Pediatric Respiratory Research Opportunities

Lung Growth, Development, and Repair
Infectious Agents
Asthma
Environmental Exposure
Regulation of Respiration
Addiction Research
Care and Impact of Chronic Respiratory Disease
Cystic Fibrosis
Sickle Cell Disease
Other Rare Conditions

Pediatric Respiratory Research Challenges

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Conclusions

The American Thoracic Society (ATS) has previously published two documents that outline future directions for research into respiratory diseases (1, 2). These documents focused on a wide range of conditions of importance to adults. The Pediatric Assembly of the ATS has put forth the following document to build on the previous documents by outlining the research priorities of particular importance to the respiratory health of children.

The pediatric respiratory system must grow and develop even when faced with injury and repair. In this context, it is not surprising that the mechanisms and consequences of disease are likely to be different in children. Many diseases that manifest themselves in adulthood, such as chronic obstructive pulmonary disease, appear to originate during childhood, obliging us to understand the ontogeny and early manifestations so that we may develop effective preventive strategies. Since 1998, there have been significant advancements in scientific knowledge and technology that make a report on priorities for research into child respiratory health timely. The new knowledge derived from genomic and proteomic research, both in human and other species (e.g., Pseudomonas aeruginosa), provides a great opportunity for new and innovative approaches to therapy. Such technologies are already being applied to the study of some lung disorders, and will certainly increase in the near future.

Advances in analytic technology and in methods to assess lung disease, including high-resolution computed tomography scans and noninvasive and minimally invasive assessment of lung function in young children, will facilitate our ability to prospectively monitor children at the earliest stages of disease and critically evaluate responses to novel therapies. However, these technologies require modification and adaptation to the small pediatric lung and the uncooperative child, and the development of age, sex, and ethnicity-specific standards.

There have been major advancements in analytic methodologies, such as bioinformatics. However, to have a major impact, bioinformatics requires large datasets. Such datasets are gradually being developed through computerized databases. These databases raise, in turn, a variety of ethical issues related to confidentiality. Coupled with these concerns are issues related to the participation of children in medical research. Recent legislation has created potential conflicts by limiting participation of children in medical research. Such research is necessary for the understanding of normal growth and development as an obligate precursor to an understanding of disease processes in children.

Major advances have been made in the assessment of the impact of disease on patients and families. In addition, we have witnessed an accelerated understanding of the importance of attitudes and perceptions of illness, and how these concepts mature and influence the course of disease. Such knowledge has had a major impact on our evolving definition of outcome measures. In pediatrics, these outcome measures are complicated by the need to view the child with lung disease in the context of the family unit.

At a time when there is an urgent need and abundant opportunity for more investigators and caregivers, there is a crisis in manpower in pediatric pulmonology around the world. Mechanisms must be developed that will excite and entice bright young minds into the field, and nurture and sustain them throughout their careers.

This document addresses several areas of particular importance to pediatric pulmonology. These include the following: lung growth, development, and repair; respiratory infections; asthma; environmental exposure; regulation of respiration; addiction research; and the care and impact of the child with chronic lung disease, cystic fibrosis (CF), and sickle cell disease. This problem-based approach has been taken because research into fundamental mechanisms was elaborated upon in the 1998 document. The current document should be interpreted within the context of the previous documents. A common theme among these problems is the requirement that fundamental and applied research be linked through translational investigation.

It is not possible to rank research priorities. From a global perspective, infectious disease prevention and control are clearly of highest priority. In industrialized nations, asthma is a top priority. However, research into lung development, repair, and remodeling might have the greatest long-term impact on disease prevention and treatment across the age spectrum in a variety of respiratory diseases. The goal of this document is to highlight where new research opportunities exist.
The regulation of fetal lung development, the adaptation to extraterine existence, and repairability of the inflammatory response, and mechanisms of repair and plasticity in children has tremendous potential for impact. The last factor has the greatest potential for impact. If we can learn to adapt the growth and repair mechanisms of immature lungs to mature lungs, we could realize the renewal of healthy lung tissue in both children and adults.

Improved survival of smaller, less mature infants increases both the risk and severity of chronic lung disease; defined as the requirement for supplemental oxygen for at least 28 days. The nature of the pathologic lesions now seen is different from that originally defined as bronchopulmonary dysplasia due to the marked immaturity of the respiratory system of the patient typically now hospitalized in neonatal units. A reevaluation of the pathogenesis and repair mechanisms that lead to this more current form of chronic lung disease of the newborn is required.

Using cellular and animal models, and ultimately human tissue, the role and timing of growth factors required for normal lung maturation, including alveolarization, branching morphogenesis, and vascular and lymphatic development, need to be explored. The role of prematurity and intrauterine infection on lung development and postnatal lung responses requires further study. The interaction of the immature lung with the external environment must be studied at all levels. This will include trials of medical, pharmaceutical, and ventilatory support that, by necessity, will require the development of study center networks with uniform protocols, and sophisticated methods of investigation and analysis that can handle the complex mix of data. Although many investigative tools already exist, others need to be developed specifically for pediatric patients. This is especially true in the investigation of inflammatory responses because of the technical issues involving invasive procedures, and limited sample sizes.

Infectious Agents

Pneumonia, whether viral or bacterial, accounts for significant mortality and morbidity. The lack of simple, noninvasive diagnostic tests often results in the inappropriate use of antibiotics, leading to the rise of resistant organisms. The development of such diagnostic ability is of high priority.

Respiratory syncytial virus has major consequences for children, both in the number of children affected and the potential for serious consequences, including death. Significant steps have been made in the development of respiratory syncytial virus treatments, including a recombinant humanized monoclonal antibody preventive strategy. However, the current product requires monthly injections and is reserved for at-risk children. A true vaccine with a simple vaccination schedule and improved efficacy is required to prevent the morbidity associated with respiratory syncytial virus infection, including hospitalization and recurrent wheezing episodes. A fuller understanding of the interaction between respiratory syncytial virus and the host, including the inflammatory response and how to prevent both the development of acute respiratory embarrassment and long-term sequelae, is needed. The same issues apply to other viral respiratory illnesses, such as seasonal outbreaks of influenza.

Other infectious agents, such as Mycobacterium tuberculosis and the emergence of resistant organisms, also are major sources of morbidity and mortality for children. For tuberculosis, rapid diagnostic field tests and shorter, more tolerable regimens are required. A fuller understanding of development of antibiotic resistance, and bacterial defenses would be of great help. In this regard, genomic and proteomic research of infectious agents will help in the development of effective antimicrobial therapies.

Asthma

Asthma prevalence has increased dramatically in children over the past 20 years. Physician-diagnosed asthma now affects between 10 and 20% of children. The reasons for this marked increase in prevalence are unclear. Asthma in childhood often has a much different clinical pattern than in adults, with long periods of quiescence punctuated by virally induced exacerbations that often diminish in frequency with time. In this context, asthma therapy, particularly the use of corticosteroids, has only been partially successful in children, who have lower thresholds for adverse effects. A new model that is appropriate for children is required to prevent and treat childhood asthma.

Work has already begun on large epidemiologic surveys to better define the risk factors and lifelong natural history of asthma. Such work involving well-defined cohorts is important, and must continue, but will only yield a true picture in many years. A fuller understanding of childhood asthma will require the combined skills of epidemiologists, geneticists, airway biologists, and clinicians. The development of noninvasive markers of disease severity and progression is important. There will need to be limited studies of a more invasive nature to elucidate not only the changes in the airway lumen but also the events in the airway wall, and the interaction between the epithelia and parenchyma. We also require animal models that demonstrate the maturational changes seen in humans to examine the role of immunologic immaturity in the development of asthma.

Environmental Exposure

Our environment, both in the developed and developing world, is becoming more complex and polluted. Yet there is little knowledge concerning safe exposure limits for most of the substances we are exposed to. In the developed world, this knowledge gap has led to major quandaries as to how to balance environmental and economic concerns, most evident in the current debate over greenhouse gas emissions. In the developing world, exposure to the fumes of biomass fuel contributes significantly to the development of lung disease in children. It is as a legacy to our children that we must have a greater understanding of the health risks associated with exposure to current chemical and natural compounds, and those to be developed and used. In particular, we must understand how health risks vary with maturational status. In this regard, the effects of passive cigarette smoke exposure, in utero and postnatal, require further study.

Regulation of Respiration

No area of pediatric lung health has been as hampered by an insufficient knowledge of normal maturation than regulation of respiration. Although there has been significant progress in the standardization of equipment and appreciation of what is statistically normal, it is still unclear which respiratory events are clinically significant (4, 5). Two principal conditions need to be more fully understood in the coming decade: sudden infant death syndrome and obstructive sleep apnea syndrome. The fact that both of these conditions are known as “syndromes” underscores our limited understanding of their nature. Recent work suggests that a genomic approach will have significant impact in the understanding of such disorders of control of breathing in children.

The realization that infants placed in a supine position to sleep are at a much lower risk of sudden death has had a dramatic effect on reducing the incidence of sudden infant death syndrome worldwide. However, the normal respiratory pattern and oxygenation status of infants in the 2- to 8-month at-risk age range is still unclear. Furthermore, it is unclear which events are pathologic. In this case, there are few animal models that accurately reflect the maturation of the human respiratory control mecha-
nisms. In humans, such investigation will require the collaborative efforts of neurobiologists and behaviorists to distinguish normal events from those with pathologic consequences. The technology now exists to study large numbers of infants over prolonged periods in their homes without loss of pertinent data due to movement artifacts. Another group that urgently needs to be investigated is the premature infant, where the lack of knowledge of normal respiratory behavior hinders the development of appropriate clinical intervention.

Snoring occurs in 3 to 12% of children. The incidence of obstructive sleep apnea syndrome, using polysomnography, is unknown due to disparate criteria used to define this syndrome. At present, it is even unclear whether primary snoring has negative long-term consequences. Clearly, the time has come to define normative developmental neurocognitive and behavioral criteria that will allow recognition of pathologic events requiring medical or surgical intervention. Children with craniofacial dysmorphisms form a particular subgroup of children at risk for obstructive sleep apnea syndrome, and more work is required to define the assessment of obstructive sleep apnea syndrome in this population, and the timing and methods of support and intervention.

Polysomnography is not available to the vast majority of patients, either because of distance from centers or cost. Once normative data and standard procedures for polysomnography are developed, then simpler, home-based diagnostic technologies could be developed and validated; these technologies have the potential for widespread utility. The ready availability of inexpensive memory devices and the ability to transmit large amounts of data, including video, over the Internet could facilitate the creation of such technologies within the next decade.

**Addiction Research**

Most smokers begin in their peripubertal years. It is at this important stage in their physical and psychologic development that they become addicted. Smoking cessation programs have only a limited impact on adults, and are mostly geared toward adults. A significant advance in the biology of addiction is required to rectify this. The combination of knowledge from the human genome, neurobiology, and behavior science can have a significant impact on our understanding of addiction and the development of effective programs for all age groups.

**Care and Impact of Chronic Respiratory Disease**

With advances in therapies, more patients are surviving longer and enjoying better health (3). However, chronic conditions can potentially impose major burdens on patients and families, the most evident being the technology-dependent child (6). More research is required into how care is provided to patients and their families. Outcome measures that encompass these domains for patients, caregivers, and siblings must be developed to more fully assess the impact of disease, and its inherent therapies. Furthermore, a better understanding of the application and use of supportive therapies, such as oxygen and noninvasive ventilatory support, in children is required.

An improved understanding of the dynamics of adherence with therapeutic recommendations is needed. Furthermore, many of our current therapies, such as wet nebulization, are time-consuming, with significant impact on patients, caregivers, and adherence. Further comprehension of the interaction between patients and therapies, such as aerosols, is required to develop newer modalities to effectively and efficiently deliver medication to the appropriate location in the respiratory tract.

**Cystic Fibrosis**

Since the discovery of the CF gene in 1989, important new knowledge about the inflammatory process and its regulation has had a significant impact on our understanding of CF and many other inflammatory conditions of the lung. Although the exact process may differ in these other diseases, the underlying mechanisms are the same, including epithelial cell signaling, cell recruitment and activation, inflammatory mediators and oxidative stress, and cell death, whether programmed (apoptotic) or not. Significant advances have been made in the care of patients with CF such that the median survival is now in the fourth decade of life, and close to 50% of patients are older than 18 years.

With discovery of the CF gene, there was great optimism that a cure would be rapidly found. However, the complete function of the CF gene product, cystic fibrosis transmembrane conductance regulator (CFTR), is more complex than originally envisioned, and the effect of each mutation is only partially understood. In particular, the link between mutations in CFTR and the dysregulated inflammatory response in the lung and other organs is still unclear and requires further study. The genotype–phenotype relation for lung disease is clearly not as tightly linked as for pancreatic dysfunction. This has led to the concept of modifier genes, whereby an understanding of the interaction of CFTR with other genes will help explain the clinical manifestations. The role of modifier genes can be resolved in the near future, particularly if there is a joining together of datasets from different countries. This is particularly important when one considers that there are only approximately 70,000 affected patients worldwide. The analysis of modifier genes will require the use of more complex statistical models than have been used to date, and will need to include bioinformatics. Together with this knowledge, rapid compound screening technologies can allow for a shorter time delay in the development of testable molecules.

The comprehension of modifier genes will require other work, involving fundamental research into CFTR processing and trafficking, altered cellular responses due to mutant CFTR, and the development of better animal models. More work is required in understanding *Pseudomonas* defense systems, including quorum-sensing genes and biofilm formation. More work is required in understanding the virulence and contagion factors of *Burkholderia cepacia* and the role of newer emerging organisms. Clinical work will require the development of methodologies to detect and follow the inflammatory process, using methodologies that can be done serially with minimal invasiveness, such as exhaled breath condensates and induced sputum analysis. However, it is likely that limited studies of the early events occurring in the airway wall will be required to better understand the progression of events. There is also the need for more study of the impact of CF on both patients and their families, and the psychology of adherence to prescribed therapies. In addition, with the expectation that all children affected by CF will become adults, more research is required to improve on strategies for transitioning to adult care. Such research can serve to develop general models for transitioning from the majority of pediatric care situations.

**Sickle Cell Disease**

The etiology of the morbidity and mortality associated with sickle cell disease, which affects approximately 50,000 patients in the United States, is incompletely understood (7). A component of airway hyperreactivity is now recognized to be a frequent occurrence. However, the origins of this hyperreactivity and the consequences of aggressive asthma treatment are unknown. The acute chest syndrome is due to multiple factors, including infection, fat embolism, platelet-derived mediators, decreased levels of nitric oxide, and increased quantities of reactive nitrogen and oxygen species. These same factors are likely to play important roles in the chronic lung disease associated with sickle cell anemia. More research is required to understand the relative impor-
tance of these factors in both acute and chronic lung disease, which account for more than 20% of the deaths.

Chronic occult pulmonary injury occurs in sickle cell disease, and methods of prevention, early detection, and treatment would have a significant positive impact on long-term complications. Pulmonary hypertension and cardiac dysfunction are relatively early complications. There are certain similarities to other hemolytic conditions, such that the interaction between hemolysis and secondary pulmonary hypertension requires further investigation. Finally, the impact of newer therapies, designed to increase the level of fetal hemoglobin, on the development and progression of lung disease requires investigation.

Other Rare Conditions

There are a variety of other conditions that occur or present in children, but due to the limited number of cases or the slow and variable rate of progression, there is little understanding of the natural history or the response to therapies for these patients. Such diseases include interstitial lung diseases, proliferative disorders, and primary ciliary dyskinesia, among others. As a first step, standards for diagnosis are required, followed by the establishment of central data registries.

**PEDIATRIC RESPIRATORY RESEARCH CHALLENGES**

**Workforce Issues**

Pedictric pulmonology is a small specialty group. To date, the American Board of Pediatrics has certified fewer than 750 pediatric pulmonologists compared with close to 4,000 neonatologists, 2,000 pediatric cardiologists, and 1,200 pediatric critical care specialists (8). The comparable number of “adult” pulmonologists certified by the American Board of Internal Medicine (> 10,000) is approximately 15-fold larger than for pediatric pulmonology (9). Less than 1% of pediatric trainees pursue a career in pediatric pulmonology; only 28 to 35 individuals complete their pediatric pulmonary training each year in the United States (8). There are established training programs in other jurisdictions, most notably in Canada and Australia; however, the trainees in these programs are needed locally. The European Respiratory Society has recently established a network of approved training programs and a common training syllabus that lays the groundwork for a recognized European certification, similar to what currently exists in the United States, Canada, and Australia. In a 1997–1998 survey of all pediatric specialists as part of the Future of Pediatric Education II project (10–12), 61% of pediatric pulmonologists identified their employment site as a medical school compared with 44% of all pediatric specialists; however, pediatric pulmonologists reported a similar distribution of work time in direct patient care (60%), clinical research (8%), basic research (6%), and teaching (11%) as all pediatric specialists. These numbers strongly suggest that there is a relative shortage of pediatric pulmonologists and that clinical demands may limit their ability to pursue research activities.

A variety of causes for the limited recruitment to pediatric pulmonology have been proposed, including demanding workload, relatively high load of chronic care patients, and primarily hospital-based practice. It is unlikely that these factors will change substantially. New methods of enriching training programs, such as through the use of computer-based and other simulation techniques, require funds for development and critical assessment. In addition, pulmonologists will need to form alliances with other investigators invested in child lung health, including neonatologists, intensivists, and allergists/immunologists, to build research networks.

**Few Pediatric Pulmonary Research Centers**

Presently, few pediatric pulmonology research centers have integrated research programs involving basic science researchers, clinical researchers, and other groups. These centers tend to focus on lung development, asthma, and/or cystic fibrosis and tend to align pediatric pulmonologists with their adult pulmonary and/or neonatology colleagues, as well as with basic scientists. More integration of investigators in child lung health and more integrated research centers are needed. In addition, international collaboration is required to hasten advances, compare populations, and investigate processes in developing countries.

**Relative Rarity of Many Pediatric Pulmonary Diseases**

Although many of the infectious and inflammatory disorders of the lung are common, most of the congenital or genetic lung disorders affecting children are rare, affecting fewer than 200,000 Americans—the limit for “rare disease” as defined by the Orphan Drug Act. Because each center monitors a relatively small number of patients with these disorders, multicenter studies are needed. However, coordination and standardization of multiple centers can be laborious, expensive, and difficult to fund.

**Ethical Challenges in Conducting Clinical Research for Pediatric Pulmonary Diseases**

When considering the research priorities for pediatric pulmonary medicine, there are three ethical issues, among a much larger set of research ethics issues, that merit special attention.

First, the criteria defining when procedural sedation for research studies is ethically acceptable must be defined. These may be used for bronchoscopy, infant lung function testing, and imaging studies. Procedural sedation may be ethically acceptable when the question is scientifically important, sedation is necessary to address the question, there is empiric evidence that the risks are not likely to be serious, and the risks have been minimized. Standard safeguards to protect the airway of especially the young child are needed.

The second issue pertains to the situations that demand controlled clinical trials. A control group is necessary when there is disagreement within the medical community about evidence for the benefits and risks of an intervention, even if an intervention is used routinely. However, when there is substantial agreement about the evidence for a standard clinical approach, control groups that don’t provide a standard clinical approach should generally be avoided. This is a particularly important issue in pediatrics because many interventions that are used routinely have not been adequately studied.

The third issue pertains to when it is acceptable for pediatric pulmonologists to recruit their own patients into clinical research studies. Although this may be necessary, particularly for rare conditions, efforts should be made to avoid manipulating patients to participate and for both the clinician and patient to clearly distinguish research from clinical care. Although in many cases, a researcher may be able to continue to provide clinical care during the study, it is preferable, whenever possible, to have other individuals involved in recruitment or decisions to withdraw. This may be accomplished by having the patient maintain a clinical relationship with another pulmonologist, or with their primary care physician. This may be particularly difficult for patients cared for in CF centers and when the pool of pulmonologists is particularly small.

**CONCLUSIONS**

This document has attempted to set out where true advances in knowledge and care can be made for child lung health. Our goal...
is to provide each child with the full potential for normal lung health throughout his or her life. We face the following challenges in realizing our goal:

1. Patient populations that are often low in numbers and disparate
2. A limited knowledge of normal growth and maturation
3. Ethical and technical difficulties in assessing small patients
4. A small workforce that requires relatively high financial support due to inefficiencies of scale, and the added time required for the study of children

These challenges are surmountable, and overcoming them will provide investigators the opportunity to make significant advances in securing lung health for children.

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