – were enrolled. The age of our patients ranged from 1 to 18 years (median 8.6 years). At first, all patients underwent lung function testing using nitrogen multiple breath washout test (N2-MBW) and tidal breath analysis. All relevant international recommendations were adhered to. Patients older than 4 years performed the testing in full consciousness and with active cooperation. In younger children, lung function testing was performed during tidal breathing under intravenous anesthesia (propofol) immediately before the bronchoscopy. Flexible bronchoscopy with endobronchial forceps biopsy was performed in the same session after addition of inhaled anesthesia (sevoflurane). The samples were processed for light microscopy and stained by hematoxylin-eosin. BM width was measured by one investigator (VK) using computer image analysis software (NIS Elements). The two study groups were compared using the Welch t test. The relationship between non-invasive parameters (anthropometrical and functional) and BM width was analyzed in the whole study group (CB + Co group). At first, Spearmen’s correlation coefficient was used to evaluate the relationship of each single non-invasive parameter with BM width. Next, more advanced approaches (principal component analysis, least angle regression method) enabling analysis of multiple predictors simultaneously were employed to evaluate the possibility of making BM width predictions using more non-invasive parameters at the same time.

There were no differences in age and z-scores relative to weight, height or BMI of patients enrolled in the CB and Co groups. Complete lung function and morphological data were available in 43 patients (64.2%). Patients in the CB group had significantly greater BM width (ΔBM width = 1.13 μm, P < 0.001) and worse lung function compared to controls. When analyzed separately, none of the anthropometrical parameters alone (weight, height, BMI and their z-scores) correlated significantly with BM width. When more anthropometrical parameters were taken into account simultaneously, a small but significant part of BM width variability (R2 = 0.111, p = 0.036) could be explained. Only a few lung function parameters individually were significantly correlated with BM width: LCl2.5 = r = 0.42, p = 0.008; Scond = r = 0.51, p < 0.001 and tPTEF/TE = r = −0.39, p = 0.013. Simultaneous analysis of more functional parameters increased the predictive power and allowed to explain 30.8% of BM width variability (p = 0.003). If anthropometrical and functional parameters were combined together, the predictive power of such model was clearly increased (R2 = 0.621, P < 0.001).

Our work focused on BM width, as a sign of airway wall remodeling. In a wide age spectrum group of patients, we investigated its relationship to anthropometrical and lung function parameters, which may be its determinants (measured non-invasively). Our data showed a clear correlation of airway wall remodeling with lung function and anthropometrical parameters. This finding is in contrast with several previous studies. Hilliard et al (Thorax, 2007) found significant relationship between lung function (measured by spirometry) and inflammation occurring in airway lumen (assessed by bronchoalveolar lavage fluid). On the other hand, changes occurring in airway wall (BM width) were not reflected by spirometry. Contrarily to this, we proved a significant relationship between ventilation inhomogeneity (as assessed by N2-MBW) and BM width. This discrepancy may be partly explained by the higher sensitivity of N2-MBW to the early stages of chronic respiratory diseases. Similarly, previous works addressing anthropometrical parameters as determinants of BM width did not reveal any relationship. Our approach, however, studied additional anthropometrical parameters as BM width determinants simultaneously, and indeed we were able to explain a small but significant part of BM width variability in this way. We hypothesize that this relationship is too complex to be described by just one determinant. Consequently, we combined both anthropometrical and functional parameters in one predictive model which further increased the predictive power of this model for BM width variability – reaching 62.1%. In our opinion, such predictive power is sufficiently high to be considered clinically relevant. However there still remains significant variability to be explained by other parameters (e.g. diagnosis itself). This finding requires further research before it can be implemented into routine care of patients with chronic bronchitis.

**J116 – Impulse Oscillometry at Preschool Age Is a Strong Predictor of Lung Function by Flow-Volume Spirometry in Adolescence.**

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**Background:** The transition from early childhood wheezing to persistent asthma is linked to lung function impairment over time. Little is known how the methods used to study lung function at different ages correlate longitudinally.

**Methods:** Sixty-four children with a history of hospitalization for bronchiolitis before six months of age were prospectively studied with impulse oscillometry (IOS) at the mean age of 6.3 years and these preschool IOS results were compared with flow-volume spirometry (FVS) measurements at mean age of 11.4 years.
Results: The baseline respiratory system resistance at 5 Hz (Rrs5) showed a modest statistically significant correlation with all baseline FVS parameters except FVC. The post-bronchodilator (post-BD) Rrs5 showed a modest statistically significant correlation with post-BD FEV1 and FEV1/FVC. The bronchodilator-induced increase in Rrs5 showed a modest statistically significant correlation with baseline and post-BD FVS parameters except post-BD FEV1/FVC, respectively, and post-BD Xrs5 showed even a strong correlation with post-BD FVC (p = 0.61) and post-BD FEV1 (p = 0.59). In adjusted linear regression, preschool Xrs5 remained as a statistically significant independent predictor of FVS parameters in adolescence; the one-unit decrease in the Z-score of preschool post-BD Xrs5 predicted 9.6% lower post-BD FEV1, 9.3% lower post-BD FVC and 9.7% lower post-BD MEF50 when expressed as %predicted parameters.

Conclusion: Persistent post-BD small airway impairment in children with a history of bronchiolitis detected with IOS at preschool age predicted FVS results measured in early adolescence.

References:

J138 – Clinical Value of Functional Parameters in the Determination of the Genesis of Prolonged and Chronic Children’s Cough

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Aim: to investigate the clinical significance of the functional parameters of the microcirculation, vegetative nervous (VNS) and respiratory systems for the differential diagnosis in children with prolonged and chronic cough.

Patients and Methods: 272 children aged from 2 to 17 years with cough during more than 4 weeks were examined. All patients were divided into six groups (Gr) according to diseases: 68 patients with postnasal drip syndrome (PNDS) of infectious genesis (Gr1); 39 patients with allergic rhinitis (AR) (Gr2); 12 patients with lower respiratory tract infection without wheezing (Gr3); 20 patients with acute wheezing (Gr4); 20 patients with postinfectious cough (PIC) (Gr5); 78 patients with mild persistent bronchial asthma (BA) in exacerbation and incomplete remission (Gr6). Catamnesis lasted from 6 to 17 months. The control Gr (C) included 60 healthy children.

From this study were excluded patients with a diagnosis of chronic bronchitis (n = 13); whooping cough (n = 13); psychogenic and...
neurogenic cough (n = 4); gastroesophageal reflux disease (n = 2); foreign body airway obstruction (n = 1); epilepsy (n = 1). All patients underwent history, examination; computer capillaroscopy of the nail bed; evaluation of heart rate variability (HRV) (*Cardiovizor-6S*, "MCS", Russia) and computerized bronchophonography (MEI, Russia).

Results: The morphological changes in the capillaries had a similar directionality in all children with a cough during more than 4 weeks. But patients with cough due to allergic diseases of the respiratory tract (Gr2, 6) were characterized by significant deformation of the arterial part of the capillaries and an increase in the length of the perivascular areas (L) compared with children with infectious genesis of cough (Gr1,3,4,5), in whom changes were often observed in the parameters of the venous part of the capillaries (P < 0.05). A more pronounced imbalance of autonomic regulation was found in patients with AR (Gr2) and BA (Gr6). A more pronounced increase of L was observed in children with BA under 7 years old compared with patients older than 7 years (P < 0.05).

Gr2 and Gr6 were characterized by the prevalence of parasympathetic activity (at HRV analysis): increase in RMSSD, pNN50% and SDNN compared with Gr1,3,4,5, C (P < 0.05). A more pronounced imbalance of autonomic regulation was found in patients with BA (Gr6): increase in VLF and reduction in HF, LF compared with Gr2 (P < 0.05).

HRV parameters of Gr1,3,4,5 had a similar orientation as the predominance tone of the sympathetic (SNS): reduction in RMSSD, pNN50%, HF and increase in VLF and LF compared with Gr2,6, C (P < 0.05). The Gr5 was characterized by more pronounced activity of the SNS (P < 0.05). This may indicate a high degree of tension in the adaptive mechanisms of the VNS in children with PIC (Gr5).

Patients with acute wheezing (Gr4) and BA (Gr6) showed a higher level of the coefficient of acoustic component of the work of breathing in the high frequency zone (5.0–12.6 kHz) (ϕ3), compared with Gr1,2,3,5,C (P < 0.05). Test with standard dose of salbutamol was positive in both Gr, although a more pronounced decrease in ϕ3 (26–72%) was typical for BA (Gr6) (P < 0.01).

Based on the data obtained, the clinical and functional parameters of the microcirculation and VNS for differential diagnosis of the allergic and infectious genesis of coughs during more than 4 weeks in patients with PNDS were determined: a rise in body temperature above 37.5°C; increased cough during exercise; a level of total IgE in blood serum; L and the coefficient of tortuosity of the arterial part of the capillaries; SDNN. As additional criteria for diagnosing BA in children with a cough during more than 4 weeks, the following clinical and functional parameters are proposed: degree of the allergenic condition of the patient; L; the unevenness of the caliber of capillaries; HF; LF; ϕ3.

Conclusion: These results showed that the functional parameters of the microcirculation, VNS and respiratory system can be used as additional criteria for the differential diagnosis of the allergic or infectious genesis of prolonged and chronic cough in children. It can be important in relation to early diagnostics of BA in children.
The correlation between SpHb and sampled Hb levels is good. SpHb device appeared feasible, even if the device was used for neonates or infants below 3 kg at a wide range of Hb levels. By attaching this SpHb device in neonates or infants below 3 kg, it is possible to detect anemia faster and to reduce unnecessary blood tests. Furthermore, pulmonary edema and circulation failure caused by excess blood transfusion may be prevented. Erythropoietin therapy is given to anemia of prematurity below Hb 12g/dL. In infants weighing less than 3 kg, SpHb tended to exhibit higher values than sampled Hb when the latter levels were below almost 13.0 g/dL. Therefore SpHb could underestimate an anemia. When SpHb was measured on a lower extremity and the sampled blood Hb was taken from an upper extremity, there was almost no difference in these values. From this fact, it is considered that the measurement location can be anywhere. It is more likely that the bioengineering factors in measurement play a significant role in this data skewing, although we do not currently have access to the information needed.

Conclusion: Application of a prototype SpHb device appeared feasible for neonates or infants below 3 kg at a wide range of Hb levels. It may be possible to measure pulmonary and hemodynamic conditions without collection of blood at the same time with a noninvasive method. However, at this time, with the SpHb device, there is still room for improving the accuracy when levels were below almost 13.0 g/dL. Data obtained in this study should be used as a reference for future improvement.

**J168 – Radiation Doses from Pediatric Chest Computed Tomography Scans Performed at a Tertiary Care Hospital.**

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The purpose of this study was to evaluate the radiation doses to which children from 0 to <18 years of age undergoing chest computed tomography (CT) examinations in the radiology department of a tertiary care hospital are being exposed.

We performed a retrospective study of all consecutive pediatric patients (age <18 years) who underwent a CT of the chest between October 2015 and October 2016. Only inspiratory chest CTs with a single acquisition (single phase) and without contrast-media injection were included. Data on radiation exposure (tube current, tube voltage, CT dose volume [CTDI], dose length product [DLP] and size-specific dose estimate [SSDE]), as well as demographic and clinical data, were recorded from 193 chest CTs (median age: 12.6 years [IQR: 9.2 – 15.5], 107 males [55%]) from which the dose estimates were calculated using a 32 cm phantom. Size-specific dose estimates (SSDE) were generated for each patient and results were compared to CTDI. Patients were grouped into 5 categories based on mean effective diameter of the chest (square-root of the anteroposterior times latero-lateral chest diameters), as follows: group 1: 15 cm; group 2: 15 – 19 cm; group 3: 20 – 24 cm; group 4: 25 – 29 cm, and group 5: >30 cm. Factors associated with higher radiation doses were assessed using multiple linear regression analysis. Statistical analyses were performed using Statistical Package for Social Sciences, version 20.0. This study was approved by the local research ethics committee.

Discussion: The correlation between SpHb and sampled Hb levels is good. SpHb device appeared feasible, even if the device was used for neonates or infants below 3 kg at a wide range of Hb levels. By attaching this SpHb device in neonates or infants below 3 kg, it is possible to detect anemia faster and to reduce unnecessary blood tests. Furthermore, pulmonary edema and circulation failure caused by excess blood transfusion may be prevented. Erythropoietin therapy is given to anemia of prematurity below Hb 12g/dL. In infants weighing less than 3 kg, SpHb tended to exhibit higher values than sampled Hb when the latter levels were below almost 13.0 g/dL. Therefore SpHb could underestimate an anemia. When SpHb was measured on a lower extremity and the sampled blood Hb was taken from an upper extremity, there was almost no difference in these values. From this fact, it is considered that the measurement location can be anywhere. It is more likely that the bioengineering factors in measurement play a significant role in this data skewing, although we do not currently have access to the information needed.

Conclusion: Application of a prototype SpHb device appeared feasible for neonates or infants below 3 kg at a wide range of Hb levels. It may be possible to measure pulmonary and hemodynamic conditions without collection of blood at the same time with a noninvasive method. However, at this time, with the SpHb device, there is still room for improving the accuracy when levels were below almost 13.0 g/dL. Data obtained in this study should be used as a reference for future improvement.

**11. THERAPEUTIC PROCEDURES**

**K55 – Management of Empyema by Video-Assisted Thoracoscopic Surgery (VATS) vs Chest Drain with Fibrinolysis (CDF): A Systematic Review and Meta-analysis**

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Purpose of the study: The ideal surgical approach for empyema in children (<18 years) remains controversial. Both VATS and CDF are accepted methods. The aim of this study was to clarify which technique provides the best outcome.

Materials & methods: A systematic review and meta-analysis (1997–2017) was conducted according to the PRISMA guidelines. Selected studies included randomized controlled trials (RCT), retrospective and prospective comparative studies (CS). Studies containing children and adults with no clear distinction were excluded. The meta-analysis was conducted with Comprehensive Meta-Analysis 2. We used the random-effect model to produce risk ratio (RR) for categorical
variables, and standard difference in means (SDM) for continuous variables, along with 95% confidence intervals (CI). I2 value was used to assess heterogeneity: I2 > 50% was considered to have substantial heterogeneity between studies. Egger’s regression test was used to assess publication biases. P values < 0.05 were considered significant.

Results: We identified 707 studies: 506 duplicates were removed, 193 did not meet the inclusion criteria, 8 studies (4 RCT and 4 CS) were included. Results of the meta-analysis are reported in Figures 1, 2 and 3. The incidence of total peri-operative complications was not different between the two groups (RR 1.09 [CI: 0.42–2.8]; p = 0.8; I2 = 44%; Figure 1); post-operative length of hospital stay was significantly shorter in the VATS group (SDM −0.6 [CI: −1.1–−0.05]; p = 0.03; I2 = 53%; Figure 2); need for re-intervention was significantly lower in the VATS group (RR 0.6 [CI: 0.4–0.9]; p = 0.04; I2 = 22%; Figure 3). Egger’s regression test did not identify significant biases between studies [p > 0.3 for all outcomes].

Conclusion: Current evidence suggests that VATS and CDF for empyema have similar incidence of peri-operative complications. However, VATS is associated with shorter post-operative hospital stay and a reduced need for re-interventions. In centers with minimally invasive surgery expertise, VATS should be considered the treatment of choice in the surgical management of empyema.

K80 – The Use of Biphasic Cuirass Ventilation with Built-in Battery as a Movable Treatment in the Emergency Department.

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Of the children who are brought to the emergency department, respiratory issues are often the cause. As Ueda et al. reported, Biphasic Cuirass Ventilation (BCV) is comfortable, fits easily and the expression of the effect is early. Therefore, we use BCV first to patients with respiratory distress as much as possible. Recently, in patients with respiratory distress, we utilized BCV using the built-in battery, in order to continue medical treatment without interruption during transportation of the sick children from the emergency department to the pediatric ward. Through the early intervention of BCV for respiratory distress in children, it is possible to start the treatment immediately and continue treatment without interruption during transportation between wards.

In our institution, on the 14 cases in which Continuous Negative Mode of BCV was started from the emergency department, their symptoms were improved shortly in all cases. Respiratory rate and heart rate were improved in 30 minutes after starting Continuous Negative Mode of BCV, and hypopnea was improved in less than 1 hours. In all cases, BCV worked smoothly and the respiratory condition was improved.

For children with respiratory distress who breathe spontaneously and do not need artificial respiration, it is difficult to maintain airway pressure using bag-mask ventilation. In such cases, bag-mask ventilation is unstable as treatment. On the other hand, BCV does not require sedation and has greater mobility due to its battery power. We can continue the same treatment after hospitalization.

We suggest that starting the treatment with BCV in the emergency department and continuing the treatment without interruption during the transportation of the patients to the ward are feasible and safe. Furthermore, the treatment conducted by loading the battery with the BCV does not require gas piping, such as oxygen or air. In other words, this treatment is available under the situation in which there is difficulty in gas supply at the time of a disaster. In our country, we experienced certain large-scale disasters and all utilities including electricity and gas supply were thus cut off. BCV can be run only on the battery power supply and can also work under the situation without gas piping, and it is considered to be an effective means even as an acute respiratory management method at the time of disaster.

We can use BCV with built-in battery as not only an early intervention in the emergency department, but also as an effective means during transportation and disasters.

K84 – Use of Inhaled Antibiotics (IAb) in Non-CF Chronic Lower Respiratory Infections.

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Introduction: Based on the experience in CF, there is a growing interest in the use of IAb in non-CF lower respiratory tract infections. Studies have been performed mostly in adults with non-CF bronchiectasis, ventilator-associated pneumonia, COPD, mycobacterial disease and other infections; applying Ab formulations for inhalation as well as "off-label" use of injectable Ab for inhalation. Also, the use of IAb for eradicating organisms such as P. aeruginosa in non-CF bronchiectasis is under investigation.

Aim: To investigate tolerance and efficacy of IAb treated non-CF infants and children.

Method: Retrospective review of data of all IAb treatment courses in young non-CF subjects in our pediatric department.

Results: Eight non-CF subjects (2 boys), age 0–15 years (median 71 months), with chronic colonization of pseudomonas or other resistant species were included.

Underlying medical condition: extreme prematurity (GA 24–25 weeks) with O2 dependent BPD (3, including 2 with pulmonary hypertension, 1 with a tracheocanula and 2 on CPAP or BiPap), Down syndrome with GA 34 weeks, severe pulmonary hypertension, O2 dependency and tracheocanula (1), congenital esophageal atresia with tracheal fistula and recurrent aspiration pneumonias with bronchiectasis (1), poly-malformative syndrome with mental retardation and intractable respiratory infection (2 adolescents), bronchiectasis after PCP pneumonia in T-cell lymphoma (1 adolescent).

Reasons for starting IAb were: absence of response to repetitive IV antibiotic courses, practical issues with IV access, increased ventilatory conditions, recurrent acute exacerbations. Seventy-five percent of treatments were started in hospital; 2 adolescents started IAb in outpatient consultation. Age at start of IAb varied from 4 months to 15 years of age; duration of treatment was from 14 days to several months.

IAb utilized were colomycin, amikacin, gentamycin, ceftazidim, in mono or bitherapy, based on sensitivity testing. Doses and preparation were extrapolated from CF guidelines, including use of salbutamol before IAb to avoid bronchial hyperreactivity. Inhalation was well tolerated and safe. Eradication was successful and resulted in clinical improvement, decreased ventilator conditions and less acute exacerbation during a 4 to several months follow-up.

Conclusion: Data on the use of IAb in prematures and young children are scarce. These pilot data show that treatment with IAb in selected non-CF subjects with severe respiratory condition is safe and effective. It is feasible in non-hospitalized children and avoids the need for parenteral administration. IAb in non-CF is currently not formally indicated and more scientific evidence from ongoing clinical trials is awaited.

K142 – Open Lung Biopsy for Chronic Pulmonary Disease in Children.

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Introduction: This study aimed to evaluate the efficacy of open lung biopsy in children with chronic lung disease.

Methods: Patients who underwent open lung biopsy in 2006–2017 at the Hacettepe University Department of Pediatric Pulmonology were examined retrospectively.

Results: Twelve patients (6 boys, 6 girls) underwent open lung biopsy for diagnostic purposes. The mean age of the patients was 8.5 years (4 months-15.1 years). Four patients were followed-up with immune deficiency. The diagnoses of these patients were chronic granulomatus disease (n: 1), CVID (n: 1) and hypogammaglobulinemia (n: 2). None of the patients had any malignancy. The mean time between the onset of respiratory symptoms and the open lung biopsies was 6 months (range 1 to 36 months). None of the patients developed acute respiratory failure on follow-up. Nine of the patients (75%) required mechanical ventilation in the first 24 hours postoperatively.

The mean chest tube withdrawal time in patients was 4.2 days (2 days to 7 days). Three patients were diagnosed with hypersensitivity pneumonitis, 1 patient with SPC deficiency, 2 patients with interstitial pneumonia. 1 patient with granulomatous lymphocytic interstitial lung disease, 1 patient with cryptogenic organizing pneumonia, 1 patient with follicular bronchiolitis, 1 patient with pulmonary hemosiderosis, 1 patient with giant air cyst and 1 patient with granulomatosis inflammation. Ten patients underwent a treatment change after biopsy results. According to biopsy results, steroid treatment was started for all of these patients, 1 patient was given mycophenolate mofetil and 1 patient was given hydroxychloroquine treatment.

Conclusion: Our results suggest that open lung biopsy is both safe and guiding for diagnosis in children with chronic lung disease.

12. CELLULAR AND MOLECULAR BIOLOGY

L40 – TIPE2 Regulates Type I Interferon Production in Antiviral Innate Immunity.

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Objective: Acute respiratory tract infection (ARTI) is the most common type of infectious disease in children. Virus infection can account for as many as 90% of ARTI and the majority of viruses are RNA viruses. In addition to the influenza virus, there is no effective treatment for RNA virus infection. Thus, we attempted to explore the regulating mechanisms of RNA virus infection, which might help to find a new approach to treatment of RNA virus infection in the future. Tumor necrosis factor-α-induced protein 8-like 2 (TIPE2), a member of the tumor necrosis factor-a-induced protein-8 (TNFAIP8) family is a negative regulator of immune response, and could prevent
hyperresponsiveness and maintain immune homeostasis. However, the regulatory role of TIPE2 in RNA virus infection and the effect of TIPE2 in the signaling pathway after RNA virus infection are poorly clarified. This study aims to investigate the effect and underlying mechanisms of TIPE2 on RNA virus infection.

**Methods:** We collected peripheral blood mononuclear cells from 154 children infected with Respiratory Syncytial Virus (RSV) (the most common virus in children) and 66 control healthy children, and detected the expression of TIPE2. We also detected the levels of TIPE2 in macrophages in vitro after VSV (the common virus used in research) infection. Meanwhile, we aimed to explore the effect and underlying mechanisms of TIPE2 in regulating RNA virus response through gain and loss of function.

**Results:** In our study, we detected a significant decrease in TIPE2 mRNA in peripheral blood mononuclear cells (PBMCs) from 154 cases of children infected with RSV compared to that in PBMCs from 66 control healthy children. In vitro, we also found that the expression of TIPE2 was down-regulated after VSV infection. It implied that TIPE2 might play a critical role in anti-RNA viral immunity. Furthermore, we observed that TIPE2−/− macrophages were more susceptible to vesicular stomatitis virus (VSV) infection and showed increased levels of VSV-G mRNA after VSV infection in vitro. In addition, the deficiency in TIPE2 was found to enhance type-I IFNs and inflammatory cytokine production by macrophages; moreover, overexpression of TIPE2 dampened the capacity of macrophages to produce type-I IFNs and inflammatory cytokines. Furthermore, TIPE2 could restrain the activation of TBK1 and IRF3 signaling pathways, thus inhibiting the production of type I interferon and inflammatory cytokines.

**Conclusions:** Taken together, our results suggest that TIPE2 could suppress type-I interferon and inflammatory cytokine production induced by RNA virus by inhibiting the activation of TBK1, IRF3 signaling pathways. This research uncovered an important negative role of TIPE2 in regulating innate antiviral immunity, and may help to provide new strategies for the treatment of viral infection clinically.

**13. Pediatric Pulmonology in Developing Countries**

**M22 – Vascular Ring Abnormalities: A Retrospective Study of 50 Cases.**

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**Introduction:** Vascular ring abnormalities (VRA) are a rare condition where clinical presentation is essentially related to the degree of compression of the trachea and esophagus. VRA is often mistaken for bronchial asthma, knowing how to evoke it on simple elements will avoid delay in diagnosis.

**Materials and methods:** This is a retrospective study over a period of 25 years (1992 to 2017) covering all cases of VRA collected in a Pediatric Pulmonology clinic. We analyzed clinical data, all radiological and biological investigations as well as surgical reports and postsurgical evolution.

**Results:** A total of 50 children were included in the study, all of whom were explored as outpatients. A male predominance was noted with a M/ F sex ratio of 1.36. The age varied from 30 days to 15 years. The onset of clinical signs was in the first month of life for 90% of our patients. All children presented with a stridor that often started from the first month of life, it was more important and earlier in the double aortic arch. Cough was present in all cases in early life, in relation to tracheal malacia and congestion, it was hoarse and worsened with effort. Wheezing was present in more than 60% of patients. Digestive signs were mainly vomiting (26% of our patients) and dysphagia (20% of our patients) which was complicated by an esophageal food bolus obstruction that required extraction in 9% of patients. Patients were hospitalized at least once in 34% of cases, 36% were treated as bronchial asthma often considered difficult to control, 15% as chronic obstructive bronchopathy and 20% as chronic cough. Chest X-rays showed a right tracheal imprint with a right deviation in 44% of cases and a right aorta in 48% of cases. Barium swallow performed in more than 50% of patients showed esophagus impressions. The type of VRA confirmed in all our patients by a CT scan was distributed as follows: arteria lusoria 16 cases (32%), Neuhauser anomaly 15 cases (30%), double aortic arch (DAA) 8 cases (16%), innominate artery 7 cases (14%), circumflex artery 2 cases (4%), retrotracheal left pulmonary artery 2 cases (4%), right aortic arch with mirror-image branching 1 case (2%). Pulmonary function testing (PFT) guided the diagnosis in 8 cases. Bronchoscopy was only performed in 10 patients confirming tracheal malacia. Congenital heart diseases were rare in our series. Surgery was performed in only 13 patients: 5 cases of DAA, 6 cases of Neuhauser anomaly, 1 case of retrotracheal left pulmonary artery and 1 case of Arteria Lusoria. Eight patients were waiting for surgery, Parents refused surgery in 4 cases and there was no surgical indication for the other patients. Postoperative complications were infectious in 3 cases, high blood pressure in 1 case, laryngeal paralysis in 1 case and persistent mild tracheomalacia in 3 cases.

**Conclusion:** VRA is a rare condition although deserves to be known by the pediatrician, the gynecologist (no prenatal diagnosis in our series) and the radiologist to be diagnosed in time. The explorations must take into account the level of irradiation, barium swallow must be abandoned and MRI must take its place in radiological exploration. PFT have an important place in the diagnosis. Surgical indications must be studied on a case by case basis. Total improvement is not always observed, it remains dependent on the degree of tracheomalacia.

**M49 – Congenital Cystic Adenomatoid Malformation: Report of Two Cases.**

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Congenital cystic adenomatoid malformations (CCAM) are the most common malformations of the lower respiratory tract, and represent 20% of the pulmonary malformations. Diagnosis is increasingly made by antenatal ultrasonography. Chest infections can compromise vital prognosis and pulmonary function. We report here two cases of children with CCAM.

**Case 1:** An 8-year-old girl with a history of recurrent bacterial pneumonia in the right lower lobe since the age of 6 years. Radiological investigations, in particular CT angiography, showed the presence of large cysts and pulmonary condensation located in the apical segment of the lower lobe without signs of pulmonary sequestration. Bronchoscopy did not find any foreign body, granuloma or hydatid cyst membrane retention, the hydatid serologies were negative. The immunological profile did not show any primary or acquired immune deficiency, exploration by pulmonary scintigraphy showed a hypoperfusion of the right lower lobe, pulmonary function testing was normal, no associated cardiac or renal malformation. Regarding all these elements, the diagnosis of CCAM was retained and the child was operated, she underwent a lower right lobectomy with good postoperative evolution. Pathology confirmed CCAM type 1 with large cysts according to the Stoker classification.

**Case 2:** a 26-month-old girl with a history of recurrent chest infections in the right lower lobe since the age of 18 months with respiratory distress that required more than five hospitalizations. The CT scan confirmed the presence of cystic lesions of the right lower lobe and two small cystic lesions of the apical segment of the left lower lobe, with no systemic vessel which eliminated a sequestration. Bronchoscopy was normal as well as hydatid cyst serology, no associated renal or cardiac malformations. The diagnosis of CCAM being retained, the patient was referred to the surgeon for right inferior lobectomy; during surgery it was decided to limit the ablation to the right ventral and paracardial segments, the immediate surgical evolution was good and pathology confirmed the diagnosis of CCAM type 1. Four months later, the child presented a chest infection in the right inflamed lobe, the CT confirmed the presence of cystic lesions of the inferior lobe; however, the left lesions disappeared. A second surgery was performed and an inferior lobectomy was carried out with a good follow-up.

**Conclusion:** None of our two patients was diagnosed at the antenatal period despite ultrasound monitoring during pregnancy. We noticed an important delay in the diagnosis despite clinical and radiological evidence, selective surgery in the second patient failed. Any recurrent chest infections must evoke a CCAM, surgery in this situation is the rule and the only possible treatment.

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**ABSTRACT**

**An Unusual Repetition of Anti-Tuberculosis Drug-Induced Hepatotoxicity in Indonesian Children.**

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**Background:** Anti-tuberculosis drug induced hepatotoxicity (ADIH) is one of the serious adverse effects ascribed to anti-tuberculosis (TB) drugs which causes an increase in serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and total bilirubin. ADIH is uncommonly reported in children, particularly recurrent or repeated ADIH. It requires stopping all the potential hepatotoxic anti-tuberculosis drugs with a systematic and regular monitoring of liver enzymes. Even though there are available British Thoracic Society (BTS) and the American Thoracic Society (ATS) guidelines for reintroduction regimens for treating ADIH in adults, there are no guidelines adopted officially in Indonesia. We aimed to report an unusual repetition of ADIH in Indonesian children.

**Case Reports:** Six cases (3 TB meningitis, 1 miliary TB and 2 pulmonary TB), age range 18–60 months, of experienced repeated ADIH were reported. The four severe TB cases received daily 4-drug anti-TB therapy comprising isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol which planned to be continued for a period of 2 months, followed by INH and RIF for a period of 10 months, whereas two pulmonary TB cases received 3 drugs (INH, RIF, PZA) for a period of 2 months and continued for a period of 4 months with INH and RIF. All patients had an increased serum AST, ALT and total bilirubin, while hepatitis markers showed negative results. No abnormalities were identified in hepatobiliary ultrasonography. When ADIH occurred, anti-TB drugs were stopped immediately without considering the severity of ADIH. Most ADIH occurred during the intensive phase of TB regimen, although one during the continuation phase. However, all cases experienced repeated ADIH when they were on INH reintroduction. Two cases experienced repeated ADIH three times, while the others experienced ADIH two times. We managed ADIH cases by modifying ATS guidelines treated individually. One TB meningitis case received levofloxacin and RIF when treating the third instance of ADIH. At present, all patients are in continuous phase and managed with full doses of INH and RIF. Good clinical responses were noted in all of them. Acetylator status of all ADIH cases was not studied.

**Conclusions:** Diagnosis of ADIH is still conducted by clinical and laboratory examinations. The reintroduction of anti-TB drugs after ADIH is to be taken with care and should be treated individually. There are no official guidelines to treat ADIH in Indonesian children and these challenges made us create our own proposed guideline for ADIH which is based on ATS guidelines.

**Keywords:** Anti-tuberculosis drug-induced hepatotoxicity, children M71 – A Retrospective Study on the Diagnostic Accuracy of TB PCR vs Culture in Diagnosing Children Aged 3 Months to 18 Years at a Tertiary Care Center.

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**Introduction:** Tuberculosis (TB) is both a preventable and treatable illness. In children, it is infrequently confirmed bacteriologically due to the lack of effective diagnostic tools. Early identification of TB is very important, as it can help in the initiation of adequate treatment for patients and in prevention of further spread of drug-resistant strains.
Objectives: This study aims to establish the diagnostic accuracy of TB PCR versus TB culture and rifampicin resistance by PCR versus conventional susceptibility testing of body fluid in inpatient and outpatient Filipino children aged 3 months to 18 years with suspected tuberculous disease seen in a tertiary care center.

Methods: This is a retrospective analytical study of out-patients and in-patients seen at a tertiary care center between January 1, 2012 to May 31, 2017. During the study period, all patients with clinical features, radiographic, tomographic, imaging and hematological findings suggestive of tuberculosis and who had diagnostic TB sampling of body fluids were recruited into the study.

Results: Among 159 patients suspected with TB, 46 (28%) were found positive by PCR, of which one was rifampicin-resistant. Forty (25%) were TB culture-positive, four (2%) of whom were PCR-negative. Overall rifampicin resistance was 1.8%. The sensitivity, specificity, positive predictive value and negative predictive values of TB PCR, using TB culture as the gold standard, were 90%, 91.6%, 78.3%, and 96.5% respectively. The sensitivity, specificity, positive predictive value, and negative predictive values of TB PCR rifampicin resistance detection, using TB culture susceptibility as the gold standard, were 33%, 100%, 100% and 95%, respectively. Overall, the accuracy of TB PCR in detecting TB disease was 91.2% and the accuracy of TB PCR in detecting rifampicin resistance was 95%.

Conclusion: The findings in our study suggest that TB PCR plays an important role in TB disease diagnosis, but clinical and radiological assessment continue to be essential in the diagnosis of childhood tuberculosis. The high accuracy of TB PCR and detection of rifampicin resistance allows a rapid presumptive diagnosis of TB disease, allowing prompt institution of therapy. However, conventional culture is still needed to detect resistance to drugs other than rifampicin.

Keywords: TB PCR, tuberculosis, Filipino, pediatrics, accuracy


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Introduction: Though cystic fibrosis (CF) is the commonest cause of bronchiectasis in the Western world, non-CF bronchiectasis is the major contributor to the burden of chronic respiratory morbidity in developing countries. Failure to expectorate collected mucus results in plugging of the airways, thus creating a vicious cycle of progressive airway damage. Therefore, airway clearance techniques play an important role in the management of non-CF bronchiectasis. Although multiple airway clearance techniques have been introduced, none of the latter have been validated. Usage of a method would depend on effectiveness, convenience, compliance, and cost. Hypertonic saline nebulization prior to airway clearance is a well-established method in managing CF and non-CF bronchiectatic adults. Hence we planned to assess the effectiveness of hypertonic saline nebulizations over conventional physiotherapy in children with non-CF bronchiectasis.

Aims: To evaluate the effectiveness of hypertonic saline nebulization prior to physiotherapy in improving lung functions in children with non-CF bronchiectasis.

Materials and Methods: All 5 – 15 year old children with non-CF bronchiectasis, attending a tertiary care hospital in Colombo, Sri Lanka from August 1st to December 1st 2017 were included in the study. Inability to comply with regular follow up, use of regular hypertonic saline nebulization during the preceding one year, chronic colonization of Pseudomonas in the respiratory tract, those who had frequent exacerbations, presence of typical extra pulmonary features of CF and children who were unable to perform spirometry test due to poor effort were excluded.

A baseline spirometry was performed on all selected patients. They were treated according to the airway clearance technique, which was prescribed by the treating physician. One group of children received hypertonic saline nebulizations followed by inhaled bronchodilators prior to chest physiotherapy and the other group received only inhaled bronchodilators prior to chest physiotherapy. The technique used to deliver bronchodilators was a metered dose inhaler with spacer device in both groups. Use of a home nebulizer was taught to parents in order to deliver the saline. An adequate training on chest physiotherapy was given to the parents in two sessions by a physiotherapist. A physiotherapy session of 20–30 min was recommended and 2 sessions were performed each day. The number of exacerbations during the 2-month period was documented and spirometric assessment was done at the completion of the two months of therapy.

Data were processed with Microsoft Excel; independent t test and Mann-Whitney U test were used to examine the statistical significance. Statistical significance was established as p value less than 0.05. Descriptive statistics are presented as mean ± SD)

Results: A total of 27 children were evaluated in the study. Fifteen children received hypertonic saline nebulizations followed by inhaled bronchodilators prior to chest physiotherapy and the other group received only inhaled bronchodilators prior to chest physiotherapy. The demographic and baseline measurements were comparable between the two groups. The most common etiology was suggested to be post infective bronchiectasis in 18 children. The mean improvement in percentage predicted FEV1 was significantly higher (p = 0.002) in the hypertonic saline nebulized group (11.3 ± 2.7) than in the non saline group –(3.5 ± 8.9). The hypertonic saline group showed a statistically significantly higher mean improvement in predicted FVC in saline group (9 ± 5.9) compared to the non saline group (2.2 ± 5.7)(P < 0.012). A significant improvement in PEFR was demonstrated in the hypertonic saline 11.3 (7.4) than conventional group –4.2(6.2)
FEV1/FVC ratio, PEFR, MEF 25
Non-CF Bronchiectasis, Hypertonic Saline, FEV1, FVC, Key Words:
neculization before chest physiotherapy

needed to test the effectiveness of use of hypertonic saline

A randomized control trial with larger numbers is

Recommendation: A randomized control trial with larger numbers is

saline nebulization also reduces the rate of exacerbation.

Conclusion: Hypertonic saline nebulization prior to use of broncho-
dilators and chest physiotherapy is an effective strategy to improve
quality of the airway clearance technique. Hypertonic saline nebuliz-
tion improves dynamic lung volume including FEV1 and FVC. A
significant improvement in PEFR and MEF75-25 is seen with the use of
hypertonic saline premedication of chest physiotherapy. Hypertonic
saline nebulization also reduces the rate of exacerbation.

Recommendation: A randomized control trial with larger numbers is

needed to test the effectiveness of use of hypertonic saline
nebulization before chest physiotherapy

Key Words: Non-CF Bronchiectasis, Hypertonic Saline, FEV1, FVC,
FEV1/FVC ratio, PEFR, MEF 25–75)

M82 – The Molecular Epidemiological Characteristics of
Subtype A Respiratory Syncytial Virus in Eastern China
from 2009 to 2014.

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Objective: To investigate the epidemiological characteristics of
respiratory syncytial virus (RSV) subtypes and genotypes in Eastern
China from 2009 to 2014, and to explore the genetic variability of the
attachment (G) protein gene among subtype A RSV strains.

Method: Nasopharyngeal secretions (NPS) from children under 5 years
of age who were hospitalized with lower respiratory tract infection
(LRTI) in three tertiary hospitals during 5 consecutive seasons from
July, 2009 to June, 2014 were collected. RSV antigen was determined
using direct immunofluorescence. 200 samples with RSV antigen
positive were randomly selected from each epidemic season. RNA was
extracted and identified as subtype A or B by using RT-polymerase
chain reaction (RT-PCR), and randomly selected subtype A strains of
the nearly full-length attachment (G) protein were amplified by PCR
and sequenced. Result A total of 25,449 specimens were collected
from patients during 5 consecutive epidemic periods, and 6416
(25.21%) were positive for RSV. Among 1000 randomly selected
samples, 462 (46.2%) and 538(53.8%) samples were identified as RSV
subtype A and B, respectively. Subgroup A types were predominant
during two epidemic seasons (2010/2011, 2011/2012). 52 strains of
complete sequences of G genes were obtained, including four group A
genotypes NA1, NA4, GA2 and ON1. NA1 genotype was the most
(39/52,75%) common one, and was the predominant form in the first
four popular seasons, followed by ON1 genotype (10/52,19%), which
were first verified in December 2011, and totally 9 strains in 2013/
2014. ON1 genotype was the only genotype of subtype A during the
season of 2013/2014. There were some different variations in the
second hypervariable region at the carboxyl-terminal of the G gene.
The rates of homology between prototype strain A2 and the 52 strains
of subtype A RSV were 80.7% to 89.3% at the nucleotide level and
74.4% to 82.6% at the amino acid level. On comparison of strains
among the sequenced subtype A RSV, the rates of homology were
81.5% to 100% at the nucleotide level and 80.2% to 100% at the amino
acid level. G protein variants included substitution, insertion and
repeat, and the N- glycosylation sites mutation was obvious. There
were several variations in the 24amino acid sequence that inserted into
the ON1 genotype.

Conclusions: NA1 is the predominant genotypes of subtype A RSV
during 4 consecutive epidemic seasons from 2009 to 2013 in Eastern
China. The variation in the nucleotide and amino acid sequence of G
protein is obvious. There were various transmission chains of RSV
caused by different genotypes during the 5 consecutive seasons.

M93 – Rupture of a Massive Pulmonary Hydatid Cyst in an
8-Year-old Girl. A Case Report

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Morbidity by Hydatid cyst in children is not uncommon in some
portions of world still. Our country (as has been reported in Lancet
2003; 362: 1295–1304, Echinococcis) is located in a hyper endemic
area. In alveolar hydatidosis, if surgical removal is unsuccessful, the
mortality rate after 10 years is more than 90%.

Case presentation: An 8-year-old girl referred to our hospital with
productive cough and intermittent decrease of consciousness level on
September 17 2017. Mild tachypnea was the only positive finding on
first physical examination. A chest X-ray was ordered that showed
surprisingly, right side massive pleural effusion and concurrent
pneumothorax which shifted the mediastina to the opposite side. A
consultation with the surgery department was performed for the
patient, and additional clinical imaging showed bronchiectasis in upper
lobe of the right lung. Water Lily-specific signs in thoracic-abdominal
CT made our preliminary initial diagnosis as Echinococcus of the lung.

After ultimately starting Albendazole 15 mg/kg treatment, surgery was
performed in an equipped hospital. After right posterolateral
thoracotomy, lung empyema from a ruptured hydatid cyst, pleural
adhesion and inter-thoracic fibrin was reported and finally wide
decortication was performed. The patient was discharged after 6 days
post-operation hospitalization with good condition and administration
of Albendazole continued and parents advised for referral to pediatrics
infectious disease clinic for serial observations. She had good
performance in school and was well on November 10 as of our last
recall date. Rapture may occur during therapy or percutaneous
aspiration and trauma can lead to severe complications, such as
massive hemoptysis and tension pneumothorax, lung abscess and
asphyxia.
Prevalence of Allergic Rhinitis and Atopic Eczema among Schoolchildren in Jordan.

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Background: The prevalence rate of allergic diseases, such as asthma, allergic rhinitis and atopic eczema are increasing worldwide among children.

Objective: This part of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III was to determine the prevalence of asthma, allergic rhinitis and atopic eczema among schoolchildren age 6–7 years and 13–14 years.

Methods: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase III questionnaires were administered to 3000 children from both age groups. The questionnaires were collected after having been completed by the parents.

Results: The total number of students included in both studied groups was 5045. The response rate was 84% for schoolchildren. Physician-diagnosed asthma was found in 9.5%. Primary school children aged 6–7 years had significant wheezing ever (27.2%) compared with older children (25.2%); P < 0.05. Asthma was more common in males. The prevalence of allergic rhinitis ever was 23.6% and 26.6% in primary schoolchildren and older children respectively (P < 0.014). Current symptoms of AR were 70.9% and 75.5% in primary schoolchildren and older children respectively (P < 0.08). Physician-diagnosed hay fever was 5.5% in primary school children compared to 7.9% in older children aged 13–14 years old (P < 0.000). The prevalence of eczema ever was 15.6% and 13.5% in primary and older schoolchildren respectively (P < 0.03). Physician-diagnosed eczema was 8% and 5.8% in primary schoolchildren and in older children respectively (P < 0.03).

Conclusion: This is the first study on the prevalence of most allergic diseases in Jordan. Asthma is increasing and other allergic diseases are not an uncommon problem in our area. Allergic rhinitis is more common in older children. Females more commonly have allergic rhinitis and eczema.


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Purpose: The aim of our study was to describe the contribution of HFNC in the management and evolution of severe bronchiolitis.

Methods: We retrospectively studied cases of severe bronchiolitis for three months (November 1, 2015 – January 31, 2016). We compared two groups: a first group including the cases of severe bronchiolitis in which HFNC was used, and a second group including patients who were not placed under HFNC due to lack of availability.
Results: Eighty cases of severe bronchiolitis were collected, of which 35 (43.8%) were placed on HFNC. The average age was 60 days (11–180 days). A history of prematurity was found in 22.5% of cases, hypotrophy in 10% of cases, neonatal mechanical ventilation in 10% of cases and congenital heart disease in 3% of cases. Viral contamination was found in 70% of cases. In all cases, HFNC was used in the first 72 hours of hospitalization, and in the first 24 hours in 38% of cases. The average duration of HFNC was 2.62 days (1–17 days). The mean total hospital stay was 6.3 days in the HFNC group versus 9.8 days in the other group, with a statistically significant difference (p = 0.028). A transfer to the intensive care unit was indicated in 13/35 of the cases (37%) in the group using HFNC versus 19/45 cases (42.2%) in the second group.

Conclusion: HFNC appears to be really effective in severe bronchiolitis, with a decrease in the use of invasive ventilation, especially in children under 3 months of age. HFNC is available in a general pediatric ward and is easy to use, improving the prognosis of patients and reducing pressure on the pediatric intensive care unit.

M125 – Vitamin D Supplementation and Tuberculin Skin Test Conversion among Healthy Under-Five Children with Tuberculosis Contact.

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Background: Tuberculosis (TB) contact increases the risk of TB infection among under-five children, whose immune systems are not fully developed. Vitamin D is known to affect innate and adaptive immunity, inhibit bacterial invasion, therefore will protect from developing TB infection indicated by TST conversion.

Objective: To evaluate the effects of vitamin D supplementation among healthy under-five children with tuberculosis contact to develop TST conversion.

Methods: We conducted a randomized, double-blind, controlled trial in 66 under-five children who had tuberculosis contact, but whose tuberculin skin tests (TST) were negative (healthy). We administered a high single dose of vitamin D3 supplementation twice, at an interval of 6 weeks. After 12 weeks, we performed a 2nd TST, with positive TST (diameter>10 mm) indicating TST conversion. Ethics approval was obtained from the Ethics Committee from Faculty of Medicine, Universitas Andalas.

Results: There were no difference in TST conversion between intervention (12.9%) and placebo groups (11.4%) with a p value = 0.855. Baseline characteristics showed mean levels of vitamin D <30 ng / ml, vitamin D supplementation significantly increased vitamin D level in the intervention groups (24.32 ± 7.50 vs. 28.47 ± 7.19, p = 0.003) compared to the placebo groups (26.93 ± 8.60 vs. 27.67 ± 9.02, p = 0.508).

Conclusion: There were no differences in TST conversion between intervention and placebo groups after vitamin D supplementation twice over 12 weeks among under-five healthy children with TB contacts, although increased vitamin D serum levels.

M158 – Study of Bacterial Agents of Pneumoniae in Children and Detection of Antibiogram Patterns in Hamadan, West of Iran.

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Background and aims: Bacterial pneumoniae is still one of the most dangerous infectious diseases and causes serious complications and mortalities in children. The aim of the present study was to identify the most common bacterial agents causing pneumoniae in children less than 12 years old and detection of their resistance to current antibiotics in Hamadan.

Methods: Overall, 542 children suspected of pneumoniae were investigated for results of pleural fluid cultures and antibiogram patterns. Frequency of age, sex and seasons of patients were also studied from 1999 to 2003. The data were gathered through a questionnaire and analyzed using Epí6 system. The species were identified by biochemical and serological methods. Antibiogram tests were also performed using the Kirby-Bauer method.

Results: Out of 542 children suspected of pneumoniae, 72 cases (13.2%) had positive bacterial culture of which 54.4% were gram-negative and 43.6% were also gram-positive bacteria. The most common species were: Staphylococcus aureus 18.6%, Streptococcus pneumoniae 16.9%, Klebsiella ozaenae 12.3%, Pseudomonas aeruginosa 11.8%, Haemophilus influenzae 9.4%, Bacteroides species 7.8%, Streptococcus β-haemolyticus 6.1%, E. coli 4.9%, Neisseria meningitidis 4.5%, Acinetobacter species 3.2% and other gram-negative bacteria 23.3%. The most positive cultures were observed in children 1–4 year age group (31.3%), male (52.4%) and during winter (41.8%). The results of antibiograms showed that the most effective antibiotics were cefixime, ceftriaxone, gentamycin, ciprofloxacin for both gram positive- and gram-negative bacteria, but they showed high resistance to tetracycline, amoxicillin and ampicillin.

Conclusions: The present study showed that some gram-positive bacteria, in particular Staphylococcus aureus and Streptococcus pneumoniae, are predominant causes of bacterial pneumoniae in children less than 12 years old in these regions. Most species showed high resistance to routine antibiotics such as tetracycline, amoxicillin and ampicillin.

M166 – The Correspondence of Client Statistics Referred to our Clinic with the Rate of Airborne Particle Pollution.

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Zanján city is located in the country of Iran, in the Middle East continent (or region). DMS latitude longitude coordinates for Zanján are: 36°40'24.96"N, 48°28'43.32"E. Zanjan (48° 28’ longitude and 36° 40’ latitude) (Figure 1).

In recent few years, our country’s climate was threatened by four main Dust Particle Focuses through our Western neighbors of which the most significant (23 cases of forty airborne particle flows in last years) was the North-West of Iraq and the East of Syria Countries. As our recorded documents in environmental organization shows, these known hotspots have been activated around March to September annually in past years and we had school closures and work shut downs for a few days in 2017. As we know, airborne particles not only can play an important role in dysfunction of the pulmonary system but can also trigger an attack in known cases of asthmatic children. In the present study, we will try to show the relationship between the number of patients referred to the Zanjan solitary pediatrics asthma and allergy clinic and the rate of airborne particles that was recorded by the Department of Environment in Zanján branch. Airborne particles are divided into two classifications: coarse, or those particles larger than 2.5 microns in diameter, and fine, those particles 2.5 microns or less in diameter. Air monitoring in Zanján is conducted by a local environmental organization which provides air pollution data regarding ozone and particulate matter (PM2.5) as has been recommended in Air Quality System (AQS) which contains data from approximately 6 monitoring stations in the city center and around the area, mainly in urban areas. We have collected only the data of the city center station.

Client statistics in our clinic correspond to the rate of airborne particle pollution that is recorded in the city center station. The negative effects of air pollutants on pulmonary function place children at a greater risk of air pollutant-induced exacerbation of asthma for the duration of their lives. All studies reviewed indicate that outdoor air pollution affects the appearance and exacerbation of asthma in children. (J Asthma. 2011 Jun; 48(5):470–81. doi: 10.3109/02770903.2011.570407. Epub 2011 Apr 13. Outdoor air pollution and asthma in children. Tzivian L.). According to “AQI”, when air pollution is even in moderate range, children with asthma should limit their time outdoors; especially from 10 a.m. to 8 p.m. Most of all, do not exercise outdoors. In such conditions, we recommend that, because of its morbidity, despite schools being open, students with a history of asthma should be exempted from school.

"AQI" in Zanján City Center Station Day/Month:

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As our recorded documents in environmental organization shows, these known hotspots have been activated around March to September annually in past years and we had school closures and work shut downs for a few days in 2017. As we know, airborne particles not only can play an important role in dysfunction of the pulmonary system but can also trigger an attack in known cases of asthmatic children. In the present study, we will try to show the relationship between the number of patients referred to the Zanján solitary pediatrics asthma and allergy clinic and the rate of airborne particles that was recorded by the Department of Environment in Zanján branch.

M179 – Performance of Interferon Gamma Release Assay and Tuberculin Skin Test for TB Diagnosis in HIV Infected Children.

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Background: Tuberculosis (TB) is an important opportunistic infection in children with Human Immunodeficiency Virus (HIV) in high burden TB countries. Diagnosis of TB in immunocompromised children is
difficult, such that the tuberculin test (TST) and interferon gamma release assay [IGRA, QuantiFERON®-TB Gold In-Tube (QFT-GIT)] are expected to be accurate for diagnosis of TB infection in HIV infected children. Reports on QFT-GIT accuracy in children with HIV infection still vary.

Objective: To evaluate the accuracy of QFT-GIT and TST to diagnose TB in HIV infected children.

Method: A cross-sectional study was conducted in 48 HIV infected children with suspected TB aged 1 month to 15 years old. Data which included history taking, physical examination, thorax radiology, TST, QFT-GIT, and bacteriological examination (Xpert MTB/RIF and MGIT culture) were collected.

Result: The prevalence of TB in HIV-infected children is 20.9% (confirmed TB 4.2% and clinical TB 18.7%). The clinical symptoms of HIV-infected children with TB are: chronic cough (90%), body weight decrement (80%), reduction of activity (80%), lymph node enlargement (60%), and prolonged fever (50%). The sensitivity of QFT-GIT towards clinical TB in HIV-infected children is 38% (CI 95%: 12–77%), specificity 100% (CI 95%: 98–100), PPV 100% (CI 95%: 98–100), and NPV 88% (CI 95%: 76–94). The sensitivity of tuberculin test towards clinical TB is 29% (CI 95%: 8–64%), specificity 97% (CI 95%: 87–100), PPV 67% (CI 95%: 21–94), and NPV 88% (CI 95%: 76–95%). The sensitivity of QFT-GIT towards bacteriological examination is 50% (CI 95%: 9–91%), specificity 96% (CI 95%: 85–99%), PPV 33% (CI 95%: 6–79%), and NPV 98% (CI 95%: 88–100%). Accuration towards bacteriological examination and tuberculin test could not be evaluated.

Conclusion: Both QFT and TST showed high specificity but low sensitivity to diagnose TB. The accuracy of QFT-GIT to detect TB in HIV infected children is slightly superior than TST. Therefore, these two methods could be a choice depending on its availability and patient comfort.

Introduction: Non-cystic fibrosis (CF) bronchiectasis is commoner than CF bronchiectasis in both developing and developed countries with a significant contribution to chronic respiratory morbidity. However, only very limited scientific data are available on its clinical profile and management. Bronchiectasis in children without CF is said to be the end result of repeated episodes of insults to the respiratory system due to several etiologies leading to permanent bronchial tree injury and dilatation. The clinical case definition of bronchiectasis is imprecise and its severity and extent is highly variable, ranging from minimum respiratory morbidity to death. Symptoms are nonspecific and chest radiographs are relatively insensitive in the diagnosis. Therefore, high degree of suspicion is needed when evaluating children with recurrent respiratory tract infections or signs suggestive of chronic respiratory insufficiency. Children who are suspected to have bronchiectasis should undergo a high-resolution computer tomographic (HRCT) scan without delay to confirm the diagnosis, to define the distribution and severity of airway involvement. Lung function tests in older children provide a measure of functional impairment and small-airway involvement. Management approach of non-CF bronchiectasis follows a similar approach to the management of CF bronchiectasis as there are no specific guidelines. Reviewing the children with non-CF bronchiectasis was done with the aim of contributing to fill the gaps in the understanding of their clinical profile and outcome.

Objective: To describe the clinical profile, etiology, specific management and outcome in children with non-cystic fibrosis bronchiectasis attending a tertiary care hospital in Colombo, Sri Lanka.

Methods: Twenty-seven children with an HRCT scan-based diagnosis of bronchiectasis, presenting to the Professorial Pediatric Unit, Lady Ridgeway Hospital, Colombo during the period of September 2016 to December 2017, were selected for the review. Absence of typical clinical features and having two negative sweat tests performed at a minimum of 6 months apart were taken to exclude cystic fibrosis. A detailed chart review of children diagnosed with non-cystic fibrosis bronchiectasis was done.

Results: The majority of the patients with non-CF bronchiectasis were females (66%) and the mean age of the study sample was 7.4 years (SD = 3.24). The mean age at the diagnosis of bronchiectasis was 5.2 years (SD = 2.50) and the indication to perform an HRCT in the majority (19 children) was the combination of recurrent respiratory tract infections with persistent crepitations on examination. Mean duration of symptoms /medical concerns prior to the diagnosis was 3.8 years (SD = 1.54). Bilateral involvement was seen in 9 (33%) patients. Only 6 (22%) patients were referred to the center by a pediatrician or a general practitioner with the suspicion of bronchiectasis and the rest (21) were diagnosed when admitted with an exacerbation, with the background of recurrent respiratory tract infections. Twelve (44%) children showed a weight for height or a BMI centile for age less than −2SD. Mean number of episodes of exacerbations per year was 6. Spirometry was done in 22 patients at the analysis of the clinical profile. Best FEV1/FVC (Forced Expiratory Volume in 1 second/Forced Vital Capacity) ratio was >80% in 16 (72%) and <80% only in 6 (28%). FVC was not reduced with a predicted value >80% in the majority (12 patients, 44%). FVC was <60–80% in 7 patients and <60% in 3 patients who were on home oxygen therapy. Predicted FEV1 was more than 80% in 14 (63%) and less than 80% in 8 children. Analysis of etiology revealed one patient each with common variable immune deficiency (14 years), with a past history of tuberculosis (15 years), intralobar sequestration (13 years) and late diagnosis of severe gastroesophageal reflux disease (3 years). The commonest etiology was post infectious where 14 (51%) had one or more episodes of severe pneumonia needing respiratory support during infancy with other common etiologies being excluded. Nine
(33%) children had no identifiable etiology. Diagnostic facilities for Primary Ciliary Dyskinesia (PCD) were not available but there were no patients with a typical clinical profile of PCD. Satisfactory postural drainage was followed by 15 (55%) and the rest had deficiencies in the technique. Pneumococcal vaccination was given for 24 patients (85%) outside of the Expanded Program of Immunization. Only 20 (74%) patients had complied with regular follow-up. Three patients had undergone lobectomy. Out of the sample, 3 children are on home oxygen therapy and were dependent on parents for activities of daily living.

Conclusion: The commonest cause of non-CF bronchiectasis in the above group is post infection. There is a significant delay in the diagnosis despite children being symptomatic. A high degree of suspicion is needed for the early diagnosis especially in children with a history of severe respiratory infections in early childhood. There is a need to create awareness about the importance of early diagnosis of bronchiectasis and the importance of correct postural drainage techniques and follow-up as it would lead to less complications and better prognosis.

14. MISCELLANEOUS

N13 – Pleuropulmonary Blastoma in Congenital Pulmonary Airway Malformation: Challenging Diagnosis of an Asymptomatic Child

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Introduction: Congenital pulmonary airway malformation (CPAM) is an abnormality of lung development and cannot be distinguished radiologically or clinically from rare primary tumors such as Pleuropulmonary Blastoma (PPB). We report a rare case of CPAM and PPB overlap in a 2-year-old absolutely asymptomatic girl with a huge cystic lesion.

Case Presentation: A 2-year-old girl was referred to our hospital for a giant cystic pulmonary lesion with a large and solid mass. This lesion had undergone a huge increase in 18 months since it was first discovered by a pediatrician during a random chest X-ray performed because of a flu. The initial clinical examination revealed a very good condition. The pulmonary auscultation was absolutely normal despite the dramatic appearance of the radiological findings. There were no reported anomalies on the antenatal ultrasound or neonatal complications. Good birth weight (w: 3000g; h: 49 cm) and development. She had no episodes of respiratory distress or pneumonia whatsoever. The first chest X-ray performed when she was 6 months old showed a cystic lesion in her right hemithorax with a round-shaped white shadow at the bottom of the lesion (Image 1). CT scan showed the cystic lesion contained a few thin internal septations with a consolidated area (Image 2). The last images performed 18 months later on X-ray and CT scan demonstrated an important increase in the cystic lesion and the round-shaped opacity (Image 3). The child underwent a right thoracotomy through the fifth intercostal space. A multiloculated giant cystic lesion was found occupying the entire hemithorax and compressed all right lower lobes which was the solid round mass. During the mechanical ventilation, this lobe got insufflated recovering its functions normally. The anatomy of the affected lobe appeared normal. The removal of the cystic mass was performed simultaneously with the posterior apical segment of the lower lobe where the lesion was fixed. Grossly, the diameter of the cystic mass was 8.0 cm. Histopathologically, the cystic epithelial layer was composed predominantly of flattened cells and at the subepithelial layer, there were foci of spindle cells with an atypical appearance. Moreover, the parenchyma showed normal microscopic characteristics. Immunohistochemical analysis detected positivity for Desmin, an intracellular intermediate filament found in muscle tissue and demonstrated in some atypical stromal cells, indicating sarcomatous differentiation characteristic of pleuropulmonary blastoma (image 5). The patient did not receive chemotherapy. She is in her first postoperative year and is being followed closely, presenting a very good condition.

Image 1. Chest X-ray showing a cystic lesion with round-shaped shadow (red arrow).

Image 2. CT scan showing a more defined multiloculated cystic lesion (red arrow) and the round mass (a).
Image 3. Eighteen months after: (A) Chest X-ray showing huge increase of cyst lesion and round mass (arrow) together with its correspondence on CT scan (B).

Image 4. Cystic mass and the compressed lower right lobe (black arrow) which was the round mass on the previous images.

Image 5. (A) Primitive mesenchymal cells located just below the epithelium (circle). (B) Primitive mesenchymal cells showing positivity for Desmin (red arrow).

**Discussion:** Congenital Pulmonary Airway Malformation (CPAM), formerly known as Congenital Cystic Adenomatoid Malformation (CCAM) consists in multicystic masses of segmental lung tissue with abnormal bronchial proliferation. It accounts for approximately 95% of all congenital cystic lung diseases and 10% of pediatric lung cancers have a history of CPAM. There are five subtypes classified mainly according to cystic size: Type I: large cysts, Type II: cysts less than 2 cm in diameter. Type III: microcysts that involve an entire lobe, Type IV: unlined cysts that typically affect a single lobe that it is indistinguishable from Type I on imaging and Type 0: very rare and lethal postnatally.

PPB is a very rare intrathoracic malignant neoplasm that originates during lung development and can arise from the lung, pleura or both. It
was described by Manivel et al. in 1988 and was later subdivided into three types on the basis of the morphological pattern: Type I: multilocular cysts containing primitive small mesenchymal cells within the cyst wall, Type II: cystic and solid components (mixed) and Type III: exclusively solid tumors, in order of increasing and malignancy. Priest et al. in 1996 reported that type I is most observed in patients in the first years of life compared to type II and III that are found in older patients – between 3 and 4 years of age. Type 1 is different from the rest because of its subtle malignant changes and good prognosis. The clinical presentation may be asymptomatic or have secondary symptoms due to the expansion or infection of the cyst, infection sometimes being recurrent. The most frequent findings on chest X-ray are: cystic lesions, hyperinflation, mediastinal shift and pneumothorax. Usually there is no adjacent rib erosion or calcification. CT scan remains the most sensitive technique including the largest cyst size, the nature of the cyst (septated or containing solid components) and the presence of a systemic vascular supply. The incidence of PPB among apparently benign lesions is 4%. Several studies have suggested that these two entities can be indistinguishable.

The precise relationship between CPAM and malignancy, especially Pleuropulmonary Blastoma (PPB) remains unknown. Some studies indicate that the PPB etiology may originate from previously existing CPAM in the lung – about 31% – but nothing has been proven to date. There are cases that correlate these two pathologies, because they present very similar histological types. Generally the diagnosis is made through the microscopic analysis of Hematoxylin & Eosin (HE), but sometimes it is necessary to perform immunohistochemistry in some conflicting cases. Biomarkers: Ki-67, Desmin and Myogenin may be observed in these borderline cases. According to Hill et al., in order to distinguish PPB from other pathologies it is necessary to observe the presence of multilocular cystic areas, a well circumscribed tumor with normal parenchyma, presence of small foci of primitive cells and an epithelial layer with flat cells which was noticed in our case.

Conclusion: Congenital Pulmonary Airway Malformation (CPAM) and type 1 Pleuropulmonary Blastoma (PPB) are indistinguishable by clinical and radiological presentation. Therefore, children with asymptomatic cystic lesion should be assessed thoroughly and the lesion resected early to avoid later complications such as its malignization. Careful histological examination of the resection specimen is mandatory to identify occult malignancy, thereby to manage the treatment properly and reach the best prognosis.

N51 – Validation of GLI-2012 Spirometry Reference Values in Italian Preschool Children

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Rationale: The Global Lung Initiative (GLI-2012) spirometry reference values are a potentially valuable tool for the interpretation of spirometry worldwide [1]. Although their validity has been proven in many countries, doubts remain for some populations. The aim of this study was to assess the validity of the GLI-2012 reference values in preschool Italian children.

Methods: Healthy children were recruited from randomly selected kindergartens in or around Florence, Italy. The subject’s history of respiratory symptoms was assessed using a standardized questionnaire (ISAAC modified), translated into Italian [2]. Children born at less than 36 weeks of gestational age or who had received oxygen at birth for more than 30 days were excluded. Children with no more than 3 episodes of wheezing ever, but no episodes of wheezing during the previous 12 months, were included. All children had no respiratory symptoms or signs at the time of testing. Spirometry was performed with the “Spiro Cosmed” spirometer (Cosmed, Rome, Italy) according to ATS/ERS spirometry recommendations for preschoolers [3]. Z-scores for forced vital capacity (FVC), forced expiratory volume in 0.75 s (FEV0.75) and in 1 s (FEV1), and forced expiratory flow between 25% and 75% of FVC (FEF25-75%) were calculated using GLI-2012. Absolute Z-score values larger than 0.5 were considered to have a clinical significance.

Analysis: The results of questionnaires and spirometry were transformed into numeric values and reported in an Excel table and subsequently analyzed using Stata/SE v.12 for Windows. The analysis was performed using the paired t-test. The t-test is a type of parametric statistical test which allows verifying if the average value of a distribution differs significantly from a certain reference value. The mean values of the spirometric parameters FVC, FEV0.75, FEV1 and forced expiratory flow 25–75% of FVC (FEF25-75%) obtained from the examined sample were compared with the predicted values for the same spirometric parameters derived from the 2012 GLI reference equations. The values with a P < 0.05 and a Z-score > 0.5 were considered statistically and clinically significant [4].

Results: A total of 109 healthy children [57 female and 52 male, age range 3.2–6.3 yr, mean age (SD) 5.1 (0.8) yr, mean height 109.7 (8.1) cm, mean weight 19 (3.9) kg] performed acceptable and reproducible spirometry maneuvers (feasibility 85%). A total of 100 (78.1%) children had >2 reproducible maneuvers and 70 (54.7%) had >3 reproducible maneuvers. Mean (SD) measured spirometry indices and predicted values using GLI-2012 are reported. A paired t-test showed that measured values were not significantly different from predicted values. The mean Z-scores of the measured values were smaller than 0.5, showing that the difference was not clinically significant.

Potential Study Limitation: The number of subjects enrolled in the study, to confirm the validity of these reference equations (GLI-2012), was less than the 300 local “healthy” controls (150 males and 150 females) that would be needed to validate published reference equations with any degree of certainty, since with smaller sample size differences of up to 0.5 z-scores may occur purely by chance [4]. Furthermore, this relative inclusion flexibility has been used to select a sample closer to the reality of the population, to avoid selecting “abnormally normal” children, which would distort the study, resulting in an overestimation of the results; this is still a topic of many discussions regarding what would be the “normal” parameters necessary to be considered [5].
Background/Objectives: Sleep is essential for optimal body functioning. The National Sleep Foundation recommends that primary school children get 9-11 hours of sleep per day. A previous study in Singapore showed that sleep duration is significantly lower in preschool children when compared to Western populations. There is little published data on the sleep habits of primary school children in Singapore. Our study aims to investigate sleep practices amongst lower primary school age children in Singapore.

Methods: This was a questionnaire survey of parents with children aged between 6 and 9 years old attending primary schools in Singapore.

Results: A total of 307 questionnaires out of 721 given out were completed (response rate 42.6%). 115 children (37.5%) felt sleepy during the day for at least 2 days per week, with 52 children (17%) falling asleep while watching television at least 2 days per week. 177 children (57.7%) slept less than the recommended 9 hours on a school day. On a non-school day, 58 children (18.9%) got less than 9 hours sleep. 106 children (34.6%) of children did not have a regular bedtime routine at least 5 nights a week. The most popular activity in the hour before bedtime was watching television; 229 children (74.6%) regularly engaged in watching television at night. 143 children (46.6%) used smartphones for games in the hour before bedtime. 52 children (6.9%) used computers to watch videos during the hour before bedtime. Despite this, 273 of 307 parents surveyed (88.9%) felt that their child did not have a sleep problem. Amongst parents, the most popular activity in the hour before bedtime was watching television (218 parents, 71.0%). 159 parents (51.8%) use smartphones for social media in the hour before bedtime.

Conclusion: Daytime sleepiness was present in a third of children. Most children surveyed were not getting the recommended duration of sleep. Some lacked regular bedtime routine and most used televisions and smartphones before bedtime (which is known to negatively affect sleep quality). However, most parents did not think their child had a sleep problem. Parental role-modeling is challenging due to parents’ own suboptimal sleep habits including a high rate of digital device use amongst themselves. Parental education is needed to ensure their children get the right quality and quantity of sleep.

N110 – Sleep-Disordered Breathing and Behavioral Symptoms in Children in a South-East Nigerian City.

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Background: Sleep-disordered breathing (SDB) comprises sleep-associated breathing difficulties which can lead to significant morbidity in children. It can be assessed with validated questionnaires as screening tools, where polysomnography (PSG) is not available. Data is scarce on these disorders in black children.

Aim: The study aims to determine the prevalence of SDB, its behavioral manifestations and associated risk factors for poor score in children in a South-Eastern Nigerian city.

Methods: A community-based descriptive study was conducted using the child sleep questionnaire (SRBD subscale-070129). Children aged 1 month to 18 years from consenting households were recruited.

Results: Three hundred and ninety nine proxy-reports were analyzed. The mean age was 70 ± 43 months, with a male to female ratio of 1:1. Up to 193 (48.4%) of these children belonged to families of the middle socio-economic status. SDB problems were present in 12.7%. Sleep habits were age-related. Significantly prevalent symptoms included difficulty in waking up from sleep among children aged 1 to <5 years (p = 0.035), and easy distractibility (p = 0.010) and disruptiveness (p = 0.005) among children aged 5 to 10 years old. SDB was highly correlated with the assessed components, with the exception of restlessness (r = 0.019, p = 0.737), easy distractibility (r = −0.085,
p = 0.108) and stoppage of breathing during sleep (r = −0.092, p = 0.759).

Conclusions: SDB prevalence rate in our setting is similar to the previously documented rates in developed countries with high prevalence rate for other components of SDB. Inattention and disruptiveness were significantly associated with SDB and were more notable in children between the ages of 5 and 10 years. Children with significant SDB noted by questionnaire-based study should be further referred for complete PSG test.

N124 – Pulmonary Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma and Epstein-Barr Virus Many Years after Cardiac Transplant.

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Introduction: Primary lung lymphoma is a rare lung disorder, mostly presenting as mucosa-associated lymphoid tissue (MALT) lymphoma; a type of extranodal low-grade B-cell lymphoma. It is a rare pathology in children, with the median age at diagnosis being 50–60 years. Lung location represents 15% of cases and gastrointestinal (GI) tract involvement is the predominant primary location for MALT lymphoma. Unlike the case of GI, MALT lymphoma of the lung has no established association with microbial infections. We present a case of a 16-year-old girl who underwent orthotopic cardiac transplant in infancy and presented with signs and symptoms concerning for post-transplant lymphoproliferative disorder (PTLD). Following recurrent pneumothoraces, she underwent lung biopsy that revealed MALT lymphoma and Epstein-Barr Virus (EBV).

Case Report: 16-year-old female with history of idiopathic dilated cardiomyopathy status post orthotopic cardiac transplant at 1 year of age. Patient had a relatively complicated course until age 15, when persistent cough and declining spirometry triggered a computed tomography (CT) of the chest and abdomen that revealed diffuse lymphadenopathy concerning for PTLD. Laparoscopic mesenteric lymph node biopsy resulted positive for EBV and infectious mononucleosis-like lesion and was followed by mediastinal lymph node biopsy due to uncertainty regarding PTLD, and resulted inconclusive as well. Cough, weight loss and significant decrease in pulmonary function test eventually culminated by recurrent left-sided pneumothoraces, leading to lung biopsy that established MALT lymphoma of the lung as well as infection with EBV.

Discussion: Primary lung lymphoma is a rare disorder and represents only 0.3% of all primary pulmonary malignancies. MALT lymphoma is the most frequent subset of primary pulmonary lymphomas. It may present with pulmonary symptoms such as dyspnea, cough, chest pain, or constitutional symptoms. Our patient developed cough, weight loss and recurrent pneumothoraces; the latter, while an unusual presentation, pointed us to a serious morbidity requiring lung biopsy for diagnosis.

PTLD is a well-recognized and relatively common complication of prolonged immunosuppression in recipients of both solid organ and bone marrow transplants, often associated with EBV. MALT lymphoma has not been classified as an entity within the spectrum of PTLD, and is infrequently associated to EBV. This report raises the question of such link in this patient with pulmonary MALT lymphoma after orthotopic cardiac transplant and in association to EBV.

N129 – Study on Bacterial Contamination of Neonatal Intensive Care Units (NICU) in a Pediatric Hospital in Hamadan, West of Iran.

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Background and aim: Bacterial contamination in hospitals is one of the major problems in hospitals that cause serious damage to humans and society. One of the major causes of the increase in bacterial contamination is misuse of disinfectants and an increase in antibiotics resistance in hospitals. The aims of this study were the evaluation of bacterial contamination of intensive care units (NICU) and determination of antibiotics resistance patterns in isolated bacteria in a Fatemeh hospital, west of Iran.

Material and Methods: This was a cross-sectional study in which 100 samples were randomly collected from environments and apparatus of neonatal intensive care units including washing sink, ward floors, patient beds, phototherapy, oxygen mask, incubator, infant scale, suction and staff fingers. The samples were inoculated into EMB and Blood agar by sterile wet swabs and transferred to the medical laboratory for identification. Strains were tested for antibiogram by NCCLS protocol. The antibiotics disks consisted of: ampicillin, imipenem, ceftriaxone, cefotizoxime, erythromycin, vancomycin, gentamicin, cephalaxine, cefepime and ciprofloxacin. Data were gathered through a questionnaire and analyzed using SPSS 13 software.

Results: The average rate of bacterial contamination of NICU of was 73%. The most contaminated areas were washing sink (98%), suction (74%) and the lowest was phototherapy (35%) and oxygen mask (44%), respectively. The most frequent bacteria isolated were as follows: Staphylococcus epidermidis (17%), Bacillus subtilis (12.5%), Acinetobacter baumannii (11.3%) and E. coli (8.2%). Most of the isolates (60%-90%) were sensitive against imipenem, ceftriaxone, vancomycin, gentamicin, cephalexine, cefepime and ciprofloxacin, whereas most of them were resistant to ampicillin, gentamicin, erythromycin and cephalexine.

Conclusion: Our results showed the considerable bacterial contamination (73%) of NICU in particular with Acinetobacter baumannii and the high drug resistance in strains isolated from hospital; it seems that sterilization and disinfection methods in hospitals were not performed
correctly. Thus, we recommended that health workers should be trained regularly to control the incidence of nosocomial bacteria.

Key Words: Nosocomial infection, antibiotic resistance, bacteria, neonates.

**Abstract:** Although the diagnosis of bronchiolitis is usually straightforward, cardiac, metabolic, musculoskeletal and hematological conditions may present in a similar way and therefore, should not be overlooked.

**Methods:** We describe four cases presenting with increased work of breathing that were treated initially as bronchiolitis. However, the progressive clinical course of these cases and further investigations revealed an alternative diagnosis.

**Results:** The first case was a 36-week baby boy who presented with symptoms of bronchiolitis and was treated accordingly. A slow response to treatment and a subsequent CT scan revealed the diagnosis of congenital lobar emphysema, which needed resection. Another 7-month-old child with similar clinical presentation, was found to have a white cell count of 1032 × 10⁹/l, Hemoglobin 34g/l; platelets of 30 × 10⁹/l. The blood film confirmed the diagnosis of Acute Lymphocytic Leukemia. A third case of a 9-week baby girl showed persistent tachypnea and intermittent grunting out of proportion to her chest signs. Her blood gas revealed metabolic acidosis, urine was persistently alkaline and renal ultrasound showed nephrocalcinosis leading to the diagnosis of distal renal tubular acidosis. Finally, we had 4-week-old boy presenting with symptoms suggestive of bronchiolitis, that was subsequently confirmed to be pulmonary vein stenosis.

**Conclusion:** This case series demonstrated that rare respiratory and non-respiratory conditions can mimic the presentation of common conditions such as bronchiolitis. This highlights the importance of a detailed history and examination in infants presenting with increased work of breathing. When atypical findings are present or there is a delay in response to standard treatment, seeking senior or specialist review and thinking out of the box, is vital.

**N153 – Correlation between Doppler Echocardiography of the Main Pulmonary Arteries and Ventilation/Perfusion Scintigraphy in a Case of Swyer-James Syndrome.**

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**Introduction:** Swyer-James syndrome (SJS) is an infrequent entity sometimes diagnosed as a casual finding on a chest radiograph of a hyperlucent lung or lung lobe. Clinically, patients may have productive cough, shortness of breath, and dyspnea on exertion, sometimes with hemoptysis. Some patients, who have little or no associated sequelae are not diagnosed until they are adults. In the appropriate clinical setting, radiography and CT usually are sufficient to diagnose the condition. Ventilation-perfusion scintigraphy scans may contribute to diagnosis by showing the displayed characteristic pattern of a matched ventilation and perfusion defect. We have recently observed in patients with complicated pneumonia, by Doppler echocardiography of the pulmonary main arteries, that pulmonary artery blood supply is markedly decreased in the affected lung. Ventilation-perfusion scintigraphy was compared with Doppler echocardiography of the pulmonary main arteries in a 2-year-old patient recently diagnosed with this syndrome.

**Case Report:** A 2-year-old boy underwent chest radiography in the context of acute bronchitis. Complete atelectasis of the left lower lobe (LLL) and lingula with bronchiectasis, and hyperinflation of the left upper lobe (LUL) with ipsilateral deviation of the mediastinum were observed. He was a healthy child with wheezing episodes triggered by upper respiratory tract infections. There was no history of cough, expectoration, choking, pneumonia or other significant bacterial infections. He was a well-nourished boy without respiratory distress. Lung auscultation showed hypoventilation and crackles in the left hemithorax. No changes in chest X-rays were observed after an oral course of amoxycillin-clavulanate. A pulmonary CT scan showed atelectasis of the entire LLL with bronchiectasis and hypoattenuation of the rest of the lung segments due to air trapping, thickening of the bronchial tree, bronchiectasis in LUL and retention of secretions. In addition, a decreased size of the left pulmonary artery and decreased vasculature of the left lung were observed. The child underwent fiberoptic bronchoscopy, discarding the presence of a foreign body, intrabronchial lesion or abnormalities of segmentation. A sample of respiratory secretions was collected, with growing of Haemophilus influenzae. Other studies (tuberculin test, sweat test and immune system evaluation) rendered normal results. Doppler echocardiography showed a clear flow asymmetry between the main pulmonary arteries with a markedly decreased blood flow in the left pulmonary artery. The ratio between the right and the left pulmonary artery flow was estimated at 6.9/1.

Ventilation-perfusion scintigraphy showed a matched severe deterioration of ventilation and perfusion of the left lung (perfusion ratio between right and left lungs 9/1). A diagnosis of SJS was established, and recommendations were made to receive respiratory physiotherapy, anti-flu and pneumococcal vaccination, and early antibiotherapy in case of respiratory exacerbations.

**Discussion:** SJS is considered to be a relatively uncommon and complex disease characterized by unilateral hyperlucency of a part of
or the entire lung, with decreased vascularization and air trapping, being currently considered as a form of bronchiolitis obliterans. The syndrome may emerge after an episode of viral pneumonia or bronchiolitis-bronchitis, with progression to a fibrous obliteration of the bronchial lumen that leads to emphysema and a component of vasculitis obliterans, with the consequent alteration of pulmonary perfusion. It is a diagnosis of exclusion, discordant other causes of pulmonary hyperlucency such as pneumothorax, emphysema, endobronchial obstruction, hypoplastic lung, pulmonary embolism or agenesis of the pectoralis major muscle. Pulmonary CT is the test of choice for diagnosis, showing destruction of the affected lung parenchyma, with or without bronchiectasis, in addition to an ipsilateral pulmonary artery with diminished caliber. Ventilation-perfusion scintigraphy scans may contribute to diagnosis. In our patient, a non-invasive and accessible test such as Doppler echocardiography revealed a decrease in pulmonary artery flow on the affected side, which correlated with the degree of pulmonary hypoperfusion observed in the ventilation-perfusion scintigraphy. This finding suggests that Doppler echocardiography of the main pulmonary arteries could be a simple method to verify the degree of pulmonary hypoperfusion in SJS and other unilateral or asymmetric pulmonary disorders.

N154 – Respiratory Health in Children with Down Syndrome in Ireland.

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Purpose: A significant proportion of children with Down Syndrome (DS) frequently suffer from respiratory conditions such Obstructive Sleep Apnea (OSA). International guidelines recommend screening for OSA in all children with DS. The prevalence of respiratory conditions in Irish children with DS is unknown. The prevalence of Down Syndrome as estimated by Down Syndrome Ireland is 1 in 546 live births. This is significantly greater compared to the worldwide incidence as reported by the World Health Organization of between 1 in 1,000 to 1 in 1,100 live births worldwide.

Methods: A respiratory health questionnaire was distributed to all parents with children with DS in Ireland registered with Down Syndrome Ireland (DSI).

Results: Three hundred and ninety three (393) surveys were returned. 27% of parents surveyed reported a diagnosis of OSA in their child. The diagnosis rate was very low compared with the high rate of report of OSA symptoms. Over 50% reported snoring, apneas and restlessness at night. In children who have not received a diagnosis of OSA, the median number of symptoms reported was 4 with older children having a higher burden of symptoms. High frequency of symptoms known to impact negatively on quality of life included daytime somnolence (47.0%) and new enuresis (20.0%) in children with a diagnosis of OSA, poor compliance with prescribed therapy was described (43% never use night-time CPAP). Compliance and perception of benefit were directly related to each other. This has an immediate and long term impact. However, those that wear CPAP report a clear benefit as most describe treatment as moderately or extremely successful.

One quarter of parents reported recurrent chest infections. One third reported concerns regarding swallow.

Implications: This is the largest survey of its kind conducted internationally with parents of children with Down Syndrome reporting significant respiratory morbidity. There is a high prevalence of OSA with variability in perceived benefit of treatments and in compliance with CPAP. A significant proportion of children have recurrent infections of prolonged duration. This survey highlights the need for increased awareness and services for children with DS who are at a higher risk of developing respiratory disorders. There are significant clinical, service provision and economic implications needed to address these findings. The authors are considering these in the context of what matters to our patients.

N192 – Sleep Study in the Pediatric Population of Castilla La Mancha. Do We Have Good Tools at The Present Time?

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Objective: The objective of the project is to analyze sleep in the pediatric population of Castilla la Mancha to produce a representative percentile graph of our population with the aim of comparing it with those used at the present time.

Method: Observational, retrospective study of the children who were attended at the healthy child’s review in our clinic for 9 months. The number of hours of sleep was recorded, including the difference between day and night hours. Each patient was associated with a percentile according to graphs currently used as a reference (Iglowstein, 2003). The data were analyzed bearing in mind the different age ranges for the elaboration of a representative percentile chart of our population.

Results: A total of 311 children were analyzed in a 9-month period: 51 children of 6 months, 56 children of 12 months, 63 children of 2 years, 46 children of 4 years, 57 children of 6 years and 38 children of 12 years. The results show a clear difference between the percentiles of our sample and those currently used as a reference. Two clear examples would be the following (our graph VS reference graph):

1- Infant of 3 months who sleeps 13 hours a day: 50th percentile vs. 25th percentile
2- Infant of 3 months who sleeps 10.5 hours a day: 10th percentile vs. 2nd percentile.
3- Infant of 3 months that sleeps 8 hours a day: percentile 3 vs percentile <1.
4- A 12-year-old boy who sleeps 9 hours a day: 50th percentile vs. 25th percentile.
5- A 12-year-old boy who sleeps 7 hours a day: percentile 3 vs. percentile <1.

Conclusions: The graphs currently used as a reference for sleep are not representative of our population because there are cultural and geographical differences.

Sleep percentiles obtained from the analysis of our population clearly differ from those currently used as a reference. The percentile ranges obtained after the analysis of our population are clearly lower than those currently used as a reference.

Reflections: Sleep disorders are very prevalent and a frequent reason for consultation. There is evidence of the inversely proportional association of sleep duration and various pathologies, mainly overweight and obesity.

Percentiles of sleep duration are a fundamental tool for detecting children at risk of developing sleep problems.

The current graphs emerge from a sample of 493 subjects from Zurich in 2003 and are not representative of our population.

The use of the graphs originated after the study of our population would allow us to identify more effectively those patients with sleep deprivation and therefore at risk of developing secondary problems to this sleep deprivation.

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N197 – A rare case of hemoptysis: mucoepidermoid carcinoma of the lung in a 12-year-old boy.

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Introduction: We present a case of a 12-year-old boy with a 12-month history of chronic cough and hemoptysis.

Case report: A 12-year-old boy with poorly controlled asthma, who was treated with inhaled steroids during exacerbations, presents with a year-long history of predominant nocturnal, productive cough, associated with two episodes of hemoptysis. There were no other relevant respiratory symptoms. A chest X-ray was performed and revealed a right upper lobe collapse and consolidation, leading to his referral to our institution for a thorough diagnostic workup. There was no history of foreign body aspiration, fever, night sweats or weight loss. He underwent an initial flexible bronchoscopy that showed an endobronchial exophytic nodular lesion at the right upper lobe (see figure 1). Given his longstanding history of respiratory symptoms and the area from which he was referred, our initial diagnosis presumption was endobronchial tuberculosis. Nevertheless, his tuberculin skin test was 0mm and both Ziehl-Neelsen stain and polymerase chain reaction (PCR) in the bronchoalveolar lavage (BAL) sample and bronchial brushing were negative for Mycobacterium tuberculosis. This sample was positive for Streptococcus pneumoniae; therefore, he was commenced on IV antibiotics, but he persisted with hemoptysis. A high resolution computerized tomography scan (HRCT scan) of the chest was performed looking for malignancy or vascular abnormalities. This study revealed a nearly complete atelectasis of the right upper lobe plus an endobronchial lesion that obliterated the right upper lobe bronchi. It also showed cylindrical bronchiectasis and some intraparenchymal cavities. A second bronchoscopy was performed showing similar findings, therefore an endobronchial biopsy of the exophytic lesion was performed. Bronchial biopsy was characterized by mucus-secreting cells with abundant fluffy cytoplasm and large mucin vacuoles, compatible with a Mucoepidermoid Carcinoma (MEC).

The child underwent a lobectomy of the right upper lobe, guided by flexible bronchoscopy. Given that worldwide reports suggest surgery rather that chemotherapy or radiotherapy, our patient did not receive any of these therapies and underwent surgical removal. The tumor was completely resected and its histopathological analysis was consistent with a well differentiated MEC (0.6 × 0.3 × 0.8 cm), stage T1N1M0 with metastasis to 1 of 39 lymph nodes without extracapsular extension. Currently, the patient continues under routine surveillance, he is thriving well, asymptomatic and his lung function remains stable.

Conclusion: Among the rare causes of hemoptysis which the pediatric pulmonologist can expect to encounter, tumors such as pulmonary adenomas or carcinomas may be present, particularly in older children. Therefore, malignancy must be always considered as part of the differential diagnosis of persistent hemoptysis in children with no underlying chronic lung disease.

Mucoepidermoid carcinoma is a rare disease that accounts for less than 1% of primary malignant lung tumors. They are derived from epithelial and mucous secretory cells with a common origin in the salivary glands. These tumors do not have a characteristic trait that differentiates them from other benign or malignant lesions. MEC generally occurs in the central bronchial region. In our patient, the tumor was arising from the right upper bronchus. The common clinical symptoms and signs include cough, hemoptysis, bronchitis, wheezing and sometimes fever; therefore, the clinical picture of MEC is similar to other common entities such as asthma, lower respiratory tract infections or pneumonia. Tumors are usually small, ranging from 0.5 to 6 cm. They are usually soft, polypoid and pink-tan in color. Their diagnosis is based solely in the histopathology report. There is no standardized treatment and their prognosis depends on the histological grade of the tumor.

MEC is a rare entity that pediatric pulmonologists should encounter and keep in mind.
Figure:
Figure 1. Exophytic endobronchial lesion with hemoptysis in right upper lobe.

Below: macroscopic and microscopic picture of the lesion.

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Choosing the Right Controller Therapy in Pediatric Patients with Asthma

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Current asthma guidelines have been directed to compiling information and attempting to standardize care to assist clinicians in the management of asthma. Algorithms were introduced to summarize a step-wise increase and decrease in medications in order to achieve optimal control. Medications are placed in a step-wise approach with a preferred and alternative medication being listed. Inhaled corticosteroids (ICS) are the cornerstone of treatment and the step-care approach utilizes a scheme of increasing ICS dose along with supplementary medications based on available studies.

With the last update of the NAEPP EPR-3 guidelines in 2007, emphasis was placed on achieving asthma control, defined within two domains, impairment and risk. Impairment consists of day and night symptoms, rescue medication use, pulmonary function and questionnaires to assess these measures over a short-term period. The term risk brings attention to the assessment of the potential for exacerbations, adverse effects to medications and progression of the disease. The Centers for Disease Control recently reported that we have reduced asthma mortality and we are seeing a reduction in hospitalizations but new goals are being set to further reduce asthma hospitalizations.

We have an opportunity to significantly reduce the worldwide burden of asthma in children and impact consequent respiratory outcomes in adults. However, as reviewed in a recent Rostrum published in the Journal of Allergy and Clinical Immunology, this will require a paradigm shift that is directed at altering the natural history of asthma, reducing asthma exacerbations and preventing long-term adverse outcomes of childhood asthma. The essential tools proposed for this proactive approach include (1) assessment of lung function over time (lung trajectories), (2) the Composite Asthma Severity Score (CASI), (3) a panel of useful biomarkers, (4) the Seasonal Asthma Exacerbation Prediction Index (SAEPI), and (5) application of adherence monitoring technology. The goal is to reduce long-term consequences of the physiologic and biologic processes leading to persistent asthma, severe asthma, and COPD.

Since the last update of the NAEPP asthma guidelines in 2007, there have been several key NHLBI and NIAID studies that should be considered in future asthma guidelines updates. It is very important to make the appropriate diagnosis, so that treatment can be started and to provide guidance on treatment choices in mild to moderate asthma severity. However, countries vary in medication regulatory approval and cost considerations. Each reiteration of asthma guidelines must also address the core needs of the health disparate population while also identifying those who are not responding for advanced care treatment strategies.

There is growing concern regarding the long-term outcomes of early and poorly controlled childhood asthma. These observations should prompt a practice change to identify patients at risk for adverse outcomes.
respiratory outcomes of childhood asthma, to monitor disease progression, and to design intervention strategies that could either prevent or reverse asthma progression in children. We also have the opportunity to implement a more personalized or individualized approach to asthma care and controller medication selection at all levels of severity and in all age groups including the elderly. Attention should be directed toward minimizing risk as well as impairment with a goal to achieve optimal asthma control.

1 | LUNG FUNCTION TRAJECTORIES

Recent reports on long-term studies have shown that asthma has the potential to lead to persistent and irreversible loss in lung function over time. The varying patterns of lung function development over time in children with mild to moderate persistent asthma were depicted by McGeachie et al from 20 years of follow-up in the NHLBI Childhood Asthma Management Program (CAMP). Of four patterns identified, reduced lung growth from early childhood was noted in two patterns and two patterns displayed evidence of early decline in pulmonary function after age 20 years. Approximately 11% of those participants met physiologic criteria for advanced levels of COPD in early adulthood. Therefore, children with persistent asthma should have ongoing measures of lung function to classify their lung function trajectory/phenotype and use it to consider an intervention strategy, such as trigger avoidance, assessment of medication adherence, increased caregiver/provider communication, assistance with medication administration in the school setting, smoking cessation, smoking avoidance, home assessment, career counseling, reversibility testing with conventional therapy and a clinical trial of immunomodulator therapy. In addition, patients should be cautioned against potential harmful effects of vaping, fracking, chemical exposures, and climate change.

2 | COMPOSITE ASTHMA SEVERITY INDEX (CASI)

The CASI was developed by the NIAID Inner City Asthma Consortium (ICAC) as a composite outcome measure to assess the impact of anti-IgE. CASI contains all of the key components in the impairment and risk domains and is the best measure currently available for overall asthma burden. The CASI score correlates with levels of asthma severity and has a defined minimal important difference. It is available free of charge at www.asthmaseverity.org. It can be used to assess the impact of an intervention and prompt step-up or step-down decisions.

3 | BIOMARKER PANEL

The NIH Asthma Outcomes Task Force identified a set of biomarkers that should be considered in developing all NIH funded asthma research. These biomarkers include a panel to assess allergen sensitization as a core biomarker for characterization and supplementary biomarkers including blood and sputum eosinophils, exhaled nitric oxide, and total serum IgE, for addressing specific study questions. These biomarkers have proven useful in identifying young children who respond best to daily ICS and older children who have a more favorable response to inhaled corticosteroids over leukotriene receptor antagonists. These biomarkers have also been applied in decisions around the use of immunomodulator therapy in severe asthma and have been associated with a likelihood for response.

4 | PREVENTING SEASONAL EXACERBATIONS

Current therapy will likely reduce the risk of an asthma exacerbation in most but not all patients. The Seasonal Asthma Exacerbation Predictive Index (SAEPI) was also developed and validated by the NIAID ICAC to identify children at risk for an asthma exacerbation. An exacerbation in the prior season and low pulmonary function are predictors of an asthma exacerbation at any time of the year, while measures such as an increased number of allergen skin test positives, increased ICS dose, increased exhaled nitric oxide, as well as increased levels of blood eosinophils, total and specific IgE may be useful for predicting a seasonal asthma exacerbation, especially during the fall season and developing prevention strategies.

5 | ADHERENCE MONITORING

It is important to emphasize education for patients and parents to achieve better adherence to the management plan. Electronic adherence monitoring techniques are now available to monitor day to day rescue and long-term controller therapy. Applying this technology can identify patients with inconsistent adherence or those with breakthrough symptoms. Application of these tools on a wider scale will not only improve adherence, but also identify adherence phenotypes. Adherence monitoring may also lead to new strategies to support adherence to the medication schedule, a reduction in medication for those that are well controlled, or justify the use of advanced therapies, such as an immunomodulator that can incur higher costs for those who remain inadequately controlled despite optimal conventional therapy and adherence.

In the past two years, a number of new medications and strategies have been added to our armamentarium for asthma management including a long-acting anticholinergic, tiotropium, and biologics such as omalizumab and anti-IL5 agents (mepolizumab, reslizumab and benralizumab) with varying levels of approval for use in children along with several other medications, such as anti IL4/13 (dupilumab) and perhaps anti-TSLP, that await approval for asthma.

At this time, these tools could be applied now in specialty care and subsequently in primary care after a suitable implementation and validation period. Applying these tools could change the dialogue
between the asthma specialist, primary care physician, the patient and parent involved and shift the paradigm from a reactive management strategy to a prevention strategy. The monitoring of risk as proposed in Figure 1 can be used to more completely assess risk for exacerbations and monitor progression of asthma to further reduce asthma burden. With the rapid advancement in technology, the introduction of new medications, and new biomarkers, we will be able to move toward a biomarker directed treatment plan and technology-oriented monitoring. Understanding the impact of social determinants of health, such as stress, access to food and shelter, and continuity in healthcare, have on asthma will provide novel strategies for supporting children in the inner city and rural environment, especially those who are affected by access to care or education opportunities.10

Expert panels for asthma guidelines face the challenge of integrating a rapidly developing and complex literature when it comes to the increased number of new medications being introduced along with potential biomarkers and patient clinical and social characteristics that could be used in personalizing such an approach. Future guidelines should incorporate recommendations to follow spirometry over time and define lung trajectories to assess risk for reduced lung growth and early decline, asthma burden, appropriate use of biomarkers in selecting and monitoring therapy, incorporating social determinants, assessing risk for seasonal exacerbations, and consideration of adherence monitoring for asthma that is difficult to manage (Figure 1).

This approach to reduce asthma exacerbations could have a long-term impact on the lifespan of asthma in individual patients.

CONFLICT OF INTEREST

S.J. Szefler has consulted for Aerocrine, Astra Zeneca, Boehringer-Ingelheim, Daiichi Sankyo, Glaxo Smith Kline, Genentech, Novartis, Roche, and Teva and has received research support from the National Institutes of Health, the National Heart, Lung and Blood Institute, GlaxoSmithKline, and the Colorado Cancer, Cardiovascular and Pulmonary Disease Program. He is also a former member of the Global Initiative for Asthma Scientific Committee and the National Asthma Education and Prevention Expert Panel 3.

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