REVIEW

Pediatric respiratory diseases: challenges to be met and promises to keep

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ABSTRACT

Respiratory disease and illnesses in children comprise a wide range of conditions ranging from the rarely seen genetic and complex metabolic disorders to the more commonly encountered diseases such as allergic rhinitis, sinusitis, pneumonia and asthma. They are among the most important causes of disease impairment in children that not only affect the health of the child but also significantly impact the family.

The purpose of the present report is to trace some of the important historical landmarks that have contributed to the field of pediatric respiratory diseases, to describe recent discoveries that are having significant clinical application and to delineate some areas for future inquiry.

An extensive research was conducted in medical literature data bases by applying terms such as pediatric respiratory diseases, tuberculosis, cystic fibrosis, neonatology, asthma.

Pediatric respiratory diseases take their origin from the many discoveries and contributions made by giants of the past from the fields of tuberculosis, cystic fibrosis, neonatology, and asthma that can provide a roadmap for the editorial leadership of the new Pediatric Respiratory Journal.

As the Editors of the new journal embark upon this exciting voyage and build upon the important discoveries and contributions of the past, we wish Professors Mario La Rosa, Giovanni Piedimonte, Fabio Midulla and the journal family success as they meet the new challenges and fulfill the promise of the new journal.

IMPACT STATEMENT

The information described in this article will be valuable to all health care practitioners who are entrusted to the care of infants and children with respiratory diseases.

KEY WORDS
Pediatric respiratory diseases; tuberculosis; cystic fibrosis; neonatology; asthma; intensive care.

THE BIRTH OF A NEW JOURNAL

The woods are lovely, dark, and deep,
But I have promises to keep,
And miles to go before I sleep.
Robert Frost

The birth of a new journal, in many ways, is like the birth of a new infant into a family…our family, which consists of the editors, the readership and those who support the ***Pediatric Respiratory Journal***. Both events start after a long waiting period during which planning, anticipation and hope for the future of the anticipated neonate takes place. With this inaugural issue of the ***Pediatric Respiratory Journal,*** the official journal of the ***Italian Pediatric Respiratory Society,*** the words of the American poet, Robert Frost, ***'miles to go'*** and ***'promises to keep'*** take on special meaning (1). ***'Miles to go'*** refers both to the challenges that the new journal will encounter and the future work the editors will be called upon to perform; ***'the promises to keep'*** pertain to the journal's obligation to meet its goals and to fulfill its pledge.

The promise of the ***Pediatric Respiratory Journal*** is the promise of pediatrics which is to assure that the health of children flourishes and is attended to by professionals with competencies and skills necessary to address the problems of pediatric respiratory diseases. The challenges of the new journal are before us. In the ensuing decades, the journal will have a dual responsibility. One is scientific; the other is advocacy. First, as a premier vehicle of communication at the cutting edge of science, the ***Pediatric Respiratory Journal*** must take an active role in advancing knowledge and medical science by disseminating substantive communications of respiratory diseases to the readership. Second, the journal must also assume the role of advocacy for children speaking on their behalf and protecting their God-given rights in order that they might flourish and prosper on this earth.

INTRODUCTION

Respiratory disease and illnesses in children comprise a wide range of conditions ranging from the rarely seen genetic and complex metabolic disorders to the more commonly encountered diseases such as allergic rhinitis, sinusitis, pneumonia, and asthma (2). They are among the most important causes of disease impairment in children that not only affect the health of the child but also significantly impact the family. Shown in **Figure 1** is a schematic representation of the many historical origins of pediatric respiratory diseases as well as the wide spectrum of pediatric specialties that are impacted by the specialty. In addition to pediatricians, the primary caregiver specialty of children, these include infectious disease, pulmonology, gastroenterology, neonatology, and intensivist specialists. The

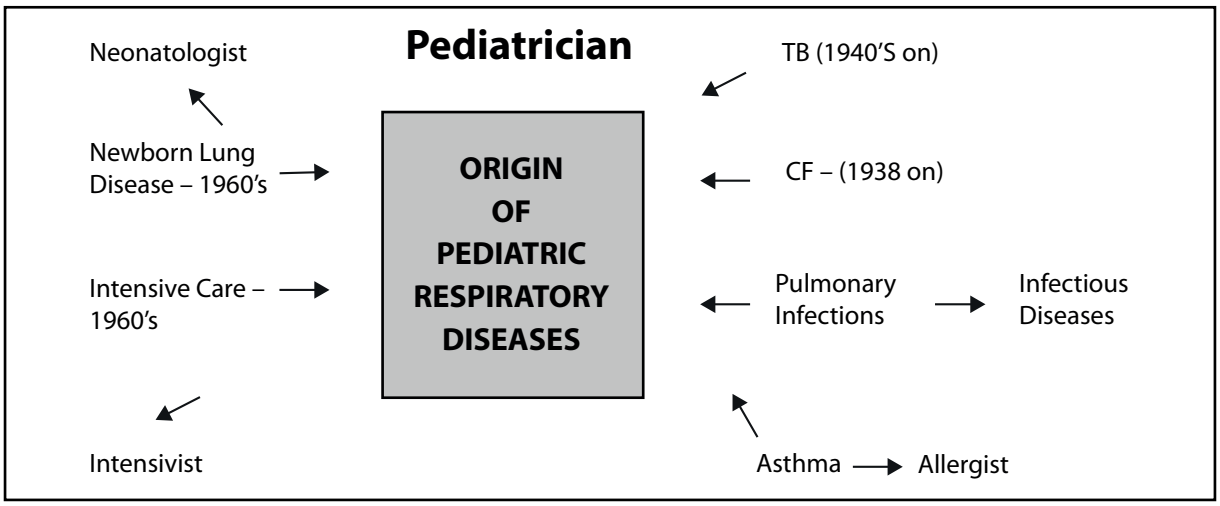

Figure 1. *Schematic representation of the historical origins of pediatric respiratory diseases and the wide spectrum of pediatric specialties that are impacted by the discipline.*
(Reproduced and modified with permission from Chernick V, Mellins RB. Pediatric pulmonology: a developmental history in north America. Pediatr Res. 2004; 55:514-20).

purpose of the present report is to trace some of the important historical landmarks that have contributed to the development and understanding of pediatric respiratory diseases and to provide a description of some recent discoveries that are having significant clinical application.

TUBERCULOSIS

There is perhaps no disease that has had greater impact on our understanding of respiratory diseases in children than tuberculosis (3) (**Figure 1**). Tuberculosis (TB) is present in all countries and all age groups, but children bear a significant share of the burden. In 2020, an estimated 10 million people fell ill with TB worldwide, 5.6 million men, 3.3 million women and 1.1 million children. Although the disease is curable and preventable, childhood and adolescent TB is often overlooked by health providers and, at times, can be difficult to diagnose and treat (4). Many of the early pediatric respiratory specialists during the past 200 years became interested in TB because they, themselves, had contracted the condition. The study of TB during this period significantly contributed to the subsequent prevention, diagnosis, and treatment of the condition. Some of the major historical milestones in pediatric TB are shown in **Table 1**.

TB had been known since antiquity and before the discovery of the bacteria that causes TB, the disease was thought to be hereditary (5). On March 24, 1882, Dr. Robert Koch announced the discovery of *Mycobacterium tuberculosis*, the bacterium that causes TB (6). During this period, TB killed one out of every seven people living in the United States and in Europe. Dr. Koch's discovery was the most important step toward the control and elimination of this deadly disease, and in subsequent decades, the study of TB was the beginning of a major branch of pediatric respiratory diseases, pediatric pulmonary diseases (7).

The ensuing decades saw other important discoveries that included the development delayed hypersensitivity skin tests by von Pirquet and Mantoux (8), the discovery of the BCG vaccine by Calmette and Camille Guérin (9), and the discovery of streptomycin, the first effective TB antibiotic by Selman Waksman (10) (**Table 1**). Following the discovery of streptomycin, other anti-TB drugs were developed which greatly improved the effectiveness of antibiotic therapy of TB (10). The development of interferon-γ release assays (IGRAS) for diagnosis of tuberculosis infection was one of the most recent discoveries that have had significant diagnostic application to the field TB and to the field of pediatric respiratory diseases (12, 13).

There are future challenges to be dealt with in the field of TB. One of these is the development of resistance of drugs that are normally effective in treating TB. Although in most cases, TB is treatable and curable, occasionally the bacteria that cause the disease can become resistant to the drugs used to treat the condition with the emergence of drug-resistant TB (DR TB) (14). Another challenge facing the field of TB, is the worsening of TB in patients with comorbid conditions that weaken the immune responses, *e.g.*, HIV, malignancy. Foremost among these is infection with both HIV and TB, a condition referred to as HIV/TB coinfection (15). Untreated latent TB infection is more likely to advance to active TB disease in patients

Year	Discovery
1882	Robert Koch isolated the tubercle bacillus and proved it to be the causative agent of TB; discovery of tuberculin (6).
1912	Development of delayed hypersensitivity skin tests to TB by von Pirquet and Mantoux (8).
1924	BCG vaccine developed by von Pirquet and Mantoux (9).
1944	Streptomycin isolated from actinomycetes *Streptomyces griseus* by Selman Waksman (10).
1946, 1952	Single and combined use of streptomycin and thiazolsulfone for treatment of TB meningitis and miliary TB; in 1952 INH introduced (11).
2004	Introduction of Interferon-γ Release Assays for diagnosis of tuberculosis (12, 13).
1970s-1980s	Future challenges in the field of TB include drug-resistant TB (DR TB) (14) HIV/TB coinfection (15).

Table 1. *Some major historical milestones in Pediatric TB.*

with HIV than in those without HIV. In patients with HIV, TB disease is considered an AIDS-defining condition and on a worldwide basis, TB disease is one of the leading causes of death among patients with HIV.

CYSTIC FIBROSIS

In the annals of pediatric respiratory diseases, the history of cystic fibrosis (CF), the most common inherited disease among Caucasians, afflicting over 100,352 patients worldwide (16) and 30,000 in the US, can be best summarized as a translational journey from dedicated clinical care to a scientific breakthrough with the development of life-changing cystic fibrosis drugs (**Figure 1**). Beginning with an exuberant moment of insight, the cystic fibrosis journey would take 30 years of persistent, methodical work to achieve a major therapeutic success, a feat of science, commerce, fundraising and patience that has become a model for other genetic diseases. Some of the major milestones in CF are listed in **Table 2**. CF was first described as a pathologic entity in 1936 by Professor Guido Fanconi *et al.* (17) and was later clearly elucidated as a clinical entity distinct from celiac disease by Dorothy H. Anderson in 1938 (18). The disease was initially named cystic fibrosis of the pancreas because symptoms focused on the malabsorptive gastrointestinal manifestations, related to exocrine failure of pancreatic enzyme production rather than on the prominent pulmonary manifestations which characterize the condition today. Paul A. Di Sant'Agnese described the high sweat chloride in 1953 after a heat wave in New York City led to prostration and death of infants with CF (19). The pilocarpine iontophoresis method for collecting sweat for analysis was described some 6 years later (20) and became the standard diagnostic 'sweat test' for CF. It became clear by the 1950s and 1960s, as pioneered by Harry Schwachman (Boston), that care of the patient with CF required a dedicated team effort with special attention to nutrition and to antibiotic treatment of pulmonary infections (21). For the more seriously affected patients with irreversible pulmonary disease, lung transplantation was introduced in the mid-80s and has become a life-saving procedure (22).

The journey of scientific breakthrough in the field of CF brings us to the discovery in 1989 of the CF transmembrane conductance regulator (CFTR) genes. The receptors encoded by these genes regulate the channel across which membranes of cells produce mucus, sweat, saliva, tears, and digestive enzymes (23) and are found in different genotypic patterns in CF patients where the CFTR gene is mutated. Mutations of the CFTR gene express their effects through a variety of molecular mechanisms that include either the failure of production or the elaboration of the CFTR protein with little or no functional CFTR activity located on the apical membrane. These mutations can be grouped into six major classes and are shown schematically in **Figure 2**. The most common mutation is delta F508, accounting for approximately 70% of all mutations. Knowledge of these genotypes and recognition of the seminal role of the mutated CFTR gene in the etiology of CF, finally led to the development and approval of the life-changing cystic fibrosis drugs in 2022 (24). These drugs are most effective in patients with the delta F508 mutation and, uncannyingly, modify the F508del-CFTR protein form the best conformational shape that can traffic to the cell surface thereby improving the function of these mutated proteins. Future challenges in the field of CF will be directed at development of effective medications for the remaining 30% of CF patients with non- delta F508 related mutations that are non-responsive to current CFTR modulator drugs.

NEONATAL LUNG DISEASES

Nowhere has the field of pediatric respiratory diseases been more impacted than by the study of neonatal lung diseases. There are a number of clinical conditions which present with or contribute to the development of respiratory disorders in the newborn period (25) (**Figure 1**). These include: 1) prematurity; 2) neonatal respiratory distress syndrome (RDS) (formerly called surfactant deficiency syndrome); 3) bronchopulmonary dysplasia (BPD); and 4) pneumonias (infectious and non-infectious, *e.g.*, meconium aspiration). A major cause of the neonatal RDS is a deficiency of surfactant production commonly seen in the prematurely born infant causing a failure the lung function, especially the capacity of the air sacs (alveoli), to open properly and to be fully developed (26). Added to the influence of lung immaturity to

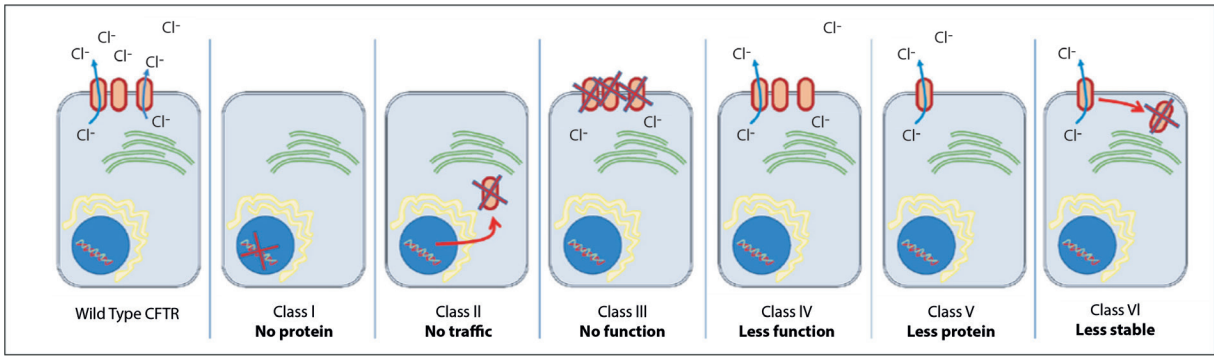

Figure 2. *Schematic representation of molecular configurations of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene-induced products that include either the failure of production or the elaboration of the CFTR protein with little or no functional CFTR activity located on the apical membrane. These mutations can be grouped into six major classes. Cystic fibrosis classification (I to VI). Class I-no protein: these mutations stop any recognizable CFTR protein from being produced due to stop codons in the gene. Class II-no traffic: these mutations affect CFTR processing in the endoplasmic reticulum (which recognizes the malformed protein leading to protein destruction). Class III-no function: these proteins reach the cell surface, but the opening of the CFTR protein is affected. These are also called 'gating defects'. Class IV-less function: this group of mutations reduce the passage of chloride ions through the CFTR protein channel, therefore reducing its function. Class V-less protein: these mutations result in a reduced amount of CFTR protein. Class VI-less stable: mutations here give a reduced amount of CFTR protein at the cell surface due to poor stability of the protein.*
(Reproduced with permission from Hine C et al. Small molecule drugs in cystic fibrosis. Arch Dis Child Educ Pract Ed. 2020 Nov 19.edpract-2020-319009).

the pathogenesis of neonatal lung disease, is the iatrogenic contribution of some of the therapies used to sustain the life of the infant, although well-intentioned, turned out to have had unanticipated detrimental effects. Neonatal BPD is a chronic respiratory disease that most often occurs in low-weight or premature infants who require supplemental oxygen or mechanical ventilation for long periods of time such as infants with acute RDS (27). High concentrations of oxygen were found to accumulate toxic quantities of reactive oxygen species (ROS). Premature infants, especially very premature babies, and those with very low birth weight, exposed to hyperoxia have altered abnormal developmental trajectories of lung tissue and vascular beds, triggering developmental disorders, such as BPD and retrolental fibroplasia (28). BPD can also occur in older infants who experience abnormal lung development or some infants that have had antenatal infection before birth or placental abnormalities such as preeclampsia. As will be described later, antenatal steroid treatment prior to preterm birth and early treatment with surfactant have reduced the need for high levels of respiratory support after birth and have lessened the development of BPD.

Year	Discovery
1936	Fanconi's description of a clinical entity (17).
1937	Dorothy Anderson's classic description separating CF from celiac disease appears (18).
1953	High sweat chloride described (di Sant' Agnese) (19).
1959	Pilocarpine iontrophoresis (Gibson and Cooke) (20).
1960-1970s	Better antibiotics; increasing attention to nutrition (21).
Mid-1980s	Lung transplantation for CF begun (22).
1989	CFTR gene described (23).
2022	Approval of four CFTR modulator therapies in the last decade (24).
2022 +	Future challenges in the field of CF will be directed to the effective medications for the other 30% of CF patients with non-delta F508 related mutations non-responsive to current CFTR modulator drugs.

Table 2. *Some major historical milestones in CF.*

Table 3 lists some of the important milestones in neonatal lung disease. In the 1950s, it became increasingly clear that to influence favorably neonatal lung disease, it would be necessary to understand pathophysiology. Dr. Robert Usher in Montreal made some of the earliest measurements of electrolyte and glucose abnormalities in infants with respiratory distress syndrome (RDS), and the "Usher Regimen" of treatment was widely promoted (29). At the same time, fundamental discoveries in premature infants with RDS were being made in Boston by Dr. Clement A. Smith and his fellows (30). In 1959, Mary Ellen Avery and Jere Mead made the seminal observation of high surface tension in the lung of infants dying with hyaline membrane disease (31) which provided the basis for subsequent therapy of the condition with surfactant replacement therapy. The early and mid-1960s also saw the beginnings of the current pediatric neonatal intensive care units (NICUs) and artificial ventilation of the sick newborn (32). Mortality rates for RDS (hyaline membrane disease) remained high until the concept of distending pressure (continuous positive airway pressure) was introduced by George Gregory in 1970 (33), followed by continuous negative chest wall pressure in 1971 by Vidyasagar and Chernick (34). Based upon the studies of Dr. Avery demonstrating the relationship of surfactant deficiency to RDS, surfactant-replacement therapy was introduced as a therapy in 1980 and is now recognized as a life-saving and safe intervention in small premature infants (35). Another major achievement in the prevention of RDS was administration of antenatal corticosteroids to pregnant women at risk for preterm birth. The effectiveness of this corticosteroid treatment was first demonstrated in 1972 by Sir Graham Liggins and Ross Howie (36) during a randomized control trial using betamethasone. Following the treatment of the at-risk mother, the fetal lung was found to have accelerated maturation with increased production of surfactant, resulting in reduction of the likelihood of infant RDS and infant mortality (37).

ASTHMA

Asthma is a chronic disease of the airways known since antiquity (38) that affects children and adults characterized by shortness of breath, chest tightness, coughing, expiratory wheezing attacks that are worsened by a respiratory virus infection (**Figure 1**). Approximately 300 million people worldwide currently have asthma, and its prevalence has been increasing by 50% every decade (39). More than 25 million people in the United States have asthma, and roughly 4 million of these are children (40). Despite its long recognition, early definitions of severe asthma focused on airway blockage and symptoms related to airway obstruction. In the 1980s, there developed a better comprehension of asthma as an inflammatory condition. The role of the immune system in causing inflammation and the need to manage asthma by controlling inflammation has been a major direction of research and management of asthma in recent years. This led initially to the development of pharmacologic agents that control obstruction referred to as reliever medications such as albuterol drugs and subsequently

Year	Discovery
1950s	1950s measurements made in sick newborn infants by Usher (29).
1950's	Fundamental discoveries in premature infants with RDS were being made in Boston by Dr. Clement A. Smith and his fellows (30).
1959	Surfactant deficiency in HMD described (Avery & Mead) (31).
1960s	Mechanical ventilation began and neonatal intensive care units established (32).
1970	Continuous positive airway pressure for HMD reported by George Gregory (33).
1971	Continuous negative pressure introduced by Vidyasagar and Chernick (34)
1980	Surfactant replacement therapy (35).
1990	Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (36, 37).

Table 3. *Some major historical milestones in neonatal lung disease.*

to the preparation of controller medications which diminish inflammation such as the corticosteroids administered systemically but more safely by inhalation. Most recently, biologic medications that are laboratory- engineered monoclonal antibody formulations that neutralize proinflammatory cytokines responsible for asthma have been developed and today hold a central place of current medications used to treat asthma.

Some of the major milestones in asthma are listed in **Table 4**. In the 19th century Henry Hyde Salter achieved acclaim for his accurate descriptions and medical drawings of what occurs in the lungs during an asthma attack (41). He defined the condition as: "Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks". In 1892, Sir William Osler, one of the co-founders of the John Hopkins Medical School, set out his own definition of asthma. He not only observed that patients with asthma were frequently characterized by recurrent bouts of bronchial spasms, but he also noted the similarities between asthma and allergic conditions, such as hay fever, the tendency of each condition to run in families and start in childhood (42). Francis Rackemann was the first to recognize that asthma is a heterogeneous collection of disease entities associated with different clinical presentations and diverse pathogenetic mechanisms particularly among children and adults (43, 44). Based upon his clinical observations, he suggested that differing etiologies played a role in the pathogenesis of asthma and coined the terms "intrinsic asthma" and "extrinsic asthma". In extrinsic asthma, the form that occurs mostly in children, there is a family history of allergic (atopic) initiated type-1 hypersensitivity induced by exposure to extrinsic antigen and in which IgE antibody in serum and skin test results are positive. Intrinsic asthma, on the other hand, has come to mean the type of asthma initiated by more diverse, nonimmune mechanisms in which no personal or family history of allergic reaction exists, and occurs in older patients in whom skin test results are commonly negative. This classification set the stage for the current understanding of the heterogeneity of asthma and the system by which we classify the biologics today.

But before this could happen, another great achievement had to occur which was critical to understanding the pathogenesis of asthma. In 1967, two Swedish researchers at the Uppsala University in Sweden, Hans Bennich and S.G.O. Johansson isolated a new class of immunoglobulin from a patient with multiple myeloma (45) which they named IgND, because the patient's initials were ND. This new immunoglobulin class (IgND) was unexpectedly found to be elevated in a patient with asthma (46, 47). Concurrently with this observation in 1967, Kimishige Ishikaka and his wife Teruko Ishizaka had been investigating the identification of skin-sensitizing, properties of reaginic antibody, the allergic antibody that gives rise to immediate Type I reactions (48, 49). Because of the infinitesimally low concentrations of what was to be the new IgE class of immunoglobulin, this posed a daunting task for the Ishizakas. The workers in both groups exchanged reagents they had developed and arrived at concurrence that a new class of immunoglobulin, IgE, had indeed been discovered. In 1968, during the WHO International Reference Center for Immunoglobulins conference in Lausanne, these researches agreed to call IgE this fifth class of serum immunoglobulin (50). This amazing discovery has had great relevance to our understanding and treatment of the allergic diseases and asthma. It specifi-

Year	Discovery
1860	Henry Hyde Salter first accurate description of asthma (41).
1892	Sir William Osler (14) asthma characterized by recurrent bouts of bronchial spasms (42).
1947	Francis M. Rackemann descripton of intrinsic and extrinsic asthma (43, 44).
1968	Discovery of IgE by Johansson and Bennich and the Ishizakas (45-50).
1970s-1990s	Better reliever and controller pharmacologics (51).
2000s to the present	Development of biologics which have been the most recent discovery, and which have revolutionized the treatment of asthma (52).

Table 4. *Some major historical milestones in asthma.*

cally provided the etiologic basis of what Rackemann had called extrinsic asthma responsible for the positive skin tests, the familial tendency as well as the pathogenetic mechanism for one of major asthmatic conditions.

Thus, although the original concept of asthma was primarily a disease of airway obstruction that drove the development of bronchodilator drugs, it was soon realized that airway inflammation underpinned the disorder. This gave way to the development of first of the controller therapies such as corticosteroids. But more, recently the discovery of complex interconnecting cytokine and chemokine networks has stimulated the development of biologics which have been the most recent discovery which has revolutionized the treatment of asthma. Shown in **Table 5** are some of biologics currently approved in the US for the treatment of moderate to severe persistent asthma. As an anti-IgE treatment, omalizumab was approved in 2002, becoming the first biological drug for the treatment of severe allergic asthma (51). This was followed by other biologics directed at the neutralization of proinflammatory cytokines of the inflammatory cascade responsible for asthma (52). Development of biologics is one of the most recent discoveries which have revolutionized the treatment of asthma and undoubtedly more will become available in the future.

INTENSIVE CARE UNITS AND INTENSIVISTS

In recent years, two major events that contributed significantly to improved care of children with respiratory diseases were the introduction of intensive care units and the training of specialists, referred to as intensivists, who care for our most critically ill patients (53) (**Figure 1**). This was seen across all age groups of children but was particularly relevant in the care of infants with neonatal respiratory diseases in units referred to as Neonatal Infant Care Units (NICUs).

One of the earliest pioneers of artificial ventilation of the newborn infant was Dr. Mildred T. Stahlman at Vanderbilt University (54) who overcame one of the major limitations of neonatal care of infants with respiratory disease. During the 1970s, there was an unfortunate lack of ventilators specifically appropriate for children and artificial ventilation had to be accomplished by adapting ventilators made for adults for use in pediatric patients. As a result of Dr Stahlman's efforts, ventilators specifically designed for the needs of infants and children began to appear.

With the advent of NICUs, another valuable member of the pediatric respiratory team was added with the beginning of respiratory therapists who specialized in pediatric ventilatory care (55). As in neonatology, intensive care of older children evolved into pediatric intensive care units (PICUs) and became increasingly available at most medical facilities.

CONCLUSIONS

In summary, we have traced some of the origins and important historical landmarks that have contributed to the field of pediatric respiratory diseases and have

Therapy	Mechanism of action	Indication	Adverse effects
Omalizumab	Anti-IgE	>6-y-old	0.1-0.2% risk of anaphylaxis in clinical trials
Mepolizumab	Anti-IL-5	>12-y-old; with eosinophilic asthma	Rare hypersensitivity reactions; activation of zoster
Reslizumab	Anti-IL-5	>12-y-old; with eosinophilic asthma	~0.3% risk of anaphylaxis in clinical trials
Benralizumab	Anti-IL-5; binds to IL-5Ra receptor	>12-y-old; with eosinophilic asthma	Rare hypersensitivity reactions
Dupilumab	Anti-IL-4R; binds to IL-4Rα receptor; blocks signaling of IL-4 and IL-13	>12-y-old; with eosinophilic asthma	Rare hypersensitivity reactions

Table 5. *Summary of some of the biologics currently approved for the treatment of moderate to severe persistent asthma.*

presented them in the context of an inaugural address launching the new ***Pediatric Respiratory Journal***. As the editors of the journal embark upon this exciting voyage and build upon the discoveries and contributions made by so many giants of the past, we wish Professors Mario La Rosa, Giovanni Piedimonte, Fabio Midulla, and the journal family success as they meet the new challenges of the future and fulfill the promise of the new journal.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interests

The Author has declared no conflict of interests.

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Professor Bellanti JA is the only responsible for the conception and design of the work as well as the acquisition, analysis and interpretation of data presented.

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