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Unmet Needs in Respiratory Diseases

"You Can't Know Where You Are Going Until You Know Where You Have Been"—Anonymous

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Abstract The care of patients with respiratory diseases has improved vastly in the past 50 years. In spite of that, there are still massive challenges that have not been resolved. Although the incidence of tuberculosis has decreased in the developed world, it is still a significant public health problem in the rest of the world. There are still over 2 million deaths annually from tuberculosis, with most of these occurring in the developing world. Even with the development of new pharmaceuticals to treat tuberculosis, there is no indication that the disease will be eradicated. Respiratory syncytial virus, severe acute respiratory syndrome, and pertussis are other respiratory infectious diseases with special problems of their own, from vaccine development to vaccine coverage. Asthma, one of the most common chronic diseases in children, still accounts for significant mortality and morbidity, as well as high health care costs worldwide. Even in developed countries such as the USA, there are over 4,000 deaths per year. Severe asthma presents a special problem, but the question is whether there can be one treatment pathway for all patients with severe asthma. Severe asthma is a heterogeneous disease with many phenotypes and endotypes. The gene for cystic fibrosis was discovered over 24 years ago. The promise of gene therapy as a cure for the disease has fizzled out, and while new antimicrobials and other pharmaceuticals promise improved longevity and better quality of life, the average life span of a patient with cystic fibrosis is still at about 35 years. What are the prospects for gene therapy in the twenty-first century? Autoimmune diseases of the lung pose a different set of challenges, including the development of biomarkers to diagnose and monitor the disease and biological modulators to treat the disease.

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Introduction

The study and management of lung diseases is of concern to allergist/immunologists and pulmonologists. The most common chronic lung disease is asthma, but there is an immunological basis for many other lung diseases, which span a vast clinical spectrum of lung disorders ranging from infectious lung disease to cancer. Several significant challenge areas include the diagnosis and treatment of certain specific infectious lung diseases, including viral lower respiratory infections caused by respiratory syncytial virus, rhinovirus, metapneumovirus, coronovirus, and enterovirus. Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoA) was responsible for the outbreak of severe acute respiratory syndrome in the early 2000s that originated in Asia and led to significant mortality in those afflicted. Other viruses such as bird flu and swine flu have the ability to cause respiratory tract disease as well. Tuberculosis is another primarily respiratory infection that has been resistant to eradication. New strains of multidrug-resistant tuberculosis have emerged. Other challenges involve the genetic diseases cystic fibrosis and alpha-1-antitrypsin deficiency, autoimmune lung diseases, lung diseases that are part of a systemic autoimmune disease, and chronic obstructive pulmonary disease (COPD). The diagnosis and treatment of hypersensitivity pneumonitis still poses problems to clinicians. Biomarkers are continually being

developed in lung and other cancers, but more research is needed [1]. The genetics of cystic fibrosis are now well elucidated, but the development of a successful gene therapy has been unexpectedly slow (Table 1).

For many of these conditions, it was and still is expected that the ongoing development of new waves of molecular biology techniques, coupled with computerized automated analysis that can provide transcription signatures, will help identify differences between patients with these diseases and spur on the development of relevant and effective treatments. The subsequent discussion takes on some of the more interesting and challenging issues in respiratory disease over the past two decades, with a focus on what to expect in the future as well.

Severe Asthma—Many Diseases, Many Problems

Asthma is one of the most common chronic diseases worldwide. The WHO estimates that there are over 300 million asthmatics worldwide and 250,000 deaths per year. In the USA, there are 22 million asthmatics, 6.5 million of whom are children. Until recently, the mortality rates from asthma had been steadily increasing. It is only in the past 5–10 years that the mortality rates have begun to stabilize and are perhaps even on a decline.

The increasing incidence of asthma has been attributed to various theories, perhaps the most popular of which is the "hygiene hypothesis" [2]. This attributes the rise in incidence to the reduced rate of infectious diseases, cleaner living environments, and, in general, those features that accompany a higher standard of living. But, conversely, the annual death rates per 100,000 asthmatics tend to be higher in the economically poorer countries. This emphasizes the most significant global concern regarding asthma care, which is access to care and medications. In developed countries, this problem is less prevalent, and in countries such as the USA, we are primarily focused on asthma education and compliance issues. In both situations, severe asthma is still a problem in that it impacts quality of life and still contributes to considerable morbidity and mortality.

Table 1 Respiratory disease with significant unmet needs

Genetic	Cystic fibrosis (CF)
	Alpha-1-antitrypsin deficiency (A1AT)
Environmental/ inflammatory	Interstitial lung disease (ILD)
	Hypersensitivity pneumonitis (HP)
	Asthma
	Chronic obstructive pulmonary disease (COPD)
	Allergic respiratory diseases (e.g., allergic rhinitis)
Autoimmune	Granulomatosis with polyangiitis (GPA)
	Microscopic polyangiitis (MP)
	Eosinophilic granulomatosis with polyangiitis (EGPA)
Infectious	Tuberculosis (TB)
	Pertussis
	Respiratory syncytial virus (RSV)
	Severe acute respiratory syndrome (SARS)
	Influenza
Neoplasms	Lung cancer

One of the problems of severe asthma is related to defining the disease. Asthma is inherently very heterogeneous, and many phenotypes of severe asthma have been described. It is increasingly clear that there is no single medication that works for all patients with severe asthma. While patient compliance is an issue, we frequently fall into the trap of believing the problem is always patient compliance, when in fact, it may be that patients are not taking their medications because they perceive that they do not work. Nevertheless, the explosive growth in the availability of new pharmaceutical interventions provides us with an arsenal of controller medications, at least in the developed world. More medications are being developed every day, including the newer class of biological modulators against cytokines and chemokines [3], such as anti-IL5 [4, 5] and anti-IL4rα [6, 7]. The next challenge will involve the identification of suitable patients for these new and existing treatments.

But how will this be done? Researchers over the years have attempted to define asthma phenotypes, trying to categorize asthma patients based on demographic and clinical characteristics in an attempt to define certain patient groups for certain preferential treatments [8–16]. In general, this has led to more confusion as the different research groups do not necessarily come up with the same classifications. Moreover, asthma in children is also significantly different from that in adults, and the response to medications varies based on multiple and not a single factor. The choice and exclusion of confounding variables has been a thorn in the side of those attempting to define a specific asthma phenotype. It has also not been found that specific childhood asthma phenotype will develop into a specific adult asthma phenotype.

The concept of asthma endotypes has now been the subject of much research because endotypes address the underlying mechanism of a disease [17–20]. However, this is also confusing because of the highly redundant inflammatory pathways that can lead to disease. The use of biomarkers to identify those patients who are at high risk for severe, life-threatening exacerbations has not been entirely fruitful. The recent commercial introduction of fractional exhaled nitric oxide (FeNO) to identify patients with eosinophilic inflammation is a potentially useful tool, but more is needed to guide treatment.

The identification of a gene for asthma has revealed that this is more complex than one might have expected. There are now over 100 genes that have been attributed to asthma. Some of the more likely candidates include ADAM33, ORMDL3, DENND1B, filaggrin, CHI3L1, and IL-33. Moreover, the existence of shared genes between asthma and other comorbid conditions such as obesity has also been demonstrated [21].

Ultimately, asthma, like many other diseases, is a heterogeneous disease with many phenotypes and endotypes [17, 18]. Not one single treatment will fit all, and the art of medicine may be to find the right peg for the corresponding hole [22]. The twenty-first century has ushered the concept of personalized or genomic medicine, which utilizes advancements in molecular biology, such as proteomics, metabolomics, and genomics, to identify the optimal therapy for each individual patient.

Cystic Fibrosis—What Happened to Gene Therapy?

It has now been 24 years since the identification of the gene responsible for cystic fibrosis (CF) [23–29]. The initial study describing the gene named "cystic fibrosis transmembrane conductance receptor (CFTR)" was first published in the late 1980s by Tsui et al. [26, 29–36]. This discovery led to a localization of the gene to chromosome 7, leading to widespread belief that a cure for CF utilizing gene therapy was right around the corner. The landmark development of a molecular biology technique which became known as genetic targeting in mice, pioneered by Capecchi [37–40], Evans [41, 42], and Smithies [43–47], promised gene replacement in humans in a similar way to that performed in mice. Twenty-four years later, there are new advancements in the management of cystic fibrosis with regard to pharmacological and supportive respiratory treatment, but still no cure. These advancements have prolonged the longevity of patients with CF, but their life expectancy still only averages to be about 35 years. So, what happened to gene therapy? What happened to all that promise that buoyed the cystic fibrosis community back in the 1980s?

The idea behind gene therapy is to introduce a missing of malfunctioning gene into the cells of a patient using a "harmless" virus that can be manufactured to carry a normal copy of the diseased gene. This technique can either target cells globally or be restricted to a certain group or location of cells. But gene therapy has not progressed as smoothly or as quickly as anticipated. Previously unrecognized barriers became apparent [48]. These included the fact that studies were initially focused on molecular or biochemical outcomes and not on clinical efficacy. Moreover, the administration of the gene would need to be repeated due to epithelial turnover. Repeated administration leads to host recognition, which may inhibit gene expression. Questions on which cells to target in order to achieve efficacy has slowed research. The use of viral material, including viral DNA and liposomes, could potentially lead to inflammatory responses. The point is that unexpected consequences were discovered as research proceeded, and this has had an impact on the progress of gene research.

In 2012, a group of British investigators began large-scale trials of gene therapy delivered by encompassing the gene in fat globules and delivering the gene by nebulization. Future methodologies will utilize a viral delivery strategy, but this is still several years into the future. Gene therapy for cystic fibrosis is not dead, but certainly moving at a far slower pace than originally expected.

Current treatments are not curative for cystic fibrosis. Gene therapy and stem cell transplants are two techniques that are still under investigation, and it may turn out that only certain mutations may be candidates for gene therapy. Mutations in the CF gene have in fact been subclassified into six classes [49], each with its own pathogenic or physiologic characteristics. For example, the common F508del mutation results in reduced amounts of CFTR channel expression, which leads to exacerbation of the disease [50].

Lung Disease and Infections—Four Major Challenges, Each of Different Nature

Respiratory Syncytial Virus—How to Develop an Effective Vaccine?

Respiratory syncytial virus is an infection of the lower respiratory tract that causes significant morbidity and mortality in infants and young children [51]. Globally, there are over 30 million new lower respiratory tract infections per year and approximately 200,000 deaths per year in children fewer than 5 years of age. The majority of these deaths occur in low-income countries where access to care may be limited. The search for a vaccine for respiratory syncytial virus (RSV) has been ongoing for many years, but like the previous case of gene therapy in cystic fibrosis, this also has been a challenge to achieve. In the absence of a vaccine, researchers have developed passive immunization to the virus in the form of a monoclonal antibody to RSV, named palivizumab. The current global strategies for the development of an RSV vaccine now target four areas: infants <6 months of age; infants >6 months of age and young children; pregnant women for whom passive immunization can be implemented; and the elderly, in whom RSV can also have significant morbidity [52–54].

The main challenges that have prevented the development of an effective vaccine so far revolve around the fact that even natural infection to RSV does not provide long-term protection from reinfection. An earlier study actually found that the vaccine may actually accentuate the disease, especially in

young infants who may not have a fully mature immune system and may be unable to effectively engage in somatic mutation, leading to a suboptimal B cell repertoire [55, 56]. This may also apply to older infants or young children who may still be RSV-naive. The issues in adults are just the opposite as most adults have been exposed to RSV and thus have RSV antibodies. The effectiveness of passively immunizing pregnant women in order to deliver IgG across the placenta to the fetus must be weighed against possible adverse effects of such a "vaccine" on the fetus. In the elderly, the challenge has been the ability to boost immunity through active immunization in an individual who is becoming immunosenescent.

There are now several vaccine development programs that pursue a variety of vaccine strategies. A live virus vaccine trial has shown that a particular vaccine candidate, MEDI-559, is safe, although effectiveness has not been proven [57]. Other strategies include subunit RSV vaccines, the use of DNA-conjugate vaccines to boost antigen presentation, and further development of passive antibody prophylaxis that is focused on F or G proteins [52, 58–72]. An additional challenge with all of these strategies is that effective vaccine studies in animals have not been translated into successful human trials.

Tuberculosis—A Third-World Public Health Problem

Tuberculosis is a global health problem. Tuberculosis is an infection caused by the bacterium *Mycobacterium tuberculosis*, which primarily affects the lung, but can also affect other tissues, including bone and the nervous system. Tuberculosis is believed to be one of the oldest infections to reportedly affect mankind, with archeological and anthropological studies showing evidence of infection in humans over 4,000 years ago. It continues to top the charts of mortality and morbidity in developing nations. It is estimated that in 2007, there were 9.27 million new cases of TB, as well as a prevalence of 13.7 million. The 1.32 million deaths in 2007 from TB in patients without HIV and 450,000 deaths in patients with HIV is a shocking statistic that shows how far we have come, yet how far we still are from effectively eradicating the disease [73].

Two very effective drugs have been developed to treat tuberculosis, isoniazid (INH) and rifampin. However, tuberculosis continues to be a global health problem. Tuberculosis is second to HIV/AIDS as the infection with the highest mortality globally. More recently, an increase in multiple drug-resistant tuberculosis (MDR-TB) has been observed, with most cases from India, China, and Russia. There were 450,000 reported cases of MDR-TB in the world in 2012. Of these, it is estimated that 9.6 % fall into the category of XDR-TB, which is an even more resistant form. Thus, drug resistance is a significant challenge in the treatment of TB in the twenty-first century. Another challenge stems from the fact that about one third of patients with HIV/AIDS are infected with TB, although many may not yet be symptomatic. The WHO defines six core functions and six strategic approaches to combat TB (Table 1).

Overall, 80 % of TB cases occur in just 22 countries, and 60 % of cases occur in China. However, as overall healthcare accessibility and technology improves, there have been significant declines in the rate of TB in some of the Asian countries, including Cambodia and China. There is no dispute that the DOTS and "Stop TB strategy," as outlined in Table 1, have contributed to significant progress in the control of TB, but significant challenges remain. One of the areas that are being focused on now has to do with the identification of biomarkers. Biomarkers can play several roles in the improvement of treatment of TB in the world. The main areas of focus for research in biomarkers are to identify those that can perform the following functions: (1) prediction of a curative state, (2) prediction of reactivation of TB, and (3) prediction of immunity to TB. In the past, biomarkers for TB would normally involve culturing for the organism, but the development of molecular biology techniques has afforded us the use of non-culture biomarkers.

The types of approaches, as described by Wallis et al. in 2013 [74], categorize biomarker development into functional categories (Table 2). Non-culture biomarkers include cytokine levels, quantifiable genetic measures of the presence of TB, other serological tests, imaging techniques, gene transcription profiles, and micro-RNA profiles. The development of a vaccine has been an ongoing challenge in the quest for a cure for TB, and limitations in these studies include the lack of valid biomarkers to assess protection in clinical trials.

The cytokines interferon-γ and IL-18 have been studied as biomarkers for latent TB infection. A tuberculosis-stimulated interferon-γ release assay can detect sensitization to TB antigens, but, unfortunately, cannot differentiate between resolved and persistent latent infection. Interleukin-18 is a marker of innate immunity. Elevated levels of plasma interleukin levels seen in TB patients indicate increased activation of innate immunity, which was not observed in controls. A chemokine that was observed to be elevated in TB were CCR7 [75], while the levels of the apoptosis inhibitor Bcl2 expression were reduced [76, 77]. IL-18 levels actually correlated with the radiographic extent of the disease [78, 79]. HIV appears also to modify cytokine production in patients with TB [80]. Other cytokines and chemokines have been profiled as potential biomarkers for TB disease activity [81–86], although to this date, none has been shown to be useful for widespread clinical application.

Fifty years ago, it was the introduction of pyrazinamide and rifampicin that reduced the duration of therapy from 18 months to 6 months. The value of biomarkers may be reflected in the implications of being able to predict cure and latency of infection, as well as active infection. From a therapeutic standpoint, this may mean the difference between the current

Table 2 WHO's Stop TB Strategy (2006)

Six core functions in addressing TB

1. Provide global leadership
2. Develop strategies, policies, and standards based on evidence-based studies for the prevention, control, care, and monitoring of TB patients
3. Assist Member States with technical support, resources, and capacity considerations
4. Monitoring global TB status and measure progress in TB care, control, and financing
5. Develop research agendas and manage dissemination and translation of knowledge
6. Facilitate and engage in TB partnerships

The WHO's Stop TB Strategy

Implementation by all countries and partners

Goal: To reduce TB by public and private actions at national and local levels, by

- Expand and enhance high-quality DOTS, which is WHO's five-point package with the following objectives:
  - Political commitment with increased and sustained financing
  - Case detection through quality-assured bacteriology
  - Standardized treatment with supervision and patient support
  - An effective drug supply and management system
  - Monitoring and evaluation system, and impact management
- Address TB-HIV, MDR-TB, and other special challenges
- Contribute to health system strengthening
- Engage all care providers
- Empower people with TB and communities
- Enable and promote research

Modified from [149]

regimen of 6 months of treatment versus a possible reduction in the duration of therapy for certain patient groups. But this depends on the biomarker being significantly accurate as to not lead to inadequate treatment of affected individuals.

Though a half century has passed since the development of effective treatment for drug-susceptible TB, the period of treatment is still at least 6 months of standard therapy, i.e., rifampicin and isoniazid for 6 months and pyrazinamde and ethambutol during the initial 2 months of treatment. Efforts to reduce the length of treatment are dependent on the discovery of more effective treatment as well as being able to monitor the treatment. At the same time, more and more patients with TB are demonstrating multiple drug resistance forms including MDR or XDR TB. The addition of second-line drugs for the treatment of these more difficult to treat patients is plagued by longer periods of treatment, higher cost, and reduced efficacy. The drugs often used for second-line treatment include aminoglycosides, terizidone, protionamide, capreomycin, fluroquinolones, cycloserine, and ethionamide. The mortality of MDR and XDR TB in HIV patients is particularly high, and researchers have focused on novel approaches to combat this global health issue, including revamping of efforts to develop a vaccine for TB [87–92], treatment of latent infection to reduce reservoir pools of infection, and the development of predictive biomarkers. One should not forget that for years we have had a vaccine for TB, the BCG vaccine named after Albert Calmette and Camille Guerin. While this vaccine has been used primarily in underdeveloped countries and has been administered to over 4 billion people worldwide, the limitations include an inability to protect against adult TB and adverse effects when used in HIV-positive TB patients. Further research is ongoing to develop an improved replacement or enhancement vaccine for BCG [91, 93–100].

Therefore, as we develop new biomarkers and new treatment strategies, one should remember that the infective landscape of TB is not a static target either. The emergence of multidrug-resistant strains as mentioned above means that the disease may become more difficult to treat and that the development of biomarkers must take new medication use into consideration. Moreover, the development of biomarkers requires the availability of large patient samples, such as those that can be found in biobanks of large high-volume treatment centers. The willingness of patients to contribute to research, and the regulatory landscape for the collection of samples for research, could potentially negatively impact the ability to conduct large-scale studies on biomarkers. For a comprehensive review of biomarkers, diagnostics, drug treatment, and vaccine development, the reader is referred to an excellent series of articles published in Lancet in 2010 [74, 89, 101].

Pertussis—Why Are People Not Vaccinating Their Children?

The incidence of pertussis appears to be increasing over the past 30 years. This trend flies in the face of an availability of, first, the killed whole organism pertussis vaccine DTwP and, subsequently, the acellular vaccine (DPaP). The acellular vaccine was less reactogenic because it incorporated a step during manufacturing that removed endotoxin, which was a major reason for the adverse side effect profile. It was clear that vaccination against pertussis afforded much improved prevention of the disease, as illustrated by the 157-fold decreased rate for pertussis between the 1930s and 1940s. DTwP vaccines were used until the 1990s, when technological development in the 1970s and 1980s led to the introduction of commercially available acellular pertussis vaccines [102].

The continuing increase in pertussis cases leads to an obvious question. Is this a failure of an immunization program? Earlier, we discussed several examples that illustrate the difficulty of bringing an effective vaccine to market (TB and RSV). The problems associated with pertussis are clearly different. There are several reasons that may explain why we have not eradicated the disease. It is well documented that the DTaP vaccine is not as immunogenic as the whole organism DTwP vaccines. Studies have indicated that the overall

efficacy of DTaP vaccines is below 70 %. We do not normally test for pertussis titers following vaccination, except in studies. But there are those who suggest that the increase in pertussis cases is mainly due to the increased ability to diagnose the disease and to an increased awareness. Yet another challenge may be that pertussis has mutated over the years, rendering the vaccine less effective. Because our current vaccine is <70 % effective, the ability of mutant strains to evade destruction would lead to their preferential survival.

It has been shown that pertussis vaccine which contains more antigens, such as the five-component vaccine that contains pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM 2/3), is superior to those containing fewer antigens. It has also become apparent that the balance of antigens in the vaccine may play a role in determining efficacy. For example, a whole-cell pertussis vaccine with antigenic components PT, FHA, and FIM was compared to an acellular pertussis vaccine in children. The whole-cell vaccine produced high levels of antibodies to PRN and FIM, but low levels to PT and FHA, in contrast to the acellular pertussis vaccine which produced high levels of antibody to PT and FHA. More than one study has suggested that the vaccine components may antagonize each other. It has been found that the antibody levels to FHA do not correlate with the efficacy of the vaccine; furthermore, it has been suggested that adding FHA to a vaccine may actually suppress efficacy.

Linked epitope suppression is another concept to explain the failure of pertussis vaccines. While one would expect that the presence of antigens that do not deliver a brisk vaccine response should not affect the response to other vaccine antigens, this may not be the case. If there were a linkage suppression between two epitopes on the pertussis vaccine, then this could be a significant consideration in vaccine design as one would then need to exclude certain antigens from the vaccine component mix. Suffice to say that vaccine development is a very complex topic, and it involves various techniques, including the use of classical adjuvants such as aluminum salts, emulsions or liposomes, or novel adjuvants such as Toll-like-receptor agonists, saponins, or immune stimulating complexes [103].

One cannot discuss challenges in pertussis without commenting on the fear of immunizations held by many families, even in developed countries such as the USA. The refusal of many parents to immunize their children, for whatever reason they may have, plays a significant role in our inability to eradicate several diseases, including pertussis, measles, rubella, and so on. This phenomenon is not limited to the uneducated population as many highly educated individuals appear to choose not to subject their children to the relatively miniscule real or imagined risks of immunizations. Certainly, one has an astronomically higher risk of being killed in a car accident than dying from a vaccination. And yet, people who refuse to vaccinate their children do not stop driving or riding in cars.

The problem with all this is that achieving "herd" immunity is important in total eradication. This means that if only a very small portion of the population do not immunize their children, there is still a possibility of eradicating a disease, but as more people choose to remain unimmunized, the likelihood of successful eradication becomes less and less. Unfortunately, people who choose to remain unimmunized fail to understand that in order that everyone not have to get immunized in the future (as in the case of smallpox), everyone must be immunized in the present [104].

SARS—Can It Happen Again?

Severe acute respiratory syndrome, or SARS, was an infection that reached epidemic proportions during the early part of the 2000s. It originated in China and rapidly spread to neighboring countries, and eventually, it was reported in many other distant nations, including Europe and the USA. Although the number of cases was far fewer, by several orders of magnitude, than the common flu, it caught the attention of healthcare professionals and public health officers because of its high mortality, with 8,000 cases and 774 deaths reported between 2002 and 2003, for a mortality rate of 9.6 %. SARS was later identified to be caused by a coronavirus and was named SARS-CoA. Travel histories of infected people were instrumental in tracing the origin of the disease [105].

But where did this virus come from and how did it suddenly cause so much havoc? Initially, in May of 2003, the virus was traced to civets, a cat-like mammal that is occasionally consumed as food by the Chinese. However, these creatures were eventually dismissed as the original source because of the lack of appearance of further infected civets. In 2005, reservoirs of SARS-like viruses were found in Chinese horseshoe bats. These were often brought to market, and it was thought that the virus was passed to humans at that time. Phylogenetic studies further provided evidence that genetically, it was likely that the SARS coronavirus evolved from viruses that infected the horseshoe bats [105–112].

So can SARS happen again? In fact, smaller outbreaks that do not attract as much attention may already be occurring in a manner that mimics SARS. A Middle East Respiratory Syndrome or MERS has been reported to also be caused by a coronavirus. The mortality in this case is high as well, 38 of 64 cases, or >50 % [112–122]. MERS is also thought to have originated in bats. Interestingly, many other viruses are thought to be transmitted by bats, including Ebola, Hendra, and rabies. The cellular receptor for MERS is CD26, or dipeptidyl peptidase 4 [123].

Lessons learned from the 2003 SARS epidemic included the fact that transmission can often be facilitated by the very medical workers who are trying to save patients [109, 110]. Strict infection control measures are critical in limiting the spread of the disease, including the use of negative pressure

rooms, N95 masks, and gowns. The optimal dosing of antiviral medications and the timing of supportive measures of respiratory care are still unknown, but previous experience should guide us to be more vigilant if this ever occurs in a large-scale fashion in the future.

Autoimmune Lung Diseases—Biomarkers and Biologics—Sparing the Steroids?

ANCA-Associated Vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA) was discovered in 1982 [124, 125]. The antigenic targets of ANCA include myeloperoxidase or proteinase-3, and the antibodies against these antigens were for a long time referred to as p-ANCA and c-ANCA, respectively, the p and c indicating their cellular staining pattern (perinuclear or cytoplasmic). This latter nomenclature has since been discouraged, and the antibodies should be referred to in the context of their specific antigenic target [126, 127].

An understanding of the pathogenesis of ANCA-associated vasculitis (AAV) would help in the development of more effective drugs to treat this group of diseases [125], which include granulomatosis with polyangiitis (formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA or Churg–Strauss disease), and microscopic polyangiitis [128].

For toxin-mediated AAV, a meta-analysis has shown a link between crystalline silica and AAV [129]. Silica is an inflammasome activator and is believed to trigger the activation of pro-inflammatory cytokines leading to the disease. Other triggers include drugs, most commonly hydralazine, propylthiouracil, and penicillamine (all of which are known to stimulate B lymphocyte activation), and infectious trigger such as *Staphylococcus aureus*. Avoidance of exposure may prove to be a useful methodology to prevent disease, but as of this time, the triggers of AAV are too diverse and too controversial to recommend any particular avoidance strategy.

Allergies and Autoimmunity

Another disease state that affects millions, perhaps billions, of people worldwide is allergies. Allergies that affect the respiratory tract can take the form of allergic asthma or simply allergic rhinitis and conjunctivitis. The hygiene hypothesis would indicate that because of our cleaner living environments, we are developing higher rates of sensitivities to common allergens, both indoor and outdoor, as well as higher rates of autoimmune diseases [130–136]. One of the main avenues of treatment has always been avoidance, but we have not really been able to define what exactly constitutes effective avoidance. Many of the studies done on dust mite and animal dander avoidance have not been able to identify a single avoidance measure that can make a significant impact on outcome, although perhaps a comprehensive avoidance plan may provide some relief. Studies are needed to (1) determine whether indeed effective avoidance is possible in the face of indoor and outdoor exposures to allergens and (2) the extent to which avoidance of allergens, if possible, provides a significant benefit to patients.

Conclusions

The diagnosis and management of respiratory diseases is plagued by numerous unmet needs, affecting both common diseases such as asthma to uncommon occurrences such as SARS. Some of the problems are common and ultimately involve improving our understanding of the mechanisms of disease. Only then can we develop tools to help us manage these patients. The advent of molecular biology has allowed us to develop genetic analyses of patients, and this has led to a realization that these diseases are frequently not one disease, but many [137]. Thus, the genomic and personalized medicine acts of 2006 and 2010 are important legislatures that will hopefully divert increased funding into studies that will help us identify which treatment should optimally be used on which patient [138, 139]. Understanding the pathogenesis of these diseases is another significant unmet need which

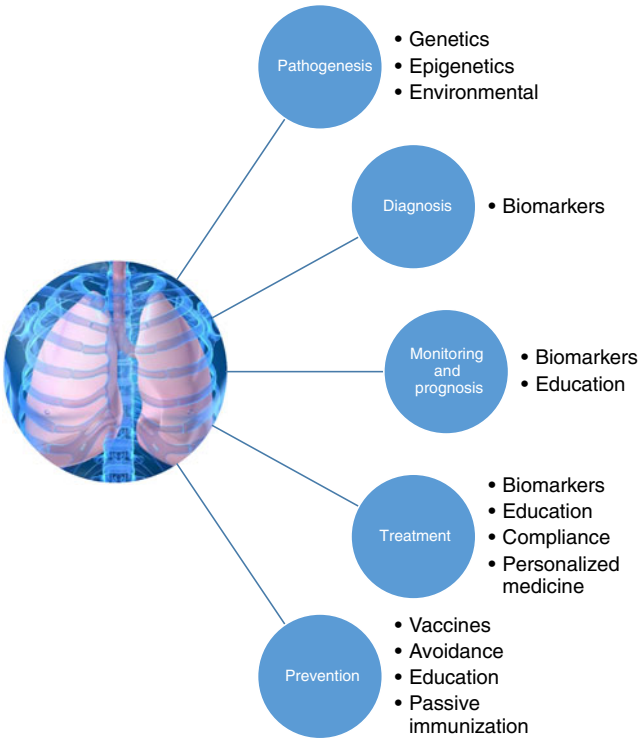

Fig. 1 General areas of unmet needs in respiratory diseases

requires commitment of funding and resources [140]. The respective contributory roles of genes, epigenetics, and the environment in the pathogenesis of lung diseases must be better elucidated [141–148]. With better understanding of disease comes better diagnostic markers and better treatment.

Other unmet needs circle around the availability of biomarkers to both diagnose disease and vaccines and other novel treatments to manage disease. New techniques for vaccination which will hopefully alleviate concerns of vaccines among vaccine-apprehensive patients may help lead to the eradication of infectious respiratory disease such as TB, pertussis, and RSV. There is much work yet to be done, and it is important to remember that diseases are not static either, especially in the context of pathogen-related diseases as pathogens are also very adept at evading our efforts to destroy them.

The challenges outlined in this article are far from comprehensive, and specific unmet needs exist for a variety of other respiratory diseases, including alpha-1-antitrypsin deficiency, hypersensitivity pneumonitis, chronic obstructive pulmonary disease, lung cancer, pulmonary hypertension in the newborn, and others. While each disease state may have its own unique set of challenges, in general, one can categorize these into three major areas of need, namely, diagnosis, treatment, and prevention (Fig. 1). More specifically, these would include the identification of biomarkers to provide less invasive methods for the diagnosis and monitoring of the disease, as well as determining prognosis, the development of new drugs and treatment modalities, and also the development of vaccines or other environmental controls to reduce the incidence of the disease.

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