

# Key Current Clinical Issues in Alpha-1 Antitrypsin Deficiency

James K Stoller MD MSc FAARC

## Introduction

### An Overview of the Standards Document

### Who Should Be Tested for AAT Deficiency?

### Who Should Be Treated With Intravenous Augmentation Therapy?

### Summary

**Alpha-1 antitrypsin deficiency is a common but under-recognized condition on which respiratory therapists can have a large impact. A key recent development is the issuance of an international evidence-based standards document regarding diagnosis and management of individuals with alpha-1 antitrypsin deficiency. This report summarizes that standards document, which recommends more widespread testing for alpha-1 antitrypsin deficiency, in order to extend the benefits of diagnosis to individuals found to have alpha-1 antitrypsin deficiency. An important aspect of the standards document is that evidence regarding the clinical efficacy of intravenous alpha-1 antitrypsin augmentation therapy is reviewed. Though no definitive support from a randomized clinical trial is available, the weight of evidence favors the clinical efficacy of alpha-1 antitrypsin augmentation therapy, at least in individuals with moderate degrees of established airflow obstruction. On that basis the standards document recommends intravenous augmentation therapy in specified clinical circumstances. Key words: alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease, COPD. [Respir Care 2003;48(12):1216–1221. © 2003 Daedalus Enterprises]**

## Introduction

Alpha-1 antitrypsin (AAT) deficiency is an autosomal codominant genetic condition that may predispose to chronic obstructive pulmonary disease. AAT deficiency is characterized by decreased blood levels of the protease inhibitor protein AAT.<sup>1</sup> Because AAT is the major inter-

stitial source of the lung's ability to inactivate neutrophil elastase (which may be released from polymorphonuclear neutrophils recruited to the lung by infectious or inflammatory insults), deficiency of AAT predisposes affected individuals to early-onset emphysema. Also, because a structural abnormality of the AAT protein causes abnormal folding of the protein as it is synthesized and secreted from the hepatocyte in individuals with the commonest severely AAT-deficient phenotype (ie, PI phenotype ZZ [PI\*ZZ] AAT deficiency), such PI\*ZZ individuals are also at risk for liver disease, manifesting as either neonatal hepatitis or cirrhosis or as adult-onset cirrhosis, sometimes complicated by hepatoma.<sup>1</sup>

Several recent reviews of AAT deficiency have addressed clinical aspects of diagnosis and management.<sup>2–4</sup> An important recent development is the publication of an evidence-based standards document, assembled by an international committee of experts, regarding the diagnosis and management of individuals with AAT deficiency.<sup>5</sup> In the context of this recent document, the present report ad-

---

James K Stoller MD MSc FAARC is affiliated with the Department of Pulmonary and Critical Care Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

James K Stoller MD MSc FAARC presented a version of this report at the 32nd RESPIRATORY CARE Journal Conference, Chronic Obstructive Pulmonary Disease: Translating New Understanding Into Improved Patient Care, held July 11–13, 2003, in Los Cabos, Mexico.

Correspondence: James K Stoller MD MSc FAARC, Department of Pulmonary and Critical Care Medicine, A90, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland OH 44195. E-mail: stollej@ccf.org.

dresses 2 key clinical questions that confront respiratory clinicians regarding the diagnosis and management of AAT-deficient individuals:

1. Who should be tested for AAT deficiency?
2. What is the role of intravenous augmentation therapy (ie, the regular infusion of purified AAT to augment deficient serum levels)?

In addressing these questions, I first present an overview of how the standards document was prepared and then address both of the questions, citing recommendations from the standards document and the results of key supportive studies.

### An Overview of the Standards Document

Recent developments regarding AAT deficiency caused members of an international Task Force to undertake a systematic review of the literature and to assemble a series of graded recommendations regarding diagnosis and management that would be helpful to clinicians. Indeed, when the Task Force first undertook the project in 1997, the most recently available guidelines were those of the American Thoracic Society,<sup>6</sup> published in 1989, and the Canadian Thoracic Society,<sup>7</sup> first published in 1992, with subsequent publication of updated Canadian Thoracic Society guidelines in 2001.<sup>8</sup> The Task Force was composed of 27 individuals from 7 countries (England, Sweden, Holland, Italy, Austria, Germany, and the United States) with expertise in pulmonary/critical care, gastroenterology, bioethics, pharmacoeconomics, and patient advocacy. Official sponsors of the document included the American Thoracic Society, the European Respiratory Society, the American College of Chest Physicians, the American Association for Respiratory Care, and the Alpha-1 Foundation.

Figure 1 shows the structure of the Task Force.<sup>5</sup> Three individual documents regarding (1) the lung aspects, (2) the liver and other disease aspects, and (3) the genetics, psychosocial, and ethical aspects were prepared by 3 writing groups, with oversight and synthesis by a Steering Committee. Where possible, based on available information, the document employed an evidence-based approach to systematically review and grade the available literature and to offer resultant recommendations reflecting the level of support deemed warranted by available data. More specifically, available studies were graded according to a scheme adapted from the United States Preventive Services Task Force (Table 1), in which the literature was rated from level I (evidence obtained from at least one properly designed randomized, controlled trial) to level III (opinions of respected authorities based on clinical experience, descriptive studies, and case reports).<sup>10</sup> Furthermore, the Task Force's testing recommendations were rated

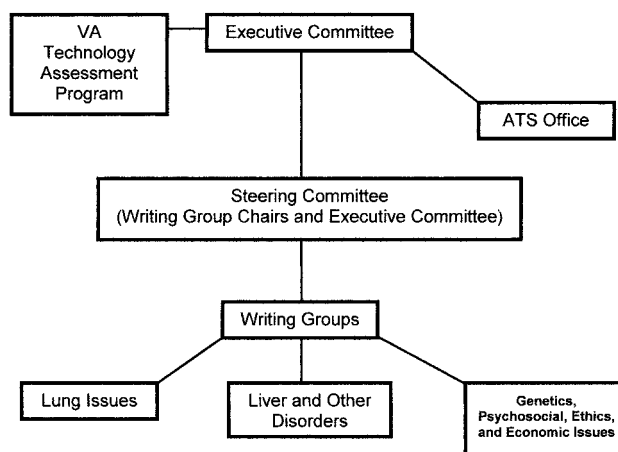


Fig. 1. Structure of the Alpha-1 Antitrypsin Deficiency Task Force. VA = Department of Veterans Affairs. ATS = American Thoracic Society.

Table 1. Grades of Evidence Used in the Standards Document Regarding Diagnosis and Management of Alpha-1 Antitrypsin Deficiency

I	Evidence obtained from at least 1 properly designed randomized controlled trial
II-1	Evidence obtained from well designed controlled trials without randomization
II-2	Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than 1 center or research group
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities based on clinical experience, descriptive studies, and case reports

There are other rating schemes for grading levels of evidence, such as that used in the Global Initiative for Chronic Obstructive Lung Disease report.<sup>9</sup> (Adapted from Reference 10.)

using a letter scheme (Table 2) from A (testing is recommended) to D (recommend that testing not be done).

In the context of this background regarding the genesis of the standards document, the 2 clinical questions that are addressed by the document can be discussed.

### Who Should Be Tested for AAT Deficiency?

In rating recommendations regarding testing for AAT deficiency the Task Force recognized 4 different types of genetic testing:<sup>5</sup>

1. Diagnostic testing, to identify symptomatic or otherwise affected individuals

Table 2. Classification of Recommendations for Genetic Testing\*†

- 
- 
- A. Genetic testing is recommended
  - B. Genetic testing should be discussed and could reasonably be accepted or declined
  - C. Genetic testing is not recommended (ie, testing should not be encouraged)
  - D. It is recommended that genetic testing not be performed (ie, testing should be discouraged)
- 

\*The recommendation type was determined by the Task Force's subjective weighing of all the issues that either supported or opposed genetic testing. The weight attributed to each issue depends on the level of the evidence supporting each issue. Accordingly, the recommendations for genetic testing are informed by both the evidence of each issue and consensus of the experts on how strongly each issue supports or opposes testing.

†This system for classification of recommendations should not be confused with the letter-designation schemes that are used for grading the quality of evidence in some other reports.

---

- 2. Pre-dispositional testing, to identify asymptomatic individuals who may be at high risk of having AAT deficiency
- 3. Carrier testing, to test prospective parents regarding possible inheritance of AAT deficiency
- 4. Screening: testing in the absence of heightened suspicion, such as with asymptomatic individuals who have no known higher risk

The level A recommendation (ie, testing is recommended) is offered in the following settings:

- Adults with symptomatic emphysema or chronic obstructive pulmonary disease (COPD)
- Symptomatic adults with asthma that is incompletely reversible despite aggressive bronchodilator therapy
- Asymptomatic adults with persistent airflow obstruction and smoking or occupational exposure
- Adults with necrotizing panniculitis
- Siblings of an individual who is a PI\*ZZ homozygote

In contrast, the level D recommendation (ie, testing should not be performed) is offered for:

- Fetal testing
- Population screening for newborns and adolescents, and for adults (unless the prevalence of severe AAT deficiency exceeds 1/1,500, in which case a level B recommendation (testing should be discussed) is offered

The level B and C recommendations are offered in a variety of other settings.

Though full discussion of the principles and the data underlying these recommendations should prompt review of the full standards document,<sup>5</sup> 2 specific underlying observations and principles warrant discussion. First, the rationale for heightened diagnostic suspicion and enhanced detection by clinicians is that detection can allow effective interventions to be offered to the affected individual and (because AAT deficiency is a genetic condition) to family members. Second, AAT deficiency is under-recognized by clinicians, and under-diagnosis can be associated with both psychosocial and clinical adverse effects.<sup>11</sup>

Because the detection of a genetic disorder can have adverse effects, including psychological trauma from learning of an inherited condition (including the possibility of transmitting it to progeny) and the possibility of insurance or employment discrimination that may follow detection, recommendations for enhanced detection must be buttressed by benefits of detection that outweigh the risks.<sup>5</sup> In the case of AAT deficiency, 3 potential benefits of detection provide this rationale:

1. Enhanced smoking cessation among those identified by population screening<sup>12,13</sup>
2. The opportunity to make (or change) job settings that minimize occupational hazards<sup>14,15</sup>
3. The opportunity to receive augmentation therapy<sup>16,17</sup>

First, regarding the impact of population screening, 2 population-based screening studies have examined the impact of being detected as having PI\*ZZ AAT deficiency on smoking behavior, compared to age-matched peers.<sup>12,13</sup> In the largest available screening study, Sveger et al<sup>12</sup> performed follow-up testing on 50 of 120 PI\*ZZ screenees at age 18. Compared with an age- and gender-matched group of teenagers, fewer of the screened PI\*ZZ individuals were current smokers (6% vs 17%) or had previously smoked (6% vs 19%,  $p < 0.05$ ).

In the next largest population screening study, in which 107,033 newborns in Oregon were tested, Wall et al performed follow-up testing on 22 screened individuals with severe AAT deficiency (mean age 15.1 years).<sup>13</sup> Compared with age-matched teenagers, fewer of the AAT-deficient screenees had ever tried smoking (27% vs 57%) and fewer were current smokers (4% vs 21%). Taken together, these follow-up studies of screened individuals suggest that detection by screening can confer benefits of parental counseling and supervision that presumably account for the lower smoking rates.

A second benefit that supports enhanced detection is that knowledge of having PI\*ZZ AAT deficiency can permit occupational choices to lessen the risk of developing COPD. For example, Mayer et al<sup>14</sup> showed that inhalation of mineral dust was associated with an increased risk of cough (odds ratio 2.95) and a significantly lower ratio of

forced expiratory volume in the first second to forced vital capacity (FEV<sub>1</sub>/FVC) than nonexposed individuals. Similarly, Piitulainen et al<sup>15</sup> observed a significant relationship between impaired lung function and occupational exposure to gas, fumes, or dust for > 3 months in a group of 225 PI\*ZZ never-smokers.

Finally, a third benefit supporting detection is that effective therapy for AAT deficiency is available.<sup>3,16,17</sup> As reviewed in the standards document and elsewhere,<sup>16</sup> the current specific therapy for AAT deficiency is intravenous augmentation therapy, which involves regular infusion of pooled human-plasma AAT. Though no definitive randomized, controlled trial has established the efficacy of intravenous augmentation therapy, available observational studies demonstrate biochemical efficacy and strongly suggest clinical efficacy.

In considering efficacy criteria, those for biochemical efficacy include:<sup>17,18</sup>

1. Evidence that augmentation therapy raises serum AAT above the protective threshold (ie, the level above which the risk of emphysema is deemed minimal)
2. Evidence that intravenous infusion preserves functional antiprotease activity, both in the lung and ideally in the interstitium (where AAT exerts its protective effect to interdict elastin breakdown)

Available studies demonstrate that intravenous augmentation therapy has biochemical efficacy.<sup>3,16,17</sup> In one of the earliest available studies, Wewers et al<sup>17</sup> showed that administration of purified pooled human plasma antiprotease, at 60 mg/kg once weekly, to 21 PI\*ZZ AAT-deficient subjects over 6 months elevated serum AAT levels acutely (to > 300 mg/dL) and generally maintained nadir serum levels above the protective threshold value of 11 micromolar. Furthermore, infused AAT maintained its functional activity to inactivate neutrophil elastase, both in the serum and in the epithelial lining fluid.

Criteria that augmentation therapy has clinical efficacy include:<sup>16,18</sup>

1. Evidence that augmentation therapy prevents or slows the rate of lung destruction
2. Evidence that augmentation therapy is safe and well tolerated

That augmentation therapy interdicts lung destruction has been suggested by 2 large observational studies in which the rate of FEV<sub>1</sub> decline was slower in augmentation therapy recipients than in nonrecipients (Table 3).<sup>19,20</sup> In the first of these studies, Seersholm et al<sup>19</sup> compared the rate of FEV<sub>1</sub> decline in 198 German PI\*ZZ recipients of augmentation therapy with that in 97 Danish PI\*ZZ nonrecipients. Overall, augmentation therapy recipients expe-

rienced a slower rate of FEV<sub>1</sub> decline (mean  $\pm$  SD  $-53 \pm 38$  mL/yr vs  $-75 \pm 60$  mL/yr,  $p = 0.02$ ); subset analyses suggested that this difference in FEV<sub>1</sub> decline rate was most pronounced in individuals with moderate degrees of airflow obstruction (FEV<sub>1</sub> 31–65% of predicted; see Table 3).

Table 3 also shows the results from the larger National Heart, Lung, and Blood Institute (NHLBI) Registry for Individuals with Severe AAT Deficiency ( $n = 1,129$  participants),<sup>20</sup> which also found that the FEV<sub>1</sub> decline rate was slower among augmentation therapy recipients than among nonrecipients. Specifically, the 747 individuals ever receiving augmentation therapy showed a mean FEV<sub>1</sub> decline rate of  $-51.8$  mL/y versus  $-56.0$  mL/y among nonrecipients. Though that difference in FEV<sub>1</sub> decline rate for the overall group failed to achieve statistical significance ( $p = 0.40$ ), subset analysis showed a significantly slower FEV<sub>1</sub> decline rate among individuals with moderate (American Thoracic Society stage II, FEV<sub>1</sub> 35–49% of predicted)<sup>21</sup> airflow obstruction ( $-66.4$  vs  $-93.2$  mL/y,  $p = 0.03$ ).

Notwithstanding potential biases inherent in an observational study in which the augmentation therapy was administered at managing physicians' discretion rather than by randomized allocation,<sup>20</sup> further support for the clinical efficacy of augmentation therapy in the NHLBI Registry was the lower mortality rate among augmentation therapy recipients. Specifically, the risk ratio for death among augmentation therapy recipients was 0.64 (confidence interval 0.43–0.95,  $p = 0.02$ ), and among those with stage II COPD, the risk ratio for death among augmentation therapy recipients was 0.21 (confidence interval 0.09–0.50,  $p < 0.001$ ).

In addition to the latter studies supporting the clinical efficacy of augmentation therapy, further supportive observations include:

1. In the only available randomized, controlled clinical trial of augmentation therapy,<sup>22</sup> the rate of loss of lung function, measured via computed tomography, tended to be lower among augmentation therapy recipients than among placebo recipients ( $p = 0.07$ ).
2. In a German series reported by Wencker et al,<sup>23</sup> the FEV<sub>1</sub> decline rate slowed after 96 severely AAT-deficient individuals began augmentation therapy (from  $-49$  mL/y to  $-34$  mL/y,  $p = 0.019$ ).
3. In a Web-based survey reported by Lieberman,<sup>24</sup> 96 self-reported PI\*ZZ individuals receiving augmentation therapy indicated a lower rate of bronchial infection than did 47 PI\*ZZ nonrecipients and a lower rate after initiating augmentation therapy than their prior baseline rate.

Table 3. FEV<sub>1</sub> Decline in AAT-Deficient Patients Receiving and Not Receiving AAT Augmentation Therapy in 2 Large Observational Studies

AAT Deficiency Registry Study Group (1998)			Seersholm et al (1997)		
FEV <sub>1</sub> Percent of Predicted Category (%)	Change in FEV <sub>1</sub> (mL/y): Treated vs Untreated*	P	FEV <sub>1</sub> Percent of Predicted Category (%)	Change in FEV <sub>1</sub> (mL/y): Treated vs Untreated	P
< 35	-44 vs -46	0.7	≤ 30	-24 ± 24 vs -31 ± 36	0.6
35-49	-66 vs -93	0.03	31-65	-62 ± 25 vs -83 ± 49	0.04
50-79	-74 vs -81	0.5	> 65	-162 ± 29 vs -140 ± 83	0.7
Overall Change in FEV <sub>1</sub> : Treated vs Untreated	-52 vs -56	0.4	Overall Change in FEV <sub>1</sub> : Treated vs Untreated	-53 ± 38 vs -75 ± 60	0.02

FEV<sub>1</sub> = forced expiratory volume in the first second AAT = alpha-1 antitrypsin

\*The untreated groups never received AAT. The treated group received AAT augmentation therapy continuously beginning within 3 months of Registry enrollment. (Adapted from References 19 and 20).

Taken together, the available evidence suggests that intravenous augmentation therapy satisfies biochemical efficacy criteria and has clinical efficacy to slow the rate of lung destruction.

That augmentation therapy is also safe and well-tolerated has been shown by 2 large observational studies in which 443 and 747 subjects, respectively, received intravenous augmentation therapy.<sup>23,25</sup> In the first of these, Wencker et al<sup>23</sup> described 124 adverse events among 443 recipients of pooled human-plasma AAT. Five of these events were deemed severe, of which 4 were anaphylaxis. However, only 1% of the adverse events in the series prompted remedial action such as discontinuation of augmentation therapy, acute hospitalization, emergency room or physician visits, or prescription of a new medication to treat the adverse event.

In a second large series examining adverse events accompanying intravenous augmentation therapy, Stoller et al<sup>25</sup> reported the frequency and types of adverse experiences among 747 augmentation therapy recipients in the NHLBI Registry.<sup>26</sup> Using a system that classified adverse events according to severity, 174 subjects reported 720 adverse events, the commonest of which were dyspnea (47%) and dizziness/fainting (17%). Altogether, 8.8% of the adverse events (63/720) were deemed severe, 72.4% (521/720) were classified as moderate, and 18.9% (136/720) were deemed mild.

Using an alternate classification scheme that categorized adverse events according to the consequences, only 24% ( $n=172$ ) of the 720 adverse events elicited a consequence: hospitalization or emergency room visit 1.7% (12/720); physician visit or prescription of a new medication 21.1% (152/720); or discontinuation of augmentation therapy 1.1% (8/720). Also, in these and other studies, no instances of hepatitis, human immunodeficiency virus, or prior disease acquisition has been attributed to intravenous augmentation therapy.

Overall, available experience suggests that the rate of adverse events associated with intravenous augmentation

therapy is low and that serious adverse consequences are infrequent, thereby supporting the clinical efficacy criterion that augmentation therapy is safe and well tolerated.

With this information regarding the biochemical and clinical efficacy of augmentation therapy as a background, the second important clinical question can be addressed.

#### Who Should Be Treated With Intravenous Augmentation Therapy?

In the context of the available evidence regarding the clinical efficacy of augmentation therapy (as reviewed above), the Task Force offered the following conclusion regarding augmentation therapy:<sup>5</sup>

In the context that no randomized, controlled trial has definitively demonstrated the clinical efficacy of augmentation therapy, the weight of available studies of the clinical efficacy of AAT augmentation therapy indicates a lowered overall mortality and a slower rate of FEV<sub>1</sub> decline in augmentation therapy recipients with FEV<sub>1</sub> values of 35–65% of predicted.

Concordant with that recommendation to offer augmentation therapy to severely AAT-deficient individuals with moderate airflow obstruction is the updated recommendation from the Standards Committee of the Canadian Thoracic Society,<sup>8</sup> which suggested reserving AAT augmentation therapy for AAT-deficient patients whose FEV<sub>1</sub> is 35–50% of predicted, who have quit smoking, and who are on optimal medical therapy but continue to show rapid FEV<sub>1</sub> decline.

#### Summary

Overall, based on the weight of available evidence regarding the clinical efficacy of augmentation therapy and the positions of the international Task Force<sup>5</sup> and of the

Canadian Thoracic Society Standards Committee,<sup>8</sup> many clinicians (including the author) advocate intravenous augmentation therapy for patients with moderate fixed airflow obstruction due to severe AAT deficiency.<sup>3,16</sup>

Future therapeutic prospects include administration of AAT by inhalation; development of recombinant antiprotease preparations for augmentation therapy both by intravenous infusion and inhalation; development of synthetic, small-molecule neutrophil elastase inhibitors; and gene therapy to effect a cure.<sup>27,28</sup>

#### REFERENCES

- Carrell RW, Lomas DA. Alpha1-antitrypsin deficiency: a model for conformational diseases. *N Engl J Med* 2002;346(1):45–53.
- Stoller JK. Clinical manifestations and natural history of alpha-1-antitrypsin deficiency. *UpToDate* Volume 11.1, 2003.
- Rovner MS, Stoller JK. Treatment of alpha 1-antitrypsin deficiency. *UpToDate* Volume 11.1, 2003.
- Crystal RG. Alpha 1-antitrypsin deficiency, emphysema, and liver disease: genetic basis and strategies for therapy. *J Clin Invest* 1990; 85(5):1343–1352.
- Stoller JK, Snider GL, Brantly M, Fallat RA, Stockley R, and the Alpha-1 Antitrypsin Deficiency Task Force. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin (AAT) deficiency. *Am J Respir Crit Care Med* 2003;168(7):818–900.
- American Thoracic Society. Guidelines for the approach to the patient with severe hereditary alpha-1-antitrypsin deficiency. *Am Rev Respir Dis* 1989;140(5):1494–1497.
- Ad Hoc Committee on Alpha-1-Antitrypsin Replacement Therapy of the Standards Committee, Canadian Thoracic Society. Current status of alpha-1-antitrypsin replacement therapy: recommendations for the management of patients with severe hereditary deficiency. *CMAJ* 1992;146(6):841–844.
- Abboud RT, Ford GT, Chapman KR; Standards Committee of the Canadian Thoracic Society. Alpha<sub>1</sub>-antitrypsin deficiency: a position statement of the Canadian Thoracic Society. *Can Respir J* 2001;8(2):81–88.
- Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163(5):1256–1276.
- U. S. Preventive Services Task Force. Guide to clinical prevention services: report to the U. S. Preventive Services Task Force, 2nd ed. Baltimore: Williams & Wilkins; 1996:231–246.
- Stoller JK, Smith P, Yang P, Spray J. Physical and social impact of alpha 1-antitrypsin deficiency: results of a survey. *Cleve Clin J Med* 1994;61(6):461–467.
- Sveger T, Piitulainen E, Arborelius M Jr. Clinical features and lung function in 18-year old adolescents with alpha 1-antitrypsin deficiency. *Acta Paediatr* 1995;84(7):815–816.
- Wall M, Moe E, Eisenberg J, Powers M, Buist N, Buist AS. Long-term follow-up of a cohort of children with alpha-1-antitrypsin deficiency. *J Pediatr* 1990;116(2):248–251.
- Mayer AS, Stoller JK, Bucher Bartelson B, Ruttenber AJ, Sandhaus RA, Newman LS. Occupational exposure risks in individuals with Pi<sup>ZZ</sup> alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2000;162(2Pt1):553–558.
- Piitulainen E, Tornling G, Eriksson S. Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with alpha 1-antitrypsin deficiency (PiZZ). *Thorax* 1997; 52(3):244–248.
- Minai OA, Stoller JK. Therapy for alpha 1-antitrypsin deficiency: pharmacology and clinical recommendations. *BioDrugs* 2000;13:135–147.
- Wewers MD, Casolaro MA, Sellers SE, Swayze S, McPhaul KM, Wittes JT, Crystal RG. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. *N Engl J Med* 1987;316(17):1055–1062.
- Hubbard, RC, Crystal, RG. Alpha-1-antitrypsin augmentation therapy for alpha-1-antitrypsin deficiency. *Am J Med* 1988;84(6A):52–62.
- Seersholm N, Kok-Jensen A, Dirksen A. Decline in FEV<sub>1</sub> among patients with severe hereditary alpha 1-antitrypsin deficiency type PiZ. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):1922–1925.
- The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV<sub>1</sub> decline in individuals with severe deficiency of alpha-1-antitrypsin. *Am J Respir Crit Care Med* 1998;158(1):49–59.
- American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152(5 Pt 2):S77–S121.
- Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DCS, Ulrik CS, et al. A randomized clinical trial of alpha 1-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1468–1472.
- Wencker M, Banik N, Buhl R, Seidel R, Konietzko N. Long-term treatment of alpha1-antitrypsin deficiency-related pulmonary emphysema with human alpha1-antitrypsin. *Eur Respir J* 1998;11(2):428–433.
- Lieberman J. Augmentation therapy reduces frequency of lung infections in antitrypsin deficiency: a new hypothesis with supporting data. *Chest* 2000;118(5):1480–1485.
- Stoller JK, Fallat R, Schluchter MD, O'Brien RG, Connor JT, Gross N, et al. Augmentation therapy with alpha 1-antitrypsin: patterns of use and adverse reactions. *Chest* 2003;123(5):1425–1434.
- The Alpha 1-Antitrypsin Deficiency Registry Study Group. A registry of patients with severe deficiency of alpha 1-antitrypsin: design and methods. *Chest* 1994;106 (4):1223–1232.
- Song S, Embury J, Laipis PJ, Berns KI, Crawford JM, Flotte TR. Stable therapeutic serum levels of human alpha-1 antitrypsin (AAT) after portal vein injection of recombinant adeno-associated virus (rAAV) vectors. *Gene Ther* 2001;8(17):1299–1306.
- Song S, Scott-Jorgensen M, Wang J, Poirier A, Crawford J, Campbell-Thompson M, Flotte TR. Intramuscular administration of recombinant adeno-associated virus 2 alpha-1 antitrypsin (rAAV-SERPINA1) vectors in a nonhuman primate model: safety and immunologic aspects. *Mol Ther* 2002;6(3):329–335.

#### Discussion

**MacIntyre:** Jamie, you have presented some pretty reasonable data that AAT augmentation does have biological activity in these patients. I guess the key question is, does it matter? I think AAT augmentation costs about

\$50,000 per year, which means it costs about \$2,500 to get a 1-mL benefit in FEV<sub>1</sub>. I'm not sure how much that magnitude of FEV<sub>1</sub> improvement translates into meaningful functional outcomes. I guess that's more of an editorial statement than a question, but it goes to what Josh Benditt is going

to talk about in his presentation tomorrow [see the January 2004 issue of *RESPIRATORY CARE*].

Medicare, about 5 years ago, when faced with a \$50,000 bill for lung-volume reduction surgery, despite having data that sounded *very* much like what you presented here, actually bit

the bullet and did a randomized, controlled trial. They did this not only to see *if* the surgery worked, but, just as importantly, how much was the effect and how much was the cost for that effect.<sup>1</sup>

My question is, why aren't we doing a large randomized trial, like the National Emphysema Treatment Trial, for AAT augmentation, which is expensive and from which the only known outcome is small change in FEV<sub>1</sub>?

#### REFERENCE

1. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348(21):2059–2073.

**Stoller:** Fair enough. My presentation begs that question, and I'm delighted you asked. AAT augmentation is very expensive. The drug itself is around \$30,000–35,000. One would have hoped that as other companies came to market with other drugs, that there would have been downward pressure on the price, but that's not been the case. To date, interestingly, the research and development costs are substantial.

About 4 months ago, we published a cost-effectiveness analysis of augmentation therapy based on the NHLBI data.<sup>1</sup> As you can imagine, the cost-effectiveness appears low by conventional criteria in the so-called league tables, which look at quality-adjusted life-years, using about \$100,000 as the upper limits of an acceptable intervention such as colonoscopy or breast cancer screening. AAT augmentation doesn't compare favorably at all; it is on the order of \$600,000 per quality-adjusted life-year, so it's very difficult to make the case that this, in and of itself, is cost-effective.

On the other hand, unlike some other modalities, this is the only currently available specific therapy for AAT de-

ciency. So one could argue that in the transitional phase between this and the next generation of effective therapies, it's reasonable to continue this as a short-term intervention, recognizing that it's not the ultimate solution—which everyone in the field recognizes.

In terms of the statistical requirements, we are using the NHLBI Registry data, which were true slopes. The estimates in 1988 by Ben Burrows and others that suggested that a randomized trial couldn't be done were based on estimates of the natural history of AAT deficiency available at that time. When we used the FEV<sub>1</sub> slope data from the largest available cohort of 1,129 patients, and made the same assumptions on drug efficacy, it turned out that a randomized trial could be done, with about 300 patients in each group. That's challenging, but it's not impossible. Many of us have made the case in various forums that, in fact, a randomized trial should be done. So, in some ways I agree with you. There are shortcomings and challenges to doing that, no doubt.

#### REFERENCE

1. Gildea TR, Shermock KM, Singer ME, Stoller JK. Cost-effectiveness analysis of augmentation therapy for severe alpha1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2003;167(10):1387–1392.

**Hill:** If one were to target a population for study, or make recommendations about using AAT augmentation at present, would you want to limit it to just COPD stage II patients for whom the NHLBI Registry showed some potential benefit? That would seem to be logical, because you've got people who still have some reserve but are showing indications that they are on the decline. Is that the population that should be targeted? Who should be selected?

**Stoller:** There are 2 issues. One is clinical and one is investigative. Investigatively, there's no doubt that it's the mid-range lung function popula-

tion, because of the sinusoidal effect of FEV<sub>1</sub> decline on baseline FEV<sub>1</sub>. Individuals whose FEV<sub>1</sub> is 15% of predicted can't suffer any detriment without great risk of dying. So we have in some ways the "sick-worker effect"—a twist on the healthy-worker effect. Obviously, investigatively, that's a very poor population to study.

On the other hand, clinically, I must say that in my own practice, I've used augmentation therapy pretty broadly. In fact, in my own practice, I don't confine the use of augmentation therapy to patients who have stage II COPD, either by GOLD [Global Initiative for Chronic Obstructive Lung Disease] or ATS [American Thoracic Society] criteria. So, until there's a better therapy, I use it broadly, but not at all in individuals who don't have any demonstrable emphysema. There's absolutely no prophylactic role for AAT augmentation.

**Wedzicha:** Jamie, you showed us Rob Stockley's data<sup>1</sup> that showed good responses with respect to inflammatory markers. We know that if you have more airway inflammation you decline more, so an obvious group to target are those patients who have high degrees of airway inflammation. This may be one situation in which inflammatory markers would be quite useful. And, again, if I'm not mistaken, Rob Stockley's data showed that sputum producers have more airway inflammation in AAT deficiency.

#### REFERENCE

1. Stoller JK, Snider GL, Brantly M, Fallat RA, Stockley R, and the Alpha-1 Antitrypsin Deficiency Task Force. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin (AAT) deficiency. *Am J Respir Crit Care Med* 2003;168(7):818–900.

**Stoller:** Yes. I think this speaks to the general trend we're all experiencing. Here, on top of a baseline phenotype, we're talking about subphenotyping, if you will. Which of these particular subsets has potentially re-

sponsive patients? I would agree: if one had to pick and target a group that would be potentially the best responders, it would be those with active inflammation and moderate airflow obstruction.

**Hansen-Flaschen:** Describe the patient who should be screened for AAT deficiency.

**Stoller:** Thank you for asking that, John. The new standards document<sup>1</sup> spends about 70 pages with evidence tables looking at that. It clearly should be individuals with established airflow obstruction. The standards document takes a rather bold position, that all individuals with established airflow obstruction should be tested for AAT deficiency. One of the limitations of screening statements is that they are fixed in time with regard to the therapeutic efficacy of drugs available at that moment. But this is a rapidly evolving field. Any screening statement made today needs to anticipate the availability of (hopefully) cheaper, more effective interventions, some of which will be quite staggering, I think.

In my own practice, I recommend screening for anyone with a family history of liver or lung disease. I'm quite liberal in testing patients with established airflow obstruction. There is an association with panniculitis and with a positive C-ANCA [anti-neutrophil cytoplasmic antibody] test, and the standards document suggests that these individuals might be tested. Individuals with bronchiectasis are an interesting subset, and the standards document says that individuals without an identifiable etiology of bronchiectasis should be tested. So the patient whom you know doesn't have Kartagener's syndrome, cystic fibrosis, hypogammaglobulinemia, or Young's syndrome—the usual differential diagnoses—should be tested for AAT deficiency. We did not advocate testing asthmatics with reversible airflow obstruction.

#### REFERENCE

1. Stoller JK, Snider GL, Brantly M, Fallat RA, Stockley R, and the Alpha-1 Antitrypsin Deficiency Task Force. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin (AAT) deficiency. *Am J Respir Crit Care Med* 2003; 168(7):818–900.

**Pierson:** I'm following up on John Hansen-Flaschen's question about who you would recommend be tested for AAT deficiency. You use no age threshold?

**Stoller:** No. These comments regard adults. I think we use 21 years as the indication. In the pediatric population, it's known that, except for siblings of affected individuals, the disease is dominated by liver manifestations. There are follow-up data from Piitulainen and Sveger:<sup>1</sup> they followed up the cohort that was screened at birth and then seen serially over time. The most recent published data show that at age 22, these individuals do not have airflow obstruction.

#### REFERENCE

1. Piitulainen E, Sveger T. Respiratory symptoms and lung function in young adults with severe alpha(1)-antitrypsin deficiency (PiZZ). *Thorax* 2002;57(8):705–708.

**Pierson:** But in the list of conditions you were describing for whom to screen for this, do you not use age as one of those? Would you screen a 70-year-old who meets your other criteria?

**Stoller:** Yes, we would.

**Heffner:** You made a comment that it may be difficult to do a placebo-controlled trial in the United States. Do enough data exist in support of probable efficacy to make AAT augmentation the standard of care, thereby disallowing placebo-controlled trials?

**Stoller:** I think the issue is a practical one. This is a patient community that is extraordinarily involved in driv-

ing research. In fact, it represents, in my view, an unbelievable marriage between the patient community and the scientific and pharmaceutical communities. John Walsh, who is the chief executive officer of the Alpha-1 Foundation has moved mountains around this stuff. In fact, the impediment to doing a randomized trial in the United States would be lack of patient recruitment, because patients are committed to the receipt of augmentation therapy in the United States.

So I think it's not so much the ethical issue—that it would be unethical to deny AAT augmentation—but rather the difficulty of recruiting patients to participate. One could argue at a more ethereal level that maybe we shouldn't do it because the data are so compelling and so it would be unethical to deny AAT augmentation, but I think it doesn't even get that far; it gets to the patient recruitment issues that would preclude its being done in the United States.

**Enright:** Has the scientific information from groups of patients informed your decision-making with regard to continuation of this expensive therapy, with an individual patient sitting in front of you? Which of the outcomes you measured do you use, if any, in making that decision? Also, given the serious consequences of the disease's progression, what smoking-cessation resources do you use in this high-risk group? I noticed that 80% were ex-smokers. Was that due to your intervention, or did they quit smoking before their diagnosis was made?

**Stoller:** Both of those are excellent questions. Let me address the second one first. Actually the NHLBI Registry indicates that only 6–8% of AAT-deficient individuals smoke. Obviously, when we see an AAT-deficient person who does smoke, we spend a lot of time counseling him or her on why and how to quit. We tell the person, "These are *your* spirometry values; these are *your* lungs; this is *your*



FEV<sub>1</sub> slope; and *this* is what's going on." We tell them about the particular predisposition of AAT deficiency. So they receive intensive counseling and we prescribe smoking-cessation medications. Scott Marlow will discuss the smoking-cessation therapies.<sup>1</sup>

Regarding the decision of whether to continue therapy, I have to say that in a highly individualized practice there are individuals who come to see me and we have this conversation every time about the pros, cons, and uncertainties of AAT augmentation. I am not a zealot for its use. But, again, with an informed patient population, patients come with expectations. So

we sit down and have a long dialogue about what we know. I frame the information and the uncertainties as I have done with you. Then we engage in a discussion. I ask the patient, should we follow your FEV<sub>1</sub> serially over time in order to make a decision? I have done that in a cohort of my patients who wanted to see if they have a declining rate now that they stopped smoking, and I have deferred therapy in a stable group. It's not been my practice to use FEV<sub>1</sub> slopes while therapy is underway as a rationale to discontinue therapy.

Again, it's a rapidly evolving field. Five years from now, this talk will

have a very different complexion: we'll be talking about gene therapy. Terry Flotte and his colleagues in Florida are going to begin human gene therapy trials soon. The data from gene therapy experiments with mice are spectacular in terms of achieving—with a single intramuscular injection of an adeno-associated virus—serum levels that exceed protective thresholds for a *year*. So gene therapy is highly promising.

#### REFERENCE

1. Marlow SP, Stoller JK. Smoking Cessation. *Respir Care* 2003;46(12):1238-1256.