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Thank you to all of the authors who contributed to this issue of Lung Health Professional magazine. We are very pleased to continue to feature 10-year anniversary articles to commemorate the past decade of progress for the COPD Foundation and COPD community.

**COPD Patient-Powered Research Network—Join Us!**

This issue of LHP features the launch of a landmark program of the COPD Foundation, the COPD Patient-Powered Research Network (COPD PPRN). PPRN is an initiative aimed at bringing together all members of the COPD community to let their voices be heard and create a platform to accelerate research focused on improving our health outcomes and development of more effective therapies. The COPD PPRN is a vital initiative, and will be a network of over 75,000 individuals living with COPD who have agreed to share their health information and the impact the disease has on their lives. **We hope that you will join us in the effort to build the PPRN and leap one step closer towards better therapies and cures for COPD. For more details, visit page 30 or www.copdpprn.org**

**Lung Health Professional Goes DIGITAL**

I also want to make you aware of a VERY exciting change for Lung Health Professional magazine and our readers—starting in January 2015, Lung Health Professional will be migrating to become a fully digital publication. The digital LHP will be modeled after the COPD Foundation’s new scientific journal (journal.copdfoundation.org). LHP will be easily viewed on mobile devices and the digital format will allow for rapid publication of new articles. In addition, the COPD Foundation plans to expand the focus of LHP to truly encompass “lung health”.

**What Does This Change Mean For LHP Readers?**

After this issue, you will receive one more printed issue of LHP in 2014. Beginning in January 2015, we will be migrating toward a fully digital publication. In 2015, we will print and mail two issues of LHP to our readers. The LHP website will include recent updates and articles that will not be included in the printed issues. It is VERY important that we have your correct email address. Please visit the LHP webpage on the COPD Foundation website www.copdfoundation.org/lhp and send us your email address. In addition to LHP, you will be entitled to receive the COPD Foundation’s scientific journal: *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation (JCOPDF)*. The COPD Foundation is pleased to be able to provide LHP and JCOPDF at no cost to readers.

For more information or questions, please contact Elisha Malanga, Associate Executive Director of Research at emalanga@copdfoundation.org

I’d like to thank all of the authors who contributed the important articles in this issue. As always, please feel free to send story suggestions to me, I am always looking for your input. You can email me at: kturner@copdfoundation.org

Best,

Katelyn Turner

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Lung Health Professional magazine is published 4 times annually and is available from the COPD Foundation free of charge. If you would like to be added as a subscriber, please email Katelyn Turner at kturner@copdfoundation.org or call the C.O.P.D. Information Line 1-866-316-COPD (2673).
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HIGHLIGHTS OF PRESCRIBING INFORMATION

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3036437-B5
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*This article is special for the COPD Foundation's 10-year anniversary.
Diabetes and the Lungs: Where Have We Been and Where Are We Going?

In the summer of 2001 I moved my family to Denver Colorado to work at the Barbara Davis Center for childhood diabetes for a study of macrovascular complications of type 1 diabetes, specifically subclinical atherosclerosis. Type 1 diabetes is fairly rare in the general population but the patients have high rates of micro/macrovacular complications; nephropathy, neuropathies and retinopathy chief among them and these indicators of diabetes severity played an important role in our research. Times change and ten years later I found a home as a researcher in a completely different area, Chronic Obstructive Pulmonary Disease. As I came to understand COPD, its effects on the lungs, other organ systems and general wellbeing of people affected it occurred to me that I had never once heard an endocrinologist mention the lungs. Not once during my years of attending the scientific sessions of the American Diabetes Association did I see discussion of “microvascular complications of the lung” or anything similar. This revelation sparked my interest in understanding why the largest vascular bed in the body did not generate a microvascular complication of diabetes.

A paper was published this year in the American Journal of Respiratory and Critical Care Medicine described Chronic Obstructive Pulmonary Disease and its co-morbidities (including type 2 diabetes) as ‘multi-morbidities’. The authors were interested in emphasizing the diverse linked diseases that appear to be driven by common smoking behaviors and lack of physical activity. Patients with multi-morbidities are likely to present for evaluation with the first condition that becomes symptomatic and future interactions with healthcare may see other conditions that evolve into a symptomatic phase as secondary effects of the first condition rather than pre-existing in a subclinical phase. This relationship likely exists between COPD and diabetes.

This does not mean that the lungs have never been considered when evaluating patients with diabetes; it simply never rose to the level of a complication because studies observed that the decrease in pulmonary function was small, did not consistently progress and was not substantially altered by glycemic control. Several papers have been published over the last decade indicating that the lungs are a target for diabetic complication but only recently has this observation been pushed into the realm of potential treatment. Some of the earliest work investigated hypoxemia as a potential causative agent of the microvascular complications associated with diabetes was done in the late 1970’s by Jørn Ditzel. This followed the observation that glucose binds non-enzymatically to hemoglobin and that the dissociation constant for oxygen bound to hemoglobin that is also bound by glucose is higher than oxygen bound to hemoglobin unaffected by glucose. In 2006 a systematic review and meta-analysis of randomized controlled trials completed between 2001 and 2006 evaluating inhaled insulin was performed. This series of studies required measurement of pulmonary function in relatively large numbers of participants with diabetes and allowed a much closer look at lung function in this population. The observation of reduced pulmonary function matched the results of the studies in the 70’s and 80’s by showing a small but consistent reduction in both Forced Expiratory Volume at one Second (FEV1) and Forced Vital Capacity (FVC) as measured by spirometry.

How common is COPD multi-morbid with diabetes?

Type 2 diabetes mellitus and COPD are both common and increasing in...
prevalence worldwide. In the US new cases of diabetes have increased from 3.5/1000 to 7.7/1000 over the last thirty years. This increase is reflected in the prevalence of diabetes which has increased by 3.8% over the same time period to 6.4% of the population (4). By 2012, COPD will likely become the third most common cause of morbidity and mortality in the adult population (5). Smoking has been shown to increase insulin resistance which increases the risk of developing diabetes and diabetes has been shown to affect the lung through several pathways. Both conditions increase as people age. In 2010 an article revealed that people with diabetes are more likely to develop COPD (6) and in 2013 another study revealed that COPD is associated with between 40-100% increased risk of developing future diabetes (6). Both COPD and diabetes are likely present in the population in early, pre-clinical states. In 2000 a study of National Health and Nutrition Examination Survey data estimated that two-thirds of people with low lung function have not been diagnosed (6) and a separate study published in the same year estimated that half of the people with type 2 diabetes are undiagnosed (5). Thus it is expected that COPD multi-morbid with diabetes will become a more common observation in a clinical setting.

How does the reduced pulmonary function associated with diabetes effect people living with COPD?

Diabetes affects the lungs in ways that may influence the diagnosis of COPD as well as the measurement of pulmonary function to assess the severity of COPD. Hyperglycemia has been shown to effect lung elasticity and total lung volume through the accumulation of Advanced Glycosylation End-products (AGEs) where circulating glucose forms covalent bonds non-enzymatically with collagen and elastin in the lungs. The turnover rate for AGE bound collagen appears to be slow resulting in a long term reduction in elasticity in patients with hyperglycemia. It is thought that this reduced elasticity and TLC may be associated with reduced FVC preferentially compared to FEV1. This is important in COPD because at present the diagnosis of COPD is based on the ratio of FEV1 to FVC where values less than 0.7 are considered to represent obstructive disease. In patients with diabetes where FVC is preferentially reduced compared to FEV1, the ratio increases and patients with COPD and diabetes may not meet the 0.7 criteria and be diagnosed. After a patient meets the 0.7 criteria, diabetes will still have an influence on COPD staging using the GOLD criteria. In 2014 we used our study of heavy smokers to show that diabetes is associated with a reduction of 1.9% in FEV1 Percent Predicted (FEV1PP) and a reduction of 2.3% in FVC Percent Predicted (FVCPP) (6). Accounting for that reduction in FEV1 in the GOLD criteria for staging COPD severity resulted in 7% of our study population shifting to a different GOLD stage (6) with the potential for different treatment.

Exacerbations of COPD may be worsened by multi-morbid diabetes. Hyperglycemia associated with diabetes was shown in 2006 to cause circulating glucose to overwhelm lung homeostasis and enter the lung surface fluid (7). In 2000 glucose in the lung was shown to have a number of affects including playing a role as fuel for bacterial growth (6). Biochemical work in 2011 showed that glucose in lung surface fluid inhibits the lungs innate immune system by binding to Surfactant-D (6). These alterations in the lung microbiome and innate immune system may play a role in the observation that people with diabetes have experience increased infections (6), infection related mortality (6) and influenza associated mortality (6). A patient with COPD and an increased propensity for bacterial growth coupled with a reduced ability to react to viral infection may be more likely to experience exacerbations of COPD and for those exacerbations to be more severe and that is what was observed in 2006 in a study of AECOPD hospital admissions (6).

Our work this year showed that dyspnea is associated with diabetes beyond the effects of COPD (6). Breathlessness is a perception made
by the patient and very difficult to measure in a quantitative way. A person who feels breathless will likely be less inclined to exercise and when exercising less inclined to reach their peak capacity and achieve the greatest benefit from that exercise. Since exercise improves insulin sensitivity and hyperglycemia it’s commonly suggested to patients with diabetes that they follow an exercise plan whose success would be affected by the combined breathlessness due both to diabetes and COPD.

**What can we expect in the next 10 years?**

There are several large, ongoing studies that have the capacity to greatly expand our knowledge of how diabetes affects patients with COPD. The COPDGene study began in 2007 as a multi-center study of participants with a heavy smoking history. 10,300 participants have completed a baseline evaluation of their pulmonary health as well as contributing DNA for GWAS studies. These participants are being brought in for a second visit after five years of follow-up. The study is collecting comparable data as well as including new markers that were not collected at the first visit. This will allow the investigators to more clearly understand how COPD changes over time and also how that change is influenced by diabetes. There may be genetic markers as well that are shared by both diseases and their identification will help us understand biological pathways that we may be able to effect with treatment.

SPIROMICS is a large, ongoing cohort study of smokers with and without COPD that began enrollment in 2011. This study will give us insight into how diabetes affects the frequency and severity of exacerbations. SPIROMICS is performing an intensive sub-study of exacerbations that will generate biological samples that may help us understand the role of hyperglycemia and exacerbation and indicate areas for early intervention. There is already interest in using insulin sensitizing agents such as metformin in patients with COPD to improve exacerbation outcomes. Metformin has been shown to reduce bacterial load in lung surface fluid in an animal model and its administration to COPD patients has been shown to be safe. It is hoped that future work will involve a randomized control design of treatment to increase insulin sensitivity in a patient population at high risk for COPD exacerbation.

Other large studies will collect data that is not specific to either COPD or diabetes but will include participants with both. A large cohort study of 16,000 Hispanic/Latino participants will contribute to our understanding of COPD and diabetes through measurement of post bronchodilator spirometry as well as insulin sensitivity/glycemic control over the next several years. The Hispanic Communities Health Study/Study of Latinos has already reported on the prevalence of diabetes, the prevalence of smoking and most recently at the national meeting of the American Thoracic Society on an association between diabetes and kidney disease and reduced pulmonary function in participants with and without pre-existing pulmonary disease. HCHS will very likely prove to be a rich source for future analyses into the effects of multimorbid COPD and diabetes.

Simply increasing research interest in the lungs as a target organ of diabetes will aid in understanding the presentation of patients that are multi-morbid with both diabetes and COPD. By understanding the basic pulmonary effects of diabetes we will be better able to understand how these effects contribute to all aspects of COPD and might suggest ways of using existing treatments for diabetes to gain off target benefits in these patients.

**References**


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My interest in COPD research began during my pulmonary fellowship training. Early in pulmonary fellowship, I began to appreciate how different COPD patients could be. For example, some patients are vigorous and active, some frail and homebound. Some patients have frequent acute exacerbations, some have none. And some respond well to medications and some seem to have no benefit. These attributes correlated somewhat to pulmonary function measurements, but not entirely. Yet I was reading guidelines which recommended treating all COPD patients alike, guided only by the FEV1 level. Since that point, my research and clinical practice has focused on improving precision in diagnosis and treatment of COPD.

This area used to be termed “personalized medicine,” though the idea of “precision medicine” has been gaining more strength recently for several reasons. First, physicians and indeed all health professionals have always practiced personalized medicine, considering each patient as an individual, providing medical advice and treatments tailored to each patient’s unique situation. Second, from a research standpoint, personalized medicine implies developing treatments for one patient at a time. While precision medicine is focused on identifying groups of patients and offering more specific treatments to these subgroups.

However you describe it, precision medicine requires not only clinical insight, but also the tools of traditional epidemiology and modern genetics and genomics. Therefore after completion of my clinical pulmonary fellowship at the Harvard Medical School combined fellowship program, I pursued a fellowship in Respiratory Epidemiology at the Channing Laboratory at Brigham and Women’s Hospital. Under the mentorship of Dr. Edwin Silverman, I trained in the genetic epidemiology of obstructive lung diseases, including COPD and asthma. I have since continued as a faculty member in what is now known as the Channing Division of Network Medicine.

Pharmacogenomics is one example of the application of genetics and genomics for precision medicine in COPD. This has been a major focus of my research. I am the Principal Investigator (PI) for a grant to perform a pharmacogenomics ancillary study to the Long-term Oxygen Treatment Trial, sponsored by the National Heart Lung and Blood Institute of the National Institutes of Health. Our study aims to use gene expression profiling and DNA genotyping to identify predictors of response to oxygen therapy in COPD. I am the PI of another grant for a pharmacogenomics ancillary study to a clinical trial of inhaled corticosteroids in airway-predominant COPD, in order to identify genetic, genomic, and epigenetic factors associated with response to treatment, to prevent COPD exacerbations. This clinical trial is an ancillary study of the NHLBI-sponsored Genetic Epidemiology of COPD (COPDGene®) Study, in which I have been involved since its inception. The COPDGene Study has been described in detail in previous issues of Lung Health Professional magazine.[1,2,3] I serve as the co-director of the BWH clinical center in COPDGene, working with my colleague Dr. Dawn DeMeo to oversee the study team. I am also a member of the Genetics Analysis Center and the leader of the Clinical Subtypes Working Group in COPDGene, which is using clinical and epidemiologic information to more precisely define subgroups of COPD patients. I also lead a pharmacogenetics project which includes COPDGene and other studies seeking to find genes which influence a COPD patient’s response to bronchodilators, measured by improvement in FEV1 after inhaled albuterol.
Although genetics and genomics are an important part of precision medicine, clinical acumen plays a major role. For example, most healthcare providers caring for COPD patients have seen patients with the diagnosis of “COPD/asthma” noted in their charts. My research group has been very interested in these patients. A skeptic might say that a diagnosis of both COPD and asthma merely represents confusion about the correct diagnosis, or maybe even misdiagnosis of COPD as asthma or vice versa. However, this asthma-COPD overlap has been described in studies from the USA, Latin America, Europe, and Asia, with frequencies ranging between 15-55%, though most people believe the prevalence to be in the lower part of that range.[4] In addition, studies show that patients with both asthma and COPD represent a clinically-relevant subgroup, with more symptoms, more medication use, more exacerbations, and more hospitalizations than patients with COPD alone.[5] Of course, this leads to greater healthcare costs in asthma-COPD overlap patients.

COPDGene is a study of genetic epidemiology, and nearly all subjects have data from a genotyping microarray that allows for the simultaneous assessment of millions of genetic variants across the 23 human chromosomes.

Therefore, we performed a genome-wide association study (GWAS) for the asthma-COPD overlap syndrome. Although we did not find any results that were strictly statistically significant, several interesting genes were identified, which deserve further investigation.

Despite the relative frequency and the clinical significance of the asthma-COPD overlap syndrome, these patients have not been well-studied. Previous studies have mostly consisted of analyses of large databases. Patients with asthma history are frequently excluded from clinical trials in COPD, and smokers are usually excluded from asthma clinical trials. However, asthma was not an exclusion criterion in the COPDGene Study, so we took advantage of this unique resource to investigate the asthma-COPD overlap syndrome. In the first phase of COPDGene, over 10,000 smokers with and without COPD were enrolled at 21 clinical centers across the USA, including Brigham and Women's Hospital. At the first study visit, subjects completed multiple questionnaires on medical history, medications, symptoms and quality of life; performed spirometry and a 6-minute walk test; had a chest CT scan; and provided a blood sample for genetic analysis. COPDGene is currently in the process of bringing back subjects for a second study visit, 5 years after the initial visit.

The first look at the asthma-COPD overlap syndrome was in a dataset from the first 2500 subjects enrolled in COPDGene, with the analysis led by Dr. Megan Hardin who was then a post-doctoral fellow and is now a faculty member in the Channing Division of Network Medicine.[6] We defined COPD based on spirometry showing a reduced FEV1/FVC ratio less than 0.7 and an FEV1 less than 80% of predicted. Asthma was defined if a subject reported a doctor having diagnosed him or her with asthma before the age of forty. Thirteen percent of COPD subjects also had the diagnosis of asthma. These subjects were more commonly African Americans. They were younger and had smoked less, though they had similar reduction in lung function, showing that asthma contributed to airflow obstruction along with aging and smoking. Asthma-COPD subjects had more frequent exacerbations and had more commonly been seen in the emergency room or hospitalized for a COPD exacerbation within the prior year.

Again conducted by Dr. Hardin, we continued this line of investigation in the complete COPDGene dataset, confirming a twelve percent frequency of asthma-COPD overlap along with the racial differences and increased exacerbation risk seen in the first paper.[6] In the larger study, women were more frequently diagnosed with asthma and COPD than men. Asthma-COPD overlap subjects more commonly had hay fever as well as a family

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history of asthma. Interestingly, bronchodilator response on spirometry could not accurately distinguish asthma-COPD subjects from COPD alone. Examining the chest CT scans, subjects with asthma-COPD overlap had less emphysema, but more airway disease.

COPDGene is a study of genetic epidemiology, and nearly all subjects have data from a genotyping microarray that allows for the simultaneous assessment of millions of genetic variants across the 23 human chromosomes. Therefore, we performed a genome-wide association study (GWAS) for the asthma-COPD overlap syndrome. Although we did not find any results that were strictly statistically significant, several interesting genes were identified, which deserve further investigation.

While COPDGene has found multiple genes with statistically significant association with COPD susceptibility, why were there no significant associations with the COPD-asthma overlap syndrome? One issue is the sample size. GWAS continue to increase in size, with some studies including hundreds of thousands of individuals. The most recent COPD GWAS included over sixty-five hundred COPD subjects and nearly six thousand smokers without COPD, when combining the results from COPDGene with three other studies. Yet the asthma-COPD overlap GWAS included on 3,170 subjects, all from the COPDGene Study.

Another issue is the definition of the asthma-COPD overlap syndrome. When searching for genetic risk factors which may indicate the underlying disease biology, one must be very specific in the disease definitions. For example, GWAS for type 1 and type 2 diabetes have yielded dramatically different results, due to the differences in pathophysiology of the two diseases. Combining these two diseases in a single genetic study would be a mistake. In our studies, and in COPDGene in general, COPD is objectively defined by airflow obstruction on post-bronchodilator spirometry, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (www.goldcopd.com). However, asthma is more difficult to define, especially in older adults, since there is no single objective test for asthma. Testing for airway hyperresponsiveness or allergies may be supportive. The Global Initiative for Asthma (GINA, www.ginasthma.org) and GOLD recently released a document on the asthma-COPD overlap syndrome which outlines a clinical and spirometric approach to the diagnosis of the asthma-COPD overlap syndrome, along with management guidelines. However, it is clear that more research is needed, and we plan to continue this line of investigation in COPDGene.

Our papers on the asthma-COPD overlap syndrome demonstrate how clinical acumen, epidemiology, and genetics can be combined to define a COPD subgroup, in the first step towards precision medicine. Integration of multiple “omic” data types is an important direction in this type of research. Our group has been involved in several collaborative projects which use integrative approaches to large datasets. This type of work requires partnerships between investigators with a wide range of expertise, including physicians, epidemiologists, molecular geneticists, statisticians, and computational biologists. Lively discussions among these experts help to propel the research forward.

Having the appropriate datasets is essential as well. We and others have been attempting to generate additional data in COPDGene beyond the completed GWAS and the planned DNA sequencing, such as gene expression profiling. These genomics studies are expensive, so there is a constant search for funding. Another major challenge is the availability of appropriate...
clinical tissues in COPD. In contrast to lung cancer, lung biopsy is not part of the standard evaluation of a COPD patient, and it would difficult to perform lung biopsies in COPD only for research. Therefore, our studies must utilize lung tissue that has been resected for clinical indications, such as lung nodules, lung volume reduction surgery or lung transplantation. Bronchoscopy is less invasive than thoracic surgery, and airway brushings and bronchoalveolar lavage samples can be used for COPD research. Ultimately, it will be important to identify genomic biomarkers of COPD subtypes in peripheral blood to allow for the large sample sizes necessary to place COPD patients into subgroups. Blood is more easily accessible and cost-efficient than bronchoscopy or lung resection samples.

We have several ongoing studies which integrate clinical, imaging and genomic data in blood samples, bronchoscopy, and resected lung tissue, and that is clearly an important future direction for my research and other investigators in my division. Continuing work in pharmacogenomics and subtyping, such as the asthma-COPD overlap syndrome, will provide the backbone results needed for precision medicine in COPD. The next step is translating the research back to patient care. Several investigators have already proposed clinical trials of existing COPD medications in subgroups of COPD patients with specific clinical features, and in the future, we expect clinical trials of new medications that will be targeted to precise subgroups. Someday, doctors will no longer diagnose patients with “COPD” and prescribe the same inhalers to all patients. Instead, a patient may be diagnosed with COPD type A or B or C, etc. and be offered a medication more specific to his or her underlying biology, with the goals of greater benefits and fewer side effects.

References
Recognizing Nontuberculous Mycobacterial Lung Disease

Infections are a common and often serious complication of chronic lung disease, including COPD and bronchiectasis. A rapidly emerging group of pathogens not well understood by both health care providers and patients are the nontuberculous mycobacteria (NTM). This family of organisms is unlike tuberculosis in that they live in the environment (including household water systems), are not generally contagious, and usually affect patients with pre-existing lung disease. There are currently almost 150 recognized species of NTM, although only a few are major causes of chronic lung infection.

MYCOBACTERIUM AVIUM COMPLEX LUNG DISEASE

The most common species in the U.S. associated with lung disease are Mycobacterium avium complex (named because they were thought to come from birds), and Mycobacterium abscessus (named because the first identified organism caused a skin abscess). Mycobacterium avium complex is often abbreviated to “MAC.” It currently consists of two major species, one being M. avium and the other M. intracellulare. The clinical disease caused by these two species appears to be the same, but their reservoirs in the environment are different.

Two different types of lung disease are seen with M. avium complex. Historically, the first recognized type caused holes or cavities in the upper lung and occurred in patients with underlying COPD, and many had some degree of alcohol abuse. The usual patient was a male in his mid to late 50s and was an active smoker. As more and more women smoked and acquired COPD, this male predominance has diminished. Their clinical disease mimicked the presentation of tuberculosis: chronic cough over many months, sometimes containing blood, fever, weight loss and poor appetite were the most common features. A chest x-ray showed abnormalities in the upper lobes of the lung that also mimicked the findings of patients with active pulmonary tuberculosis. Until the advent of modern microbiology, many of these patients were considered to have tuberculosis and were treated with standard antituberculosis drugs.

The second patient population with MAC differs dramatically from the one just described. This type produces small nodular areas of infections that are hard to see without a high resolution computerized tomography (CT) scan. It occurs in much greater numbers in Caucasian women in their 60s and 70s who have been lifelong non-smokers and are otherwise healthy. They do have underlying bronchiectasis, in which their breathing tubes become damaged and enlarged and produce excess mucus. The women also tend to have an unusual morphotype in that they are taller and more slender than the average woman, with a body mass index that is at the lower limits of normal. Approximately 50% of this patient subset has mild scoliosis.

Their clinical presentation is much more subtle than the first group. Slow progressive fatigue and clearing of their throat may be the only signs that all is not right. The average patient is asymptomatic for several years before a diagnosis is made. This disorder is often referred to as the “Lady Windermere Syndrome,” an allusion to the Oscar Wilde play about a fastidious woman who would never have coughed (these patients may clear their throats softly but rarely cough).

Related to the older patients with nodular disease in the setting of bronchiectasis is this same disease seen usually in adolescent patients with cystic fibrosis. Because of pre-existing lung disease, recognition of NTM is difficult to make and many cases are unsuspected until the patient undergoes bronchoscopy or has sputum cultures for mycobacteria. Patients that do have symptoms usually show a decline in their lung function, worsening of cough and mucus production with only temporary response to the usual treatment for exacerbations of CF, and fever that likewise responds only temporarily to other therapy.
TREATMENT OF MYCOBACTERIUM AVIUM COMPLEX LUNG DISEASE

The treatment of NTM infections in general take much longer than other bacterial infections and involve multiple drugs. For patients with upper lobe cavitary disease and underlying COPD, treatment often involves four drugs - three oral drugs given daily (rifampin, ethambutol, and clarithromycin or azithromycin) combined with an injectable drug (either streptomycin or amikacin) given three times weekly. The drugs are generally expensive and associated with significant side effects. Patients are treated until their cultures are negative for 12 months which often results in a total of 16-18 months of therapy. Unfortunately, this requires diligence and compliance on the part of the patient, and this group is not good about such compliance.

To make matters worse, large cavities or holes in the lung are very difficult to sterilize with the M. avium complex drugs and often require resection of the cavities to effect a cure. This type of disease constitutes a serious infection, and when superimposed on significant COPD may result in the patient's death despite the best efforts of the physicians caring for them. Earlier detection of NTM lung disease in patients may help increase the success rates of treatments.

Treatment of the nodular form of MAC is less complex with a much higher rate of cure, but this has happened only in recent times. The standard therapy was the same three oral drugs used for upper lobe cavitary disease given on a daily basis. Unfortunately this group of patients has very low tolerance for medicines in general, and daily medications usually result in nausea, vomiting and other gastrointestinal side effects. Hence, successful therapy was uncommon despite the availability of relatively good drugs. More recently the drug frequency was changed to three times weekly, resulting in a good clinical response and much better drug tolerance.

Having said that, the physician needs to work with the patient to help them tolerate the medications, as adding 7-8 pills on medicine days still elicits some unwanted reactions. A recent study by experts in therapy of the disease showed the results of therapy for daily and three times weekly treatment to be equivalent with a cure rate of approximately 80%, and with much better tolerance with the three times weekly regimen. This three time weekly regimen is now the recommended standard of care for this type of MAC lung disease by the American Thoracic Society (the medical arm of the American Lung Association) and the Infectious Disease Society of America.

Mycobacterium abscessus lung disease

M. abscessus is a rapidly growing (for a mycobacterium which typically takes 2-4 weeks to grow) species which produces disease very similar to M. avium complex. It most commonly produces nodular disease in the setting of bronchiectasis, either in older women with “Lady Windermere Syndrome” (often referred to by their CT findings as “nodular bronchiectasis disease”) or young adults with cystic fibrosis. In older women, M. avium cases outnumber M. abscessus by 4:1, while in patients with CF the majority of infections are due to M. abscessus. The reason for this difference is unknown. Both M. avium complex and M. abscessus seem to produce disease in the same patient populations. If followed long enough, many of the older patients with nodular bronchiectasis disease will develop infections due to both species.

TREATMENT OF MYCOBACTERIUM ABSCESSUS LUNG DISEASE

M. abscessus is divided into three subspecies. The most important of these is abscessus and massiliense. They differ dramatically in their antibiotic susceptibility and therefore in the outcome of drug therapy.

Many cases of M. abscessus lung disease are relatively stable or exhibit very slow clinical progression and allow a good quality of life without a need for treatment, which is good because M. abscessus is one of the most drug resistant organisms causing lung disease. Some
physicians say they would rather treat a patient with multidrug resistant tuberculosis (MDR-TB) than M. abscessus because MDR-TB is easier to treat. Most isolates of M. abscessus (especially subspecies abscessus) are resistant to ALL oral antibiotics, and the only potential therapy is with intravenous medications over many months - and then the hope is clinical improvement but not cure.

The difference in the two groups relates to an enzyme that alters the ribosomal RNA binding site of a group of drugs called the macrolides that include two well known drugs called clarithromycin and azithromycin (both related to erythromycin). The DNA that codes for the enzyme, called erythromycin methylating (or “Erm”) gene, when functional, results in the macrolide being unable to block protein synthesis in the cell. Hence the M. abscessus is resistant. This type of gene is in subspecies abscessus.

In subspecies massiliense, however, the gene has somehow been shortened and the methylase enzyme does not work, and the isolates and their DNA are susceptible to the macrolides. One study in South Korea estimated that up to 80% of patients with this subspecies can be cured of their M. abscessus infection compared to only about 15% of patients infected with subspecies abscessus. When a functional erm gene is present, therapy of M. abscessus requires a long term (minimum of 3-6 months) intravenous access device, and often toxic or side effect-producing antibiotics such as amikacin, cefoxitin, and imipenem. For this reason there are continued efforts to find new drugs to treat these infections, with one drug currently undergoing clinical trials involving a
form of amikacin which can be inhaled into the lungs rather than taken intravenously (the latter being much more toxic).

RECURRENT INFECTIONS IN PATIENTS WITH UNDERLYING BRONCHIECTASIS

Though not all risk factors for NTM disease are known, we do know that people with similar circumstances, or even living in the same residence, do not all get infected. This is fortunate as NTM are common in the environment and avoidance to exposure is almost impossible, though not all exposures lead to infection and disease. An unfortunate aspect of patients with bronchiectasis is that it is incurable, and it is bronchiectasis or factors related to bronchiectasis that place patients at risk for acquiring NTM disease.

Recent developments in molecular identification and fingerprinting of NTM have opened the door to better understanding of the disease and its acquisition. Techniques such as pulsed field gel electrophoresis (PFGE) and variable number of tandem repeats (VNTR) now allow us to determine if isolates from water in the patient's household matches the patient's isolate and is the likely source of infection. Of the two major species of M. avium complex, M. avium is known to be present in the biofilms of pipes that direct household water and a match between the pipe biofilm cultures and the patient's sputum is achieved currently in about 50% of studies. Factoring in the sampling error in culturing household pipes, that number is probably much larger.

Interestingly, the other major species of M. avium complex using molecular studies has been shown not to be present at all in household water, making the outdoor environment the almost certain reservoir. Although what measures could be used to eradicate M. avium from the water has not been established, without the molecular methods to track down the individual strains of MAC we would be much farther from finding answers.

Another advantage of the molecular DNA fingerprinting techniques in use is that patients with underlying bronchiectasis and M. avium complex lung disease appear to be infected multiple times in a lifetime. When a patient appears to have been successfully cured of M. avium complex with drug therapy becomes culture positive again, it is rarely clear if this is a relapse and a drug failure, or a new infection. The former often requires more aggressive drug therapy to eradicate the relapse, but a new infection is as easy to eradicate as any infection. The information (relapse or reinfection) is key to the physician and the patient as they decide on a treatment plan for that episode. With the use of DNA fingerprinting, one can readily separate the original isolate and the new isolate.

The ability to sequence DNA has become increasingly faster and less expensive, and in the last few years the entire chromosome of an isolate of NTM can now be sequenced within a few days for less than $500. Analyzing the sequences takes longer, but this technology allows for the ultimate DNA fingerprint of an organism and should greatly expand the accuracy of our studies of the patient isolates and their potential sources in the environment.

THE FUTURE

The future of diagnosis and treatment of NTM, and understanding how and where NTM disease is acquired is brighter than it has ever been, particularly in terms of the available technologies such as DNA fingerprinting. The darkness is that because NTM lung disease is not as common or well known, it has competed poorly with other diseases for research dollars. Many of the studies discussed above were done with little in the way of outside research dollars from either the federal government or private sources. The number of good NTM research labs in the U.S. can probably be counted on one hand - clearly not enough to make a difference at the speed that is needed. The same can be said for physicians experienced in the care of patients with NTM. Although the number is greater than the number of research labs and is slowly increasing, it is still too small to deliver the care that patients deserve. Both of these areas remain a major challenge if we are to ever to bring NTM to its knees and under control.
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A Decade of Progress in Asthma

A steady rise in asthma prevalence and mortality in many countries during the 1990s brought this disease to the attention of medical and other health agencies. This was not the first such "asthma epidemic" to occur in the second half of the twentieth century. In the 1960s clinicians as well as epidemiologists saw a similar trend affecting those suffering from asthma. Many investigators following the trend of this earlier development attributed the change to the use of powerful inhaled bronchodilators using isoproterenol for the treatment of bronchoconspasm, and this suspicion was reinforced by the finding of decreasing asthma mortality following the removal of these products from the market.

In addition the quest for new information concerning this disease has blossomed. Over the past 10 years the number of published studies in the field of asthma as recorded by PubMed was more than 55,000 (compared to the previous 10 years of slightly more than 39,000).

Two major multicenter collaborative clinical centers have addressed important clinical issues in this period.

The NHLBI Asthma Clinical Research Network was established in 1993 and has recently completed its work after twenty continuous years of study. The purpose of this network was to perform controlled clinical trials to investigate the safety and effectiveness of existing as well as novel therapies for asthma. These trials among other benefits helped establish the newly developing guidelines on a solid evidence based foundation. Fifteen major trials were performed along with a number of spin-off investigations. Some of the addressed issues were:

1. The Global Initiative for Asthma (GINA), a collaboration between the NHLBI and the World Health Organization launched in 1993 issues a strategy report updated annually, based on a twice-yearly review of scientific literature by an international panel of experts on the GINA Science Committee.

2. The International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma has specifically addressed address the issue of difficult to treat asthma

3. The Global Asthma Network, an agency supported by The International Union Against Tuberculosis and Lung Disease, offers readily accessible standardized information through printed and electronic media

1. The dosing, variability of response, and predictors of response to inhaled corticosteroids. These studies characterized the efficacy of lower dose inhaled corticosteroids as well as the variability between patients. Also noted was the unwanted ability of high dose ICS to suppress the body's ability to produce cortisol an important marker of potential side effects.

2. Patients with mild asthma can be managed with intermittent ICS and may not require daily therapy.
3. Long acting beta agonists should not be used as monotherapy for asthma.

4. Leukotriene receptor antagonists should not be used to replace ICS when they are combined with long acting beta agonists.

The American Lung Association, Asthma Clinical Research Center (ALA-ACRC) Network began in 1999 has been dedicated to conducting real-world clinical research in asthma and related conditions. It comprises some 20 major medical centers which have investigated a number of clinically relevant problems. Among those studied were:

1. Is the Flu vaccine safe for people with asthma? This study put to rest previous concerns about the potential for possible side effects, including exacerbation of the disease, in persons with asthma, thereby reassuring and endorsing the use of annual flu prophylaxis for one of the highest risk groups for flu complications.

2. Can an inexpensive medicine (theophylline) be used safely at lower doses in the management of asthma? Theophylline had been the primary drug used in the treatment of asthma before the advent of long acting inhaled corticosteroids. It had fallen out of favor primarily because of its side effect profile, particularly at higher doses. The study found that low dose theophylline did not improve therapy as an add on to standard therapy, but in those patients who were not able or willing to take inhaled corticosteroids low dose theophylline was a useful alternative.

3. Can patients with mild asthma have their disease controlled with a simpler regimen? Patients with mild persistent asthma, well controlled with ICS medication taken twice a day can be managed as effectively with a combination of ICS and long acting beta agonist taken once a day. Oral treatment with once a day montelukast was not as effective as the twice daily ICS regimen but did provide good control for most patients.

4. What is the role of GERD in asthma? Silent acid reflux was considered to be a major contributor to asthma symptoms and many physicians used prescription anti-heartburn medication to reduce asthma severity. The findings of the ACRC study suggests that in those asthma patients without symptoms of acid reflux, the use of anti-acid therapies were not useful in controlling asthma exacerbations.

While these multi-center studies have been extremely useful in shaping and determining the validity of current therapies a number of novel questions have been studied by individual investigators and commercial concerns interested in advancing the field.

Some of the other topics that have interested researchers in this period include:

1. Do asthmatic children grow into adults with Chronic Obstructive Pulmonary disease (COPD)? There have been indications from several studies that children with asthma are more likely than non-asthmatic children to develop COPD. Beginning with early epidemiologic studies from the 1960s which indicated that patients with COPD are more likely to recall childhood breathing problems. In a more recent study published in Thorax a group of children with childhood asthma were followed from the age of 7 to the age of fifty. The major conclusion of this study was that children in this study with severe asthma had an adjusted risk of developing COPD 32 times higher than that controls. Cigarette smoking was as common in both asthmatic and non-asthmatic groups and was not associated with a more rapid rate of decline of lung function. The issue however is far from resolved owing to the difficulty of following such groups over long periods of time.

2. What is the role of nitric oxide in asthma and is exhaled NO a useful test in following asthma? The single breath exhaled Nitric Oxide (FENO) test has recently moved from a mainly investigational tool to a widely
available diagnostic test. This is due in part to the rapid advance in technology of the instrument used to measure NO and the decline in price of the apparatus. It has been found that the measurement of FENO correlates with eosinophilic airway inflammation, that following initiation of corticosteroid therapy in asthma FENO decreases within days in a dose related fashion and increases after steroid withdrawal. Higher levels of FENO have been observed in difficult to treat asthma patients in spite of treatment with corticosteroids. Finally the use of FENO measurements have been shown to enhance the compliance of patient who do not adhere to their corticosteroid regimen.

3. What role does obesity play in asthma? Since the late 1980s a number of epidemiologic studies have indicated a higher prevalence of asthma among overweight and obese individuals. Some of these studies indicate that the greater weight the more likely the occurrence of asthma. In addition asthma associated with obesity is characterized by poorer asthma control and weight loss has been associated with improvement in symptoms and a reduction in the amount of reliever medication required to control the disease. While several mechanisms have been suggested by which excess fatty tissue influences asthma (including a chronic inflammatory response generated by adipose tissue) the role of these is not yet defined.

4. Are anticholinergic agents useful in the treatment for asthma? Some patients with asthma do not achieve adequate control of their disease with low to medium doses of inhaled corticosteroids (ICS). Current strategies include increasing the dose of inhaled corticosteroids, or adding a long acting beta agonist (LABA) or a leukotriene inhibitor. Recent concern about the safety of long acting beta agonists and in particular FDA mandated warnings about possible fatal complications with LABA have increased the need to find alternative treatment strategies in order to limit the use of LABAs for the management of asthma.

It has been appreciated since the 1970s that short acting anticholinergic inhaled therapy both alone or in combination with a short acting beta agonists such as albuterol can be beneficial for the treatment of patients with asthma.

Recent studies with the long acting anticholinergic agent Tiotropium, a therapy well established and approved for the treatment of COPD indicate that it may have an important role in asthma.

In a study involving 210 patients with poorly controlled asthma, the benefits of adding Tiotropium to an inhaled corticosteroid was compared to the benefit of doubling the dose of the inhaled corticosteroid or adding a long acting beta agonist (salmeterol) to the current dose of inhaled steroid. Improvement was measured by comparing the effect of treatment on morning lung function (peak flow). The combination regimen was shown to be more effective in improving this lung function, as well as the same measurement in the evening. In addition the number of days with better control of asthma, and other lung function measures such as FEV1 were all better with the combined regimen.

In another study involving 912 patients with poorly controlled asthma treated with a combination therapy of ICS and LABA investigators compared the effect of adding Tiotropium to the original regimen versus adding a placebo. The results showed that addition of the anticholinergic agent improved lung function and reduced the frequency of asthma exacerbations.

Although not as yet approved for the treatment of asthma, Tiotropium as well as a number of newer anticholinergic agents show promise for a role in the management of asthma.
5. Can macrolides be used for the prophylactic treatment of asthma? The role of azithromycin as an agent capable of reducing the incidence of COPD and bronchiectasis exacerbations has recently been established. Macrolides enjoy properties that suggest their usefulness in asthma. They are antibacterial, immunomodulatory and have potential antiviral properties. Initially used in the mid-twentieth century for their potential steroid sparing property (Troleandomycin) hepatic toxicity discouraged widespread use of this agent. Current reviews of the literature suggest that the evidence for their use in asthma is still inadequate.

6. Does airway smooth muscle contribute to bronchospasm in asthma and can thermoplasty correct it? Bronchial thermoplasty is a relatively new, non-pharmacologic approach to the treatment of poorly controlled asthma. The treatment consists in applying radiofrequency energy endobronchially in order to reduce bronchoconstriction by reducing the amount of airway smooth muscle. The procedure is currently FDA approved since 2010 for the treatment of severe refractory asthma. The treatment is applied at 3 separate sessions at least 3 weeks apart and patients are carefully selected to avoid complications. The first results of thermoplasty were reported in 2006. Since then controlled trials have shown that the treatment is followed by improved asthma symptoms fewer severe exacerbations and decreased health care use. Follow-up of patients show that benefits continue for at least 2 years and possibly five. The criteria at present are relatively strict for selection but the possible extension of this therapy to other groups of asthmatics remains a possibility.

7. Is the genetic characterization of asthma patients useful? Genetic characterization of patients with asthma has identified a large number of genetic loci associated with asthma susceptibility, asthma subtypes and responsiveness to asthma medications. Since the early 2000s advances in genotyping and the identification and mapping of a large number of single-nucleotide polymorphisms (SNPs) has led to the wide-spread adoption of genome wide association studies (GWAS). Since 2007 numerous loci have been associated with different aspects of asthma. These findings suggest that we have much to learn about the mechanisms underlying asthma and the potential for influencing the course of the disease by adopting a "personalized approach" to this disease.

Additional areas where research is currently going on include:

8. Are novel cytokine blocking agents useful in the therapy for asthma?

9. What are the effects of indoor and outdoor air pollution on asthma?

10. What is the ultimate role for Anti-IgE therapy in allergic asthma?

11. What is the best strategy for treating asthma and exacerbations?

12. What is the role of self management in poorly controlled asthma?

13. What is the role of biomarkers in asthma?

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The COPD Patient-Powered Research Network: Help Your Patients Take Charge

Patients empowered. That’s the motivation for the new COPD Patient-Powered Research Network (COPD PPRN), a registry aimed at bringing together all members of the COPD community to let their voices be heard. By encouraging your patients to join the COPD PPRN, they will become a part of establishing the largest community of individuals living with COPD ever assembled.

Participating in the COPD PPRN Registry will change the future of COPD for better – and your patients will be at the forefront.

The COPD PPRN will ultimately be a network of over 75,000 individuals living with chronic obstructive pulmonary disease (COPD), who have agreed to share their health information and the impact the disease has on their lives. The goal of the COPD PPRN is to further COPD research that is driven by patient needs and priorities. This network is unique in that it will be operated and governed by groups of patients in conjunction with dedicated researchers.

“We are excited to launch this network, and need your help encouraging individuals with COPD to sign up to participate to make this registry as successful as possible,” John W. Walsh, president and co-founder of the COPD Foundation, says. “Our goal is to support research to improve health outcomes and find new and more effective therapies for those living with COPD, as well as facilitating research to find cures.”

The COPD PPRN is part of a larger project funded by the Patient-Centered Outcomes Research Institute (PCORI) and is one of 29 that were approved for a total of $93.5 million to form this new national resource that aims to boost the efficiency of health research. PCORI’s mission is to fund research that will provide patients, their caregivers and clinicians with evidence-based information needed to make better informed healthcare decisions. The information gathered from participants will allow the COPD Foundation to join with other networks studying various medical conditions to advance research in the U.S. around a number of chronic disease conditions in a new initiative led by the National Patient-Centered Clinical Research Network (PCORnet).

Please encourage your patients to get involved by directing them to visit the COPD Foundation website at www.copdfoundation.org. If you would like to do more to promote the COPD PPRN, please call our C.O.P.D. Information Line at 1-866-316-COPD (2673) to request a health care provider toolkit which will include valuable resources to help you spread the word about the COPD PPRN. The COPD Foundation will send this kit to your office at no cost.

Questions Your Patients May Ask About the PPRN:

How do I know if I am eligible to enroll?
Anyone over the age of 18 with a confirmed diagnosis of COPD is eligible to participate.

How do I enroll?
Please visit www.copdpprn.org to begin the enrollment process.

How long will the PPRN run?
The PPRN does not currently have an end date. Since the growth of the network is critical to improving research, we anticipate it will run for a very long time.

How long will I be enrolled in PPRN?
You will be enrolled in PPRN for the duration of the program unless you elect to withdraw from the network.

Is participation voluntary?
Participation in the COPD PPRN is completely voluntary and you can withdraw at any time.

Will I be automatically enrolled in a clinical trial?
No. You are not automatically enrolled in a clinical trial or a study. By joining the COPD
PPRN you are only asked to share your personal medical information through filling out a brief survey. You may be contacted in the future to assess your willingness to participate in clinical trials or studies. You are under no obligation to participate in any future clinical trials or studies.

What is in it for me?
COPD PPRN participants will have access to current information on COPD from the COPD Foundation. Some of this information is specific to COPD disease stages and difficulties. This information is meant to help you and your caregiver (if you have one) manage your disease, and help you make well-informed treatment decisions.

Additionally, COPD PPRN participants, by sharing their medical information, will help focus research questions. This focus will reduce the time it takes to start new studies and improve treatment options. COPD PPRN participants will work with researchers to jointly determine research priorities.

Where will my information be kept?
Your information will be kept in a secure database to be used for research, ultimately leading to a deeper understanding of the disease.

What if I have questions now or need help with the process?
We are here to help! Call the C.O.P.D. Information Line at 1-866-316-COPD (2673) to speak with a trained patient or caregiver Associate.

How does the COPD PPRN promote research?
An estimated 300 million individuals worldwide have COPD, but there is no resource to locate these individuals for clinical research or hear their research priorities and concerns. By joining the COPD PPRN, you will enable this registry to serve as an unprecedented clinical research resource for physician and patient communities.
Tuberculosis (TB) is a global public health crisis despite being a largely preventable and treatable disease. In 2012, there were 8.6 million new TB cases and 1.3 million TB-related deaths around the world. A major driver of the TB epidemic is the high prevalence of tobacco smoking and exposure to second hand smoke. There are an estimated 1.3 billion tobacco users, with the majority residing in low and middle-income countries, where 90% of global TB burden is also concentrated. Tobacco use results in approximately 6 million deaths per year, and more than 20% of global TB burden is said to be attributable to tobacco use, especially as there is generally high prevalence of smoking among TB patients. The tuberculosis and tobacco epidemics are highly intertwined and it has been suggested that improved tobacco control is key to significantly improving global TB incidence and burden.

The aims of this paper are to review the current literature to establish both active and passive tobacco exposure as salient risk factors for tuberculosis by demonstrating that tobacco exposure increases the risk of poor outcomes at every stage of the disease. In particular, this paper will show that: 1) tobacco smoking increases the risk of latent TB infection (LTBI), 2) tobacco smoking increases the risk of progression of latent infection to active disease, 3) tobacco smoking increases the risk of TB mortality, and 4) tobacco smoking reduces the effectiveness of TB treatment and cessation reduces TB risk, in order to make the case for a concerted and integrated approach to TB and tobacco control efforts.

Smoking increases the risk of latent TB infection

Although one third of the world’s population is infected with Mycobacterium tuberculosis, the organism in general is contained by the immune system and individuals cannot transmit the disease. This is the latent, asymptomatic state of the infection, acquired when someone inhales tuberculosis bacteria expelled from the lungs of a patient with active tuberculosis disease. Individuals with the latent infection have a 5-10% risk of developing active disease over their lifetime.

Studies from around the world show that smoking increases the risks of latent TB infection (LTBI) incidence, probably by weakening the lung’s natural defense systems. According to an analysis of the 1999-2000 US National Health and Nutrition Examination Survey (NHANES) data set, Horne and colleagues (2012) indicated that smoking was independently associated with increased risks of LTBI. Specifically, the odds of LTBI were 1.8 times more likely among current smokers compared to non-smokers. In fact, data suggest that both active and passive smoking have the possibility of putting individuals at an elevated risk for LTBI compared to nonsmoking adults. In addition, a South African cross-sectional study in a high tuberculosis incidence area showed that active smoking increases the odds of infection among adults (OR: 1.90) compared to non-smokers. According to these studies, smoking has relevance for LTBI risk among individuals living in or originating from both low or high TB prevalent areas. Both studies suggested the need for smoking reduction strategies to decrease LTBI prevalence. These studies suggested the need for smoking reduction strategies to decrease LTBI prevalence.

Smoking not only increases the risk of LTBI in the individual, but also increases the risk of infection in their contacts through second hand exposure, possibly by increasing the infectiousness of the person already sick with TB. Godoy and colleagues (2013)’s study in Spain showed that smoking among TB patients put their contacts at an increased odds for LTBI (OR: 1.5) and was responsible for 12.8% of TB infections.

There is also evidence regarding the dose response relationship between exposure and its consequent risk for LTBI. Shin et al (2013)
conducted a cross-sectional study in Mexico among injection drug users, where there were high TB (67%) and smoking prevalence (97%)\textsuperscript{11}. The authors found that there was a dose-response relationship between active smoking and infection in this population, lending insight into understanding the relationship between smoking and LTBI among high-risk individuals \textsuperscript{11}. Du Preeze and colleagues (2011) also examined the dose-response relationship between tobacco exposure and infection status. Among South African children living in high TB burden settings who were exposed to high household environmental tobacco smoke exposure (ETS), there was a statistically significant dose response effect between the degree of ETS experienced by children (measured in pack-years of exposure) and infection\textsuperscript{12}.

The significance and strength of association in these studies provide support for cigarette smoking as an important risk factor for latent TB Infection. According to Gajalackshmi and den Boon the role of smoking on TB burden could be due to an increase in new incident cases of smokers becoming infected with latent TB and then developing clinical disease \textsuperscript{9,13}. The biological plausibility for these increased risks is suggested to be due to smoking’s adverse impacts on the body’s immune system, required for defense against M. tuberculosis. In particular, smoking impairs mucociliary clearance of pathogens and disrupts macrophage and T cell activity and functionality \textsuperscript{12}.

**Smoking increases the risk of developing active TB disease**

The literature shows that once someone has latent infection, smoking increases the likelihood of developing active TB. In a cohort study of an elderly population in China, Leung et al (2004) showed that current smokers had 2.87 times the hazard of developing pulmonary TB compared to never smokers\textsuperscript{14}; smokers and ex-smokers had hazard ratios of 2.60 and 1.68 respectively of culture confirmed TB compared to never-smokers. There was a dose-response relationship with increasing number of cigarettes smoked and the risk for active and culture-confirmed TB \textsuperscript{14}.

Ariyothai et al examined the role of active and passive smoking on the occurrence of pulmonary tuberculosis in adults in a case-control study in Thailand\textsuperscript{15}. Researchers found that passive exposure to tobacco more than 3 times a week was significantly associated with pulmonary TB \textsuperscript{15}. Current active smoking as well as early age of smoking onset were both associated with higher odds of developing pulmonary TB \textsuperscript{15}. Similarly, Prasad’s case-control study in India showed that current smokers had an elevated risk (nearly 4 times!) of developing pulmonary TB compared to never smokers\textsuperscript{16}.

Children are vulnerable to developing TB, especially from passive smoking exposure in the home. In Tipayamongkholgul’s case-control study in Thailand, exposure to close passive smoking increased the odds of childhood tuberculosis by 9.31 times compared to no exposure \textsuperscript{17}. Patra’s case-control study in India showed passive smoking exposure increased the odds of developing childhood tuberculosis by nearly twice \textsuperscript{18}. Lin’s representative cohort study of Taiwan’s population found that tobacco smoking was associated with a two fold increased odds of active tuberculosis compared to never smokers, and a significant dose-response relationship was found for cigarettes per day, years of smoking, and pack-years.\textsuperscript{3}

In Lienhardt’s multicenter case-control study in three west African countries, HIV infection and current tobacco use played the biggest role in TB risk, with smoking status exhibiting a dose response effect \textsuperscript{19}. Sterling and colleagues from the Tuberculosis Trials Consortium found, as did Lienhardt, that smoking status and HIV infection emerged as the two most salient risk factors for TB\textsuperscript{20}. Strikingly, in both studies, smoking had a greater effect on the risk of TB than did HIV infection\textsuperscript{3,20}. These data are consistent with other studies that estimate the overall burden of TB caused by tobacco. Lonnroth and colleagues found that the population attributable fraction (PAF) (i.e. the amount of TB caused by smoking) was 15.8%, while the PAF for HIV was 11.0\%\textsuperscript{21}. This underscores the point that there is a need to recognize tobacco as a serious and substantial risk factor for TB.
Smoking increases the risk of poorer outcomes and TB-related mortality

Studies show that smoking increases likelihood of increased TB disease progression and severity. In Spain, a cross-sectional observational study of TB cases comparing smokers and non-smokers found that smoking led to a more rapid TB disease progression and severity21. TB patients who smoked had higher odds of requiring hospitalization, and developing more severe disease22.

Several studies investigated the role of tobacco use on excess risk of dying from TB. Gupta’s cohort study in India, investigating the effect of bidi and other smokeless tobacco on excess mortality concluded that tobacco use resulted in 30-50% excess overall mortality for male cigarette and bidi smokers23. A retrospective study in Iran also showed that among patients with pulmonary TB, smoking was a major risk factor for death with an adjusted OR of 6.824.

Lastly, Gajalakshmi et al. (2003) conducted a case control study of urban and rural men in India to investigate the role of smoking on TB-related mortality and other diseases13. The study showed that the risk of mortality from TB was more than four times higher among smokers than non-smokers (urban RR: 4.5 and rural RR: 4.9) and that smoking was attributable for more than half of TB deaths among Indian men13. There was also a positive association between heavier tobacco consumption and TB prevalence. The authors suggested that smoking increases TB-related mortality due to increasing the number of new clinical tuberculosis cases, rather than increasing the probability that clinical disease will lead to TB death13.

Smoking inhibits effectiveness of TB treatment and quitting smoking reduces TB risk

There are a number of studies that indicate that smoking inhibits the effectiveness of TB treatment by increasing treatment defaults, failures, and relapse. Chiang and colleagues found that among TB patients in Taiwan a high level of tobacco consumption (>20 cigarettes/day) was significantly associated with decreased odds of a cure or treatment completion, reducing the chance of a successful outcome of treatment by nearly 75%25.

In another study, a cohort of TB patients in South India was followed up 6, 12, and 18 months after treatment completion for acid fast bacilli and culture to examine relapse. The study found that the odds of relapse were three times more likely for smokers compared to non-smokers26.

Quitting smoking is known to reduce TB risk. Wen and colleagues assessed the benefits of quitting smoking on TB mortality27. Smokers with a history of TB had 44 times the hazard of death from TB compared to never-smokers and the hazard was reduced by 34% when they quit smoking27. Smokers with no prior TB history had 9 times the hazard of death from TB compared to never-smokers and the hazard was reduced by 65% when they quit smoking. This reduced risk was similar to those who never smoked27. In light of high TB-mortality rate among smokers and the finding that quitting smoking reduces risks to such a considerable extent, Wen’s study lends support for integrating tobacco control with TB control, which could have enormous public health benefits for both diseases27.

Awaisu and colleagues (2011) looked at the benefits of an integrated tobacco cessation and TB intervention program in impacting TB treatment outcomes28. They conducted a prospective non-randomized controlled intervention across five chest clinics in Malaysia. 120 TB patients who were also current smokers were either enrolled in the conventional TB directly observed therapy program or in an integrated program which included a smoking cessation intervention. The study found that those in the smoking cessation group had a 77.5% chance of successfully quitting smoking vs. 8.7% in the DOTs group28. At the end of the treatment regimen, those in the cessation group had significantly lower rates of treatment default (2.5% vs. 15.2%) and treatment failure (0% vs. 6.5%), as well as higher cure rates (80.0% vs. 52.2%)28. This study...
provides evidence for a policy and clinical practice for a tobacco-integrated approach to TB treatment that could improve therapy outcomes, as well as present an opportunity to concurrently tackle the problem of tobacco use in high risk populations.

**Conclusion**

It is only in the past few years that there has been a realization that tobacco contributes substantially to the global tuberculosis epidemic. We have reviewed studies that have established the evidence for tobacco as an important risk factor for TB. Smoking increases the risk of latent infection, active disease, and TB-mortality, as well as worsens disease progression, severity, and negatively affects anti-TB treatment outcomes.

Basu and colleagues constructed a mathematical model of the effects of tobacco smoking on worldwide tuberculosis cases and deaths. The model predicted that by 2050, smoking would cause an excess of 18 million TB cases and 40 million TB deaths, while a 1% decrease in smoking prevalence per year would save 27 million TB deaths attributable to tobacco. The model also predicted that smoking would delay the millennium development goal for TB by 20 years in all WHO regions. Basu’s model lends further support to the idea that tobacco control is absolutely necessary for TB control efforts and that aggressive tobacco control measures need to be prioritized in order to prevent projected deaths of millions of people from TB in the coming decades. In light of these calamitous predictions, as well as other studies that have shown the benefits of smoking cessation on TB risks, there is a need for restructuring of TB control efforts, from treatment based control to incorporating tobacco cessation strategies. Not only is there a need for nationwide policy changes to coordinate this effort but clinicians and healthcare workers who are at the front lines of patient care should incorporate these findings into their clinical and educational practices.

Because TB is largely a treatable disease, the role of smoking on exacerbating TB disease progression and mortality had generally been ignored, as tobacco use was considered a separate health issue. However, in this review we have established the evidence for the deleterious association between tobacco smoking and TB; in particular that tobacco use is a significant risk factor for TB infection, disease, and mortality, attributing more than 20% of global TB burden. We have also established that tobacco use reduces the effectiveness of treatment among TB patients, increasing rates of treatment failure, default, and relapse. Quitting smoking, on the other hand, increases the chances of positive TB treatment outcomes, significantly reducing mortality risks as well as the possibility of reversing smoking-induced immunological damage to levels comparable to never smokers. Stated simply, tobacco control is tuberculosis control.

**References**

14 Leung CC, Li T, Lam TH, et al. Smoking and tuberculosis among the elderly in Hong Kong. Am J Respir Crit Care Med 2004; 170:1027-1033
27 Wen CP, Chan TC, Chan HT, et al. The reduction of tuberculosis risks by smoking cessation. BMC Infect Dis 2010; 10:156
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INDICATION FOR GLASSIA

GLASSIA is an Alpha₁-Proteinase Inhibitor (Human) (Alpha₁-PI) indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of Alpha₁-PI (alpha₁-antitrypsin deficiency). GLASSIA increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha₁-PI.

The effect of augmentation therapy with any Alpha₁-PI, including GLASSIA, on pulmonary exacerbations and on the progression of emphysema in alpha₁-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.

GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha₁-PI deficiency has not been established.

DETAILED IMPORTANT RISK INFORMATION FOR GLASSIA

HYPERSENSITIVITY

- GLASSIA is contraindicated in immunoglobulin A (IgA) deficient patients with antibodies against IgA or individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha₁-PI products.
- Hypersensitivity reactions have been reported in patients following administration. Patients should be closely followed and vital signs monitored continuously. Discontinue the infusion if hypersensitivity symptoms occur and administer appropriate emergency treatment.

TRANSMISSION OF INFECTIOUS AGENTS

- GLASSIA is derived from pooled human plasma and may carry a risk of transmitting infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Despite manufacturing steps designed to minimize the risk of viral transmission, such products may still potentially transmit human pathogenic agents.

USE DURING PREGNANCY

- GLASSIA should not be given to pregnant women unless clearly needed, as reproduction studies have not been done in animals or humans.

ADVERSE REACTIONS

- The serious adverse reaction observed during clinical trials was exacerbation of chronic obstructive pulmonary disease (COPD). The most common adverse reactions occurring in >0.5% of infusions in clinical trials were headache and upper respiratory infection

Please see GLASSIA Brief Summary of Full Prescribing Information on the adjacent page.


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March 2014  USBB/341/14-0009
GLASSIA (Alpha1-Proteinase Inhibitor (Human))
Injection Solution - For Intravenous Use Only

Brief Summary of Prescribing Information. Please see package insert for full prescribing information.

INDICATIONS AND USAGE
GLASSIA is an Alpha1-Proteinase Inhibitor (Human) (Alpha1-PI) indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of Alpha1-PI (alpha-antitrypsin deficiency). GLASSIA increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha1-PI.

- The effect of augmentation therapy with any Alpha1-PI product, including GLASSIA, on pulmonary exacerbations and on the progression of emphysema in Alpha1-PI deficiency has not been conclusively demonstrated in randomized, controlled clinical trials.
- Clinical trials demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been conclusively established.

DOSE AND ADMINISTRATION
- For Intravenous Use Only.
- Use aseptic technique for all preparation and administration steps.
- Dose = 60 mg/kg body weight intravenously once weekly.
- Administer at a rate not to exceed 0.2 mL/kg body weight per minute, dependent on patient response and comfort.
- Dose ranging studies using efficacy endpoints have not been performed.

CONTRAINDICATIONS
GLASSIA is contraindicated in immunoglobulin A (IgA) deficient patients with antibodies against IgA or in individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha1-PI products.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
GLASSIA may contain trace amounts of IgA. Patients with selective or severe IgA deficiency and with known antibodies to IgA, have a greater risk of developing severe hypersensitivity and anaphylactic reactions. Monitor vital signs continuously and observe the patient carefully throughout the infusion.

Discontinue the infusion if hypersensitivity symptoms occur and administer appropriate emergency treatment. Have epinephrine and other appropriate supportive therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction.

Transmissible Infectious Agents
Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, the variant Creutzfeldt-Jakob disease (vCJD), and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens.

The risk of transmitting an infectious agent has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process (see Descriptions [11] in full prescribing information for viral reduction measures). Despite these measures, such products may still potentially transmit human pathogenic agents.

帏 infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kamada Ltd. at 1-886-GLASSIA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

No seroconversions for hepatitis B or C (HBV or HCV) or human immunodeficiency virus (HIV) or any other known infectious agent were reported with the use of GLASSIA during the clinical trials.

ADVERSE REACTIONS
The serious adverse reaction1 observed during clinical trials with GLASSIA was exacerbation of chronic obstructive pulmonary disease (COPD).

The most common adverse reactions (≥0.5% of infusions) in clinical trials were headache (6 of 960 infusions or 0.6%) and upper respiratory infection (8 of 960 infusions or 0.8%).

1 An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began within 72 hours following the end of product infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to product administration, or (c) an adverse event for which causality assessment was missing or indeterminate.

Adverse Reactions Occurring in > 5% of Subjects During the First 12 Weeks of Treatment

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>GLASSIA No. of subjects: 33</th>
<th>Prolastin No. of subjects: 17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of subjects with adverse reactions% (AR) (percentage of all subjects)</td>
<td>No. of subjects with adverse reactions% (AR) (percentage of all subjects)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (9%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (9%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of GLASSIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
- Gastrointestinal Disorders: Nausea
- General Disorders and Administration Site Conditions: Fatigue

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C

Animal reproduction studies have not been conducted with GLASSIA. It is also not known whether GLASSIA can cause fetal harm when administered to pregnant women or can affect reproductive capacity. GLASSIA should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether Alpha1-PI is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GLASSIA is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical trials of GLASSIA included 11 subjects of 65 years of age or older. This number of subjects was not sufficient to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation. Safety and effectiveness in patients over 65 years of age have not been established.

PATIENT COUNSELING INFORMATION
- Inform patients of the early signs of hypersensitivity reactions, including rashes, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.
- Inform patients that GLASSIA is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk of GLASSIA transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing (see Warnings and Precautions). Symptoms of a possible virus infection include headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice.
- Inform patients that administration of GLASSIA has been demonstrated to raise the plasma level of Alpha1-PI, but that the effect of this augmentation on the frequency of pulmonary exacerbations and on the rate of progression of emphysema has not been established by clinical trials.

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