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EDITORIAL: PAEDIATRIC ASSEMBLY

Paediatric respiratory disease: past, present and future

Paediatric Assembly contribution to the celebration of 20 years of the ERS

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Paediatric respiratory disease has changed in the past 20 yrs; we could fill a whole issue of the journal paying tribute to our famous forebears. We are posing new challenges to our colleagues in the field of adult respiratory disease. They have to learn to deal with conditions that 20 yrs ago were rare in the adult chest clinic, such as cystic fibrosis (CF) and the long-term consequences of premature birth and congenital malformations of the respiratory tract. Furthermore, studies in childhood are challenging pathophysiological concepts throughout life.

The many great prospective birth cohort studies have shed light on the different patterns of wheezing, their risk factors and their evolution through childhood. Who would have thought it was good to be born in a barn! It is becoming increasingly clear that even for ''adult'' diseases, such as chronic obstructive pulmonary disease (COPD), antenatal and early life events are at least as important as smoking in adulthood [1]. CF has become a disease also of adults [2]. Although many factors have contributed, the main reason has been the development of expert special CF centres, a model increasingly adopted by adult teams. This can serve as a model for other diseases; how a well-structured multidisciplinary approach to treatment can translate into benefits for patients. Perhaps numerically the most important achievement is in the field of public health. The benefit of the decrease in invasive bacterial infections, due to vaccination programmes for infants, is among the most important achievements of the past.

Other areas of change include the survival of ever smaller preterm neonates. These children are reaching adult life with impaired lung function and abnormal computed tomography scans. What will happen to their ageing lungs? Interstitial lung disease (ILD) is becoming increasingly well understood, with new genetic entities, such as surfactant protein C mutations, having relevance to adult ILD [3]. The advent of powerful new therapies, in particular antibiotics and anti-inflammatories, has led to the need for better monitoring tools, including bronchoscopes small enough to examine even preterm babies, and novel physiological testing. Specific future challenges are dealt with below; first, specific disease areas; secondly, monitoring tools; and, thirdly, paediatric intensive care.

SPECIFIC DISEASES

The newborn child

Much progress has been made in neonatal practice including better application of established therapies such as antenatal corticosteroids and exogenous surfactants, and recognition of their long-term effects. This lesson has also resulted in larger trials, such as the use of nitric oxide in preterm infants [4] and noninvasive ventilation, in this population [5]. Physiological definitions have been improved (such as that of chronic lung disease of prematurity (CLD) or bronchopulmonary dysplasia (BPD)) and ongoing trials throughout the world are focusing on the optimal oxygen saturations for preterm infants (BOOST (Benefits of Oxygen Saturation Targeting) and BOOST 2). Longer term respiratory outcomes are essential to determine if prematurity is a risk factor for development of COPD, and there is increasing recognition that children with mild neonatal lung disease may have significant long-term consequences [6]. The recognition of antenatal infection with *Ureaplasma* spp. [7] as a cause of preterm birth is re-emerging as potential targetable option to decrease the burden of CLD/BPD.

Paediatric asthma

Childhood asthma will continue to be a main focus of the speciality. Although prevalence may have plateaued in parts of the developed world, it is rising elsewhere [8]. New approaches to the understanding of underlying mechanisms increasingly depend upon phenotype characterisation [9], and cutting-edge biology techniques are needed to define phenotypes, as exemplified by U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes), a partnership between academia and industry under the Innovative Medicines Initiative of the European Union. The very early origins of asthma, including antenatal lung health, will continue to be a focus [10, 11], particularly including epigenetic mechanisms.

Allergic sensitisation is a common, but not obligate, feature of asthma. Immunoglobulin E sensitisation to specific allergens alone is not sufficient to produce allergic disease. Recent discoveries have focused upon epithelial barrier function;

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ORMDL3, recently shown to be important in sphingomyelin metabolism [12], and the genes expressed in the epithelium, *e.g.* filaggrin [13], are implicated in asthma. Does the combination of reduced barrier function in concert with infection and allergen exposure lead to asthma?

Although many children with asthma are easily treated with low-dose inhaled corticosteroids, a hard core of severe therapy-resistant asthmatics continue to be symptomatic. The challenge will be to characterise these children, and select the appropriate novel, likely cytokine-specific therapy, for the individual. We must find a way of safely and ethically testing these medications in children.

Cystic fibrosis

The past focus on symptomatic therapies has been important, but a better understanding of the cellular consequences of cystic fibrosis transmembrane conductance regulator (CFTR) mutations has led to strategies that target the primary abnormality. Gene therapy, CFTR-specific pharmacotherapy and ion channel modulators are currently in clinical trials and some compounds will probably become available in the near future [14]. Ultimately, combination therapy addressing different aspects of cellular dysfunction (*e.g.* intracellular trafficking and channel opening) may show the highest efficacy, but defining the best combinations will be challenging.

Newborn screening will probably become available throughout Europe in the next decade. An early diagnosis and implementation of CF care alone will not be sufficient to avoid early lung damage [15]. While studies are currently underway to find more efficacious early intervention strategies, there are no validated outcome measures for infants and young children. Therefore, in parallel to developing new therapies, validation of new outcome measures is a high priority for the near future [16].

Primary ciliary dyskinesia and non-CF bronchiectasis

In primary ciliary dyskinesia (PCD), knowledge of the spectrum of gene mutations and their functional consequences will, most likely, increase. In combination with noninvasive screening tests, such as measurement of nasal nitric oxide, this knowledge will help to clarify the incidence of this underdiagnosed disease [17]. Ciliopathy is an expanding spectrum: ciliary dysfunction has been found in cystic kidney and liver disease, retinitis pigmentosa, heterotaxy and congenital heart disease, and complex syndromes. The multiple functions of primary, nodal and motile cilia are only just becoming understood, and these will undoubtedly be a major research thrust. Treatment strategies have been largely copied from CF. Longitudinal observational studies will help to define key factors that drive structural airway damage in both PCD and non-CF bronchiectasis.

Paediatric sleep medicine

Current research focuses on assessing the prevalence of obstructive sleep apnoea (OSA) and on the relationship of OSA with subsequent cardiovascular disease, neurological impairment and metabolic syndrome. The treatment of OSA in children is not easy or straightforward, and at present there are very few data on what the threshold for treatment should be, or what the consequences of under-treatment would be [18]. Paediatric sleep medicine is one of many areas that will be impacted by the epidemic of childhood obesity. The research focus in this field will be upon development of clinical pathways for screening children at risk and identification of trigger points that lead to more detailed investigation or intervention.

Paediatric lung transplantation

Paediatric lung transplantation is a much smaller field than adult lung transplantation. It is, therefore, inevitable that paediatric specific research is limited, and that many advances follow on from adult research and practice. The improved outcomes reported in adults have also been reported in paediatric subjects, with international data now reporting a median post-transplantation survival of ~5 yrs, and some centres reporting outcomes better than this [19].

The focus of the next decade will be collaboration with adult colleagues to establish a new definition of bronchiolitis obliterans syndrome and chronic graft dysfunction, which in turn can act as a springboard for a better understanding of the pathophysiology and potential treatment of this heterogeneous condition.

MONITORING TOOLS

Paediatric respiratory physiology

The past decade has seen important advances in respiratory physiology in children of all ages. There has been further standardisation of infant lung function testing, to the point where a great majority of infant lung function laboratories now use commercial equipment and perform testing according to internationally agreed protocols. In the same period, the gap between infant lung function and school age lung function has been bridged. Collaboration between international groups of researchers on standardisation and quality control has culminated in publication of a joint European Respiratory Society/American Thoracic Society guideline in 2007 [20]. The third major feature of the last decade has been a resurgence of interest in alternative functional measurements. Inert gas washout, oscillometry, interrupter resistance, plethysmographic airway resistance and structured light plethysmography have all made great advances. In many cases these are not new techniques but developments and modifications of old ideas.

The challenge of the next decade will be to provide clinicians and researchers with new tools for the management of individual patients and as outcome measures in epidemiological and intervention studies.

Paediatric airway endoscopy

Ultrafine flexible instruments with a working channel of 1.2 mm can be used to traverse and examine the entire airway, from nostril to bronchus with minimal mechanical distortion of the airway anatomy and dynamics.

Today, paediatric flexible bronchoscopy (FB) is a well-established diagnostic investigation. The evaluation of airways obstruction, which may involve the upper and lower airway or both, is the most common indication for FB in infants [21].

The diagnostic yield of FB in many clinical circumstances can be increased by the information obtained with bronchoalveolar lavage (BAL) [22]. BAL is an important tool in the diagnosis of

lung infection in both immunocompromised and immunocompetent children, because pathogens can easily be identified from small BAL samples. In children with chronic ILDs, BAL may have an important role in excluding or confirming a specific diagnosis, in characterising the alveolitis and in monitoring the patient during treatment and follow-up.

Interventional bronchoscopy is increasingly important, and involves the restoration of airway patency or stability, or the removal of tissue or substances from the airways or alveolar spaces that interfere with normal function. Interventional bronchoscopy includes laser therapy, dilatation of airway stenosis, placement of a stent, total lung lavage and treatment of bronchopleural fistulae [23]. Our colleagues in adult practice are ahead of us with techniques such as endobronchial ultrasound; as the equipment is miniaturised, children will be able to benefit from the techniques. Better instruments, better training and better research applications of endoscopy to improve our understanding of paediatric respiratory diseases are still needed.

INTENSIVE CARE

In paediatric intensive care there has been major progress. Protection of the lung against ventilator-induced barotrauma and volutrauma continues to press us to reduce pressures and volumes. Newer technology in ventilators is helping with this, and the prospect of patient-driven ventilators (*e.g.* neurally adjusted ventilatory assist) is close. Our understanding of ventilator-associated infection also helps to minimise morbidity, and lessons from adult practice are showing us just how avoidable such complications are. There is also a growing recognition that the longer term care of children with neuromuscular disease needs addressing [24].

A GLORIOUS PAST, A GREAT FUTURE

The number of surviving children born very prematurely (before 25 weeks gestation, birth weight $<$500 g) will increase. For adult physicians, this will be a new population at high risk for COPD.

Virus-induced bronchitis and bronchiolitis will continue to be a cause of respiratory morbidity in infants and pre-school children. There is no effective treatment for bronchiolitis, and this is a gap that must be plugged. Further development of vaccines for prevention of early infections could have a major impact on risk of asthma later in childhood. We need strategies to prevent episodic (viral) wheeze progressing to multiple trigger wheeze and asthma. We know that inhaled corticosteroids are not able to prevent this change. Novel insights are needed.

Asthma is and will be the most common chronic disease in school children and adolescents. In allergic rhinitis and asthma, new individualised allergy vaccines could become a possible treatment to prevent asthma and/or deterioration. Novel therapies and biomarkers to select children and monitor the effects of treatment will be essential.

In CF diagnosed by newborn screening, we need new therapeutic combinations to change morbidity. As genotype-specific treatments become available and, most likely, are applied to young children before the disease has progressed, we need biomarkers to select those at risk of more rapid deterioration, and validated end-points in very young children, in order to assess the response to treatment. The risk from the recrudescence of tuberculosis and, especially, multidrug-resistant and extensively drug-resistant disease requires multiprofessional and international attention. The same is true for other emerging infections, for example methicillin-resistant *Staphylococcus aureus*. New diagnostic tools, such as interferon-γ assays, might provide more specific test results than the tuberculin skin test.

We will become better and better at salvaging the very sick child. Chemotherapy for cancer, and transplantation of bone marrow, lung and other solid organs will improve the prognosis of malignancy and progressive lung diseases like ILD in children. Conversely, this will lead to increased pulmonary complications. We need to be alert to detect and properly manage these new complications.

The use of technology, both noninvasive and invasive, to keep children with neurological and airway diseases alive and at home will become increasingly important. As ever smaller children use these techniques, development of child-specific machines and interfaces will become ever more important.

Orphan lung diseases, such as pulmonary fibrosis of unknown origin, autoimmune diseases with lung complications, ILD and congenital malformations of the respiratory tract, will continue to pose a burden on healthcare and require highly specialised tertiary care centres. Increasingly, international networks are cooperating to accumulate big series of patients to learn more about these patients.

So what are the themes of the past decades, and for the future? Much work has been done, but many more questions are being developed [25]; above all, we need horizontal collaboration between groups of specialist paediatric pulmonologists, and vertical collaboration with adult respiratory colleagues. The future is with the young paediatric pulmonologists, and we must ensure that they have the best possible training; the pHERMES initiative bids fair to deliver this [26]. *Floreat ERS*!

STATEMENT OF INTEREST

A statement of interest for E. Baraldi can be found at www.erj.ersjournals.com/misc/statements.dtl

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