

Alpha-1 Antitrypsin Deficiency: An Under-Recognized But Important Issue for Respiratory Therapists

In this issue the Journal is reprinting the Executive Summary of the new evidence-based standards regarding the management of individuals with alpha-1 antitrypsin (AAT) deficiency.^{1,2} Upon reading the summary, respiratory therapists (RTs), like all clinicians, will ask themselves several important questions about AAT deficiency, namely:

1. How well do I understand AAT deficiency?
2. What is the relevance of AAT deficiency to my respiratory care practice now?
3. What implications do the new findings and recommendations regarding AAT deficiency in the standards document have for my future practice?

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Indeed, the standards document is a definitive text in which an international group of experts collaboratively sponsored by the American Thoracic Society, the European Respiratory Society, the Alpha-1 Foundation, the American College of Chest Physicians, and, importantly, by the American Association for Respiratory Care, have used an evidence-based medicine approach to develop current recommendations for managing individuals with AAT deficiency.² Notwithstanding that the recommendations in this encyclopedic document will need to be re-examined over time as new evidence becomes available in this fast-moving field, this document helps to define current optimal care for individuals with AAT deficiency.

Keeping the important questions posed above in mind, my goal in this editorial is to offer responses and, in so doing, to demonstrate that AAT deficiency is important to RTs, for 4 compelling reasons:

1. AAT deficiency is a common but under-recognized condition, in which RTs can play a vital diagnostic role.³
2. Establishing the diagnosis of AAT deficiency is important for the affected individual, especially because specific, effective therapy is available⁴⁻⁷ and also because establishing the diagnosis may have important consequences for family members.
3. In the era of so-called “augmentation therapy” for AAT deficiency (which involves the intravenous infusion of purified human AAT into individuals who lack this important lung-protective protein,⁸) RTs may participate directly in these patients’ care, either by administering

traditional respiratory care treatments (eg, nebulized bronchodilators, supplemental oxygen) or by administering the augmentation therapy.

4. As new treatments for severe AAT deficiency emerge that involve the inhalation of purified AAT (either derived from human plasma or made by recombinant protein techniques with yeast or sheep milk), RTs will assume even greater involvement in administering AAT therapy.

What then is AAT deficiency, and what is the evidence that supports these statements?

AAT deficiency is a genetic disorder characterized by abnormal accumulation of AAT in the liver. The accumulation within the liver cells occurs because of a structural abnormality of the AAT protein that prevents normal secretion from the hepatocyte, with resultant deficiency of AAT in the blood.⁹ Because the role of AAT is to defend the lung against breakdown by a degradative enzyme called neutrophil elastase, deficiency of blood levels below a so-called “protective threshold” value (of 11 micromolar) predisposes the affected individual to emphysema, which may occur unusually early in life (eg, by age 40) and in the absence of traditional risk factors such as cigarette smoking.¹⁰

To help respiratory clinicians explain to patients the pathogenesis of emphysema due to AAT deficiency, and to help patients understand, I offer the following metaphor.¹¹ Imagine the lung as a jungle gym—the playground structure upon and through which children climb (Fig. 1). The jungle gym in this metaphor is made of iron bars, which represent the support structure of the lung—the interstitium. The air spaces between the bars, into which children climb, represent the alveoli. Now imagine that the jungle gym is exposed to rain, which is neutrophil elastase in this metaphor. Neutrophil elastase is the degradative enzyme that lives within our neutrophils and is released to combat bacteria and in response to other inflammatory insults. Imagine too that AAT is the paint that is used to coat the bars of the jungle gym and to protect it from the rain and from becoming rusted and ultimately degraded if left unprotected. Emphysema, then, is the condition in which the bars become rusted to the point that they crumble, thereby threatening the structural integrity of the jungle gym and allowing the air spaces between the bars to



Fig. 1. The jungle gym playground structure represents the lung in a metaphor useful for explaining to patients the emphysema caused by alpha-1 antitrypsin (AAT) deficiency. The iron bars represent the interstitium, which supports the lung, and the open spaces represent the alveoli. The iron bars are protected by "paint" (AAT), and if there is not enough "paint" (AAT deficiency), then "rain" (neutrophil elastase) will rust and break down the bars.

enlarge irreparably. This irreparable enlargement represents the development of bullae that typify emphysema.

With these elements of the metaphor in place, we can now explain to our patients how severe AAT deficiency predisposes to emphysema. If we lack paint to protect the bars of the jungle gym (ie, AAT deficiency), and if it rains a lot (ie, the neutrophil burden in the lung is increased, as it is in smokers and in those exposed to other lung inflammatory conditions such as infections, occupational and environmental dusts, or fumes), then rust (emphysema) can develop more quickly and more extensively. In other words, emphysema could develop at an unusually early age (eg, perhaps at age 40) and could progress at an unusually rapid rate. Indeed, these features—early onset of emphysema, rapid progression, and occurrence even without cigarette smoking (ie, with only a normal amount of "rain")—may characterize individuals with AAT deficiency and, if present, should lead the astute clinician to consider the diagnosis.

In the context of this understanding of AAT deficiency and how to describe it to our patients, the standards document provides an opportunity to discuss this important

but under-recognized clinical entity and to debunk some of the commonly held myths about AAT deficiency. What are these myths and what is the truth?

First, in contrast to the perception that AAT deficiency is rare, it is actually a relatively common clinical problem.^{3,12,13} As pointed out in the standards document and in earlier studies,^{12,13} population-based screening studies in Sweden and Oregon suggest a prevalence of severe AAT deficiency (the so-called PI*ZZ type [PI phenotype ZZ]) of approximately 1/2,800 to 1/5,000 individuals. Consecutive testing of individuals with established chronic obstructive pulmonary disease suggests that severe AAT deficiency (ie, the blood level of AAT falls below the minimum value of 11 micromolar believed necessary to protect the lung against breakdown by neutrophil elastase) accounts for approximately 3% of all such individuals.¹⁴ Given that recent prevalence estimates suggest that approximately 2.1 million of the 16 million Americans with chronic obstructive pulmonary disease have emphysema,¹⁵ these 2 observations agree in indicating that approximately 100,000 Americans have severe AAT deficiency.¹⁰ This likens the frequency of AAT deficiency to that of cystic fibrosis, a condition that is far better recognized, despite its similar frequency.

Despite its prevalence, AAT deficiency is under-recognized by health care providers.³ For example, results of a survey administered to individuals with PI*ZZ AAT deficiency suggest that the mean time interval between their first symptom (dyspnea) and the first diagnosis of AAT deficiency was 7.2 years.³ This delay occurred in the context that the mean age of the respondents in this study was 48 years, clearly very young to be affected by fixed air flow obstruction likely to cause dyspnea. Furthermore, although 25% of respondents reported having the diagnosis of AAT deficiency made by the first doctor they consulted, 44% reported seeing at least 3 physicians before the first diagnosis was made and 13% reported seeing at least 6 physicians before the initial diagnosis.

Here then lies one very important reason that RTs must know about AAT deficiency. Specifically, because AAT deficiency is common and under-recognized and because RTs frequently care for individuals with fixed air flow obstruction, the astute RT is frequently in a situation to prompt suspicion of AAT deficiency and to facilitate the diagnosis in an affected individual.

The sharp clinician will, of course, ask why it is important to make the diagnosis, especially when doing so might create concern that the patient and possibly other family members could have a genetic condition. This is especially pertinent in the era of risk regarding genetic discrimination in the workplace and insurance discrimination?² Though the question is apt, the standards document concludes that there are effective interventions for AAT deficiency, including counseling for the individual and other family mem-

bers at risk: to avoid or discontinue cigarette smoking, to exercise choices regarding environmental exposures, and to consider intravenous augmentation therapy.^{2,4-7} Indeed, as amply discussed in the standards document, the weight of available evidence suggests that augmentation therapy has clinical efficacy to slow the rate of lung function decline, at least in individuals with air flow obstruction of moderate degree.^{2,4-7} The availability of effective therapies and the possibility that detection will permit healthful interventions for family members recommend enhanced awareness and diagnostic efforts by all health care providers, and perhaps especially by RTs.

Beyond the availability of current roles in diagnosis and management that RTs may play, promising new developments in treating AAT deficiency are likely to expand RTs' role in managing AAT-deficient individuals and to require an even greater degree of RT expertise. Indeed, promising treatments currently being evaluated include inhaled purified AAT protein, derived from a variety of sources,⁸ including pooled human plasma and recombinantly-produced AAT made in yeast and in the milk of sheep into which the human AAT gene has been introduced.¹⁶

Overall, the publication of the new standards document regarding management of individuals with AAT deficiency has important consequences for respiratory therapy. Along with this detailed, careful synthesis of existing knowledge and comprehensive examination of emerging trends in AAT deficiency come new opportunities for RTs to enhance the care we provide to patients and their families. In helping to sponsor this important scholarly activity, the American Association for Respiratory Care and the American Respiratory Care Foundation have admirably exercised their leadership position and have further empowered RTs as unique and indispensable contributors to health care.

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