INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive life-threatening disease characterized by airflow limitation that is associated with sporadic episodes of symptomatic decompensation. Airflow limitation typically results from exposure to noxious particles or gases, leading to a chronic inflammatory response in predisposed hosts. The most common source of inflammation is smoking, but other etiologies include environmental or occupational lung exposure. Some people who develop COPD have never smoked and not all people who smoke will develop COPD; this suggests that both host factors and genetics play a role in its development. A small but important number of individuals develop COPD secondary to a genetic deficiency in alpha-1 antitrypsin (AAT). Genetic factors contribute to COPD’s development, and among those, AATD is of interest as it is both rare and under-recognized. Approximately 2% to 3% of patients diagnosed with COPD have AATD, and severe AATD has been reported in 1% to 2% of patients in the U.S.©12

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is led by an international group of scientists who collaborate with health care professionals and public health officials to raise awareness of COPD and improve prevention rates and treatment options.1 Periodically, the group publishes guidelines on diagnostic and treatment strategies based on the best available clinical evidence. As well as providing recommendations for pharmacologic treatment modalities, GOLD provides comprehensive non-pharmacologic prevention and treatment recommendations, such as testing for genetic risk factors for developing COPD, specifically AAT deficiency (AATD).

Prevalence

Chronic obstructive pulmonary disease is recognized as a major cause of morbidity and mortality. Estimates suggest it causes more than three million deaths each year—accounting for 5% of all deaths globally3—more than 90% of which occur in low- and middle-income countries. The prevalence of the disease largely depends on the population being studied; most information is based on data from developed countries.3 Worldwide, the incidence of COPD stages 2–4 is believed to be 10% to 12%, rising to 15% among regular smokers and up to 47% in smokers with a ≥ 15 pack-year history when spirometric screening criteria are used to diagnose the disease.©7

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Societal Cost of COPD

The greatest determinants of COPD’s cost to society are the severity of illness, presence and frequency of disease exacerbations, and presence and number of comorbid medical conditions.1 In addition, an under-recognized fourth determinant is the high prevalence of undiagnosed disease.5 According to GOLD, direct costs exceed $32 billion per year in the U.S. alone; indirect costs are linked to another $20.4 billion per year.1 A number of studies have evaluated the human and economic costs of this disease.13 Patients with substantial airflow limitation and moderate-to-severe symptoms experience significant impairments in quality-of-life scores and have excessive rates of disability. The correlation between the severity of the disease and the decrease in quality of health and daily activities appears in many regions throughout the world.13

The economic costs of COPD vary widely depending on geographic location.14 This most likely arises from variations in the true cost of the disease, differences in calculation methods, and differences regarding access to routine preventative and urgent medical-care services. The largest number of published economic studies on COPD have been conducted in industrialized countries. A more appropriate assessment would be studies based on an examination of those components that contribute to the overall cost of the disease.

The severity of COPD, the increasing prevalence of comorbid conditions, and patient susceptibility to disease exacerbations are associated with a greater economic burden,14,15 including greater expenditures for direct and indirect medical costs (loss of productivity, home-based care, etc.). In patients with milder forms of COPD, clinic visits and medications comprised the largest component of medical costs, and in patients with severe or very severe COPD, hospitalization costs were the largest component. Patients with more frequent hospitalizations are typically older and have a greater number of comorbid conditions, such as cardiovascular disease, congestive heart failure, diabetes, and depression. These patients also appear to be more susceptible to exacerbations representing a distinct phenotype that is recognized in the new GOLD guidelines.3

An important component of COPD’s societal cost is the large number of undiagnosed individuals: worldwide, approximately 70% of people with the disease remain undiagnosed.5 The reasons for under-diagnosis vary, and involve patient and social factors. Individuals may under-report symptoms, making it unlikely that they will seek diagnosis or treatment.

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Further, they may have no access to health care (particularly in underserved populations) or lack the means to undergo formal testing and evaluation. Studies on the medical costs incurred by patients before receiving a formal COPD diagnosis have found that they exceed those incurred by patients in control groups.\textsuperscript{15} The frequency of clinic visits and hospitalizations was 50% greater among patients with a delayed COPD diagnosis. Earlier diagnosis and treatment could slow disease progression and reduce complication rates.\textsuperscript{15}

A delayed diagnosis may be especially consequential for patients with AATD because new therapies can reduce the risk of irreversible lung damage.\textsuperscript{8,11} Patients with AATD are under-diagnosed for a number of reasons, but they can be more readily identified when an index of suspicion is present among physicians. Patients with AATD have different patterns of presentation compared to typical patients with COPD. In most cases, they are less likely to have a history of exposure to the usual COPD risk factors (e.g., smoking, biomass-fuel exposure, or chronic exposure to air pollution) and an onset of symptoms occurring at an earlier age. A substantial number of physicians are unaware of the guidelines concerning patient screening for AATD or believe there is no treatment available for this form of COPD, which reduces any perceived urgency of making a diagnosis.\textsuperscript{2} Patients with severe AATD are typically evaluated by at least three physicians and experience an average delay of seven years between symptom onset and definitive diagnosis.\textsuperscript{2}

The lack of familiarity with guidelines and the subtle differences in presentation mean that among the estimated 100,000 cases of AATD in the U.S., approximately 15,000 individuals have been diagnosed.\textsuperscript{2} Local, regional, and national education campaigns are critical for expanding awareness and improving identification of this unique patient population.

**ALPHA-1 ANTITRYPSIN DEFICIENCY**

Alpha-1 antitrypsin deficiency is a genetic disorder characterized by inappropriately low levels of AAT, which inhibits neutrophil elastase—a protease with elastolytic properties that can attack lung elastin and other structural components of the alveolar wall, leading to lung injury and parenchyma destruction.\textsuperscript{10-12} The disorder can affect multiple organ systems, but primarily affects the lungs and liver. Liver disease in patients with AATD is caused by an alternative mechanism, and is not related to active destruction as in lung disease. Rather, disease is caused by an over-accumulation of abnormal AAT protein in the liver, where it is synthesized. A lack of breakdown of this protein can lead to liver damage, but the process is not universal to all patients with AATD and it can vary greatly.\textsuperscript{19}

There are multiple genetic variants of AAT. A normal phenotype is a variant of the “M” phenotype, which is present in 99% of the world’s population; deficient phenotypes typically contain the “S” and “Z” variants. These mutant phenotypes result in deficient AAT levels and can cause disease. The null phenotype occurs in patients whose plasma is devoid of AAT. There is also a dysfunctional phenotype in which the plasma carries normal amounts of AAT but the enzyme does not function appropriately.\textsuperscript{16} More than 90% of patients with AATD have the deficient Pi“ZZ” genotype, making it the most common mutation of the disorder.\textsuperscript{8,17} Patients with AATD are typically homozygous for the autosomal recessive trait.\textsuperscript{18} Genotyping and phenotyping of AAT are usually examined simultaneously; genotype evaluation can easily be performed in office with a finger stick or buccal swab, and sent to specialized laboratories for analysis.\textsuperscript{10} Results are then submitted to the health care provider and used in further decisions regarding care.

Patients with AATD can present in several ways, with dyspnea being the most common manifestation. Other frequent complaints are similar to the classic presentation of COPD: phlegm production, wheezing, cough, and recurrent upper respiratory tract infections. With AATD, the typical age of presentation is one aspect that differs from the typical presentation age with COPD or emphysema: most people with AATD present with symptoms between the ages of 20 and 40, as opposed to people with “traditional” COPD, who tend to present before age 40.\textsuperscript{16} Also, people with AATD commonly have a characteristic panacinar emphysema pattern with bullous changes that are more evident at the lung bases than at the apices.\textsuperscript{16} Patients with classic COPD emphysema, on the other hand, usually present with more centrilobular disease, often located in the lung’s apical region.

Once a patient has been diagnosed with COPD, testing for AATD should be included.\textsuperscript{10} Certain characteristics of individuals who are diagnosed with emphysema should raise
suspensions of AATD: < 45 years old; nonsmoker or minimal smoker; chest radiograph with prominent basilar pattern; familial history of AATD—which is important; and adult-onset asthma.16 In families with multiple members who have obstructive disease but lack the typical risk factors, AATD should also be investigated. Laboratory diagnosis is confirmed with a serum AAT-level test.20

There is significant under-recognition of AATD as a cause of COPD.10,20 Many clinicians are not intimately familiar with AATD, having little knowledge of the testing and available treatments.17 Potential nonspecific respiratory symptoms of AATD can be misdiagnosed as classic COPD or asthma.17 Because patients with AATD show the same clinical features of untreated COPD, the World Health Organization recommends testing all patients who have COPD or adult-onset asthma for AAT.21,22 Diagnostic AAT testing (grade A recommendation) is recommended for symptomatic adults with emphysema, COPD, or asthma with airflow obstruction that is not completely reversible after aggressive treatment with bronchodilators.8

The Alpha-1 Foundation and the European Respiratory Society (ERS) have formulated guidelines for AATD testing.11,23 By themselves, AAT levels are insufficient for identifying patients with or at risk for the disease: the levels can change with inflammation and with pregnancy. As such, confirmatory testing is strongly recommended via AAT genotyping to identify normal, deficient, or non-functioning alleles. Further, genotyping can enable the identification of more rare AAT alleles, which otherwise would go unrecognized.23 Both Alpha-1 and ERS recommend an initial baseline lung-function evaluation that includes measurement of diffusing capacity when a diagnosis of AATD is made.11,23 Clinicians can then follow lung function over time to help them decide when or whether to initiate treatment.

The pharmacotherapy of patients with COPD as a result of AATD is the same as that of similar patients with COPD: evidence-based use of a bronchodilator, inhaled steroids, supplemental oxygen, vaccinations, smoking cessation, and pulmonary rehabilitation.2 Standard COPD treatments may not be as effective for individuals with AATD, and certain patients will require specific treatment with weekly infusions of augmentation therapy.2,24

**Alpha-1 Antitrypsin Replacement**

Recommendations for initiating AAT replacement therapy vary to some degree by professional society. Replacement therapy in AATD is typically recommended for patients with moderate airflow obstruction (forced expiratory volume in the first second [FEV1], 35–60% of predicted) and AAT levels < 11 µM.10 Treatment for individuals outside these criteria can be individualized after the patient and care team have discussed the risks and benefits. Alpha-1 antitrypsin therapy, which is derived from human donor plasma, has been available commercially since 1987. Vials of lyophilized alpha-1 proteinase inhibitor and diluent are stored at room temperature before reconstitution; the specific diluents vary with available products.25–28 These products, one of which can be self-administered by the patient/caregiver at home after proper training,26 are administered by intravenous (IV) infusion only. Although the products are generally well tolerated, vital signs and infusion-related reactions should be monitored continuously during administration, as there is a risk of viral transmission. Alpha-1 proteinase inhibitor levels can be followed with chronic treatment.

The cost of augmentation therapy can be as much as $150,000 annually, depending on such variables as patient weight, frequency of dosing, specific product pricing, line access, and cost of nursing care.17,29,30 The most common dose is 60 mg/kg/week, although it may be given biweekly or monthly. Candidates for replacement therapy who do not smoke, are adherent to therapy, and have mild to moderate COPD are more likely to have therapy initiated at established treatment centers.29 Augmentation therapy is not recommended for patients with the MZ genotype, patients who continue to smoke, or patients with emphysema who do not have airflow obstruction.22

**CASE REPORT**

A 70-year-old man who is an avid cyclist presented to the pulmonary clinic with complaints of dyspnea and wheezing while cycling on a recent trip to Europe. He had been followed and treated by primary care providers for years. He has a 1-pack-year history of cigarette smoking but quit 40 years ago. Pulmonary function testing was performed and was notable for mild obstructive lung disease. He was started on an inhaled long-acting muscarinic antagonist, and a computerized tomography (CT) scan of his chest was performed, which revealed emphysematous changes. At follow-up six months later, the patient continued to have intermittent symptoms but was doing well overall. Approximately one year after his initial presentation to the lung specialist, an alpha-1 level was drawn and found to be deficient, at 21 mg/dL. After testing, the genotype was determined to be ZZ. Interestingly, the patient had a gradual decline in his pulmonary-function testing over the year of evaluation and, given his continued decline, the decision was made to initiate augmentation therapy. His lung function has since stabilized but he has developed exercise-induced hypoxia; therefore, he maintains his active lifestyle with supplemental oxygen, and rides his bicycle upward of 15 miles daily.

**CONCLUSION**

Chronic obstructive pulmonary disease is a preventable, heterogeneous disease that can be attributed to multiple risk factors, including genetic conditions and predispositions. Alpha-1 antitrypsin deficiency is a significant, under-recognized risk factor for the development and progression of the disease. Aggressive guideline-based AAT screening for all patients with COPD or adult-onset asthma is encouraged. Identifying patients with deficient, null, or dysfunctional phenotypes of AATD will enable clinicians to initiate individualized treatments to prevent further lung-function decline. Although AATD infusion-replacement therapy may be beneficial, it must be administered in conjunction with other important guideline-based approaches and treatments, such as smoking cessation.

The data supporting AATD replacement therapy were generated by multiple small studies. Recruiting large AATD populations is challenging because of the limited number of patients who have been identified with the disease. Replacement therapy raises plasma AAT levels, but the clinical impact of enzyme replacement remains difficult to quantify. Small studies have
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shown a reduction in the rate of lung-function decline, with a corresponding decrease in mortality. Continuing research is needed into additional or new modalities for quantifying disease progression or regression in patients with AATD and COPD. One such modality is more specialized imaging via CT scans, which could improve our understanding of the impact of replacement therapy among patients with AATD.

REFERENCES


