Concise Clinical Review

A Review of α_1-Antitrypsin Deficiency

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α_1-Antitrypsin (AAT) deficiency is an underrecognized genetic condition that affects approximately 1 in 2,000 to 1 in 5,000 individuals and predisposes to liver disease and early-onset emphysema. AAT is mainly produced in the liver and functions to protect the lung against proteolytic damage (e.g., from neutrophil elastase). Among the approximately 120 variant alleles described to date, the Z allele is most commonly responsible for severe deficiency and disease. Z-type AAT molecules polymerize within the hepatocyte, precluding secretion into the blood and causing low serum AAT levels ($\sim$3–7 μM with normal serum levels of 20–53 μM). A serum AAT level of 11 μM represents the protective threshold value below which the risk of emphysema is believed to increase. In addition to the usual treatments for emphysema, infusion of purified AAT from pooled human plasma—so-called "augmentation therapy"—represents a specific therapy for AAT deficiency and raises serum levels above the protective threshold. Although definitive evidence from randomized controlled trials of augmentation therapy is lacking and therapy is expensive, the available evidence suggests that this approach is safe and can slow the decline of lung function and emphysema progression. Promising novel therapies are under active investigation.

α_1-Antitrypsin (AAT) deficiency is a common but underrecognized genetic condition that predisposes to chronic obstructive pulmonary disease (COPD) and liver disease, especially cirrhosis and hepatocellular carcinoma. This review considers the history of AAT deficiency (AATD) as well as its epidemiology and detection, pathophysiology, and genetics. Clinical manifestations, including pulmonary and extrapulmonary features (e.g., liver disease, panniculitis, and vasculitis), are reviewed, followed by a discussion of diagnostic strategies, natural history, and treatment. Because understanding of AATD can be clouded by unfamiliar terms, a glossary of terms (*see* Table E1 in the online supplement) that are used throughout this paper is provided.

HISTORY

Pasteur's observation in 1854 that "Chance favors the prepared mind" (1) frames the first description of AATD by Laurell and Eriksson in 1963. In reviewing serum protein electrophoreses submitted to his laboratory in Malmo, Sweden, Laurell noted the absence of the band of α-1 protein in 5 of approximately 1,500 serum protein electrophoreses (SPEP) received over a 6-month period (2, 3). Further inquiry showed that three of the five patients had emphysema at young ages (i.e., 35–44 yr of age) and that one patient had a family history of emphysema, thereby establishing the cardinal clinical features of AATD: absence of a protein in the α-1 region of the SPEP, emphysema with early onset, and a genetic predisposition (2, 3).

A second clinical landmark was the recognition of AATD-associated cirrhosis by Sharp and colleagues in 1969. They described cirrhosis in 10 children from six families, all with marked decreases in the α-1 globulin on SPEP patterns and tryptic inhibitory capacity (4).

Since these defining descriptions less than 50 years ago, much has been learned about AAT and AATD, including the full structure of the protein; the mechanism of its binding to its major substrate, neutrophil elastase; the mechanism of its intrahepatic accumulation; and the main clinical manifestations and natural history of AATD. However, major gaps in understanding persist, including the precise mechanism and risk factors for liver disease, clarification of determinants of emphysema beyond cigarette smoking and occupational risk, the role of genetic modifiers of disease expression, and optimal therapy.

EPIDEMIOLOGY AND DETECTION

Two themes summarize the epidemiology of AATD: (*1*) AATD is relatively common, and (*2*) AATD is underrecognized by clinicians, which may cause significant adverse effects.

Estimates of the frequency of AATD have been developed using indirect epidemiologic approaches and direct population-based screening. The indirect approach uses published genetic epidemiologic surveys to estimate the frequency of deficiency alleles in a given population and extrapolates the prevalence of specific deficiency phenotypes for the total population at risk by applying the Hardy-Weinberg Equilibrium principle. For the United States this approach estimates 33,088 PI*ZZ individuals (95% confidence interval, 28,113–38,932) (5). Combining the results of two studies by de Serres and colleagues, there are an estimated 173,430 individuals with PI*ZZ and 1,011,069 with PI*SZ in 94 countries that encompass more than 75% of the world population (5, 6).

The alternative, direct approach for estimating the prevalence of severe AATD is based on population-based screening studies (7, 8). In the two largest such studies, the frequency of PI*Z individuals was 122 of 200,000 screened newborns in Sweden, or 1 of 1,639 (8) and 21 of 107,038 screened newborns in Oregon, or 1 of 5,097 (7). Combining the results of the largest studies in he United States (>10,000 screened) (7, 9, 10) yields a frequency estimate of 1/4,455, suggesting that the number of PI*ZZ individuals in the United States (with a population of $\sim$310,000,000) (11) is approximately 70,000.

Table E2 summarizes the results of available screening studies, grouped by main language origin (7–10, 12–35). The PI*Z prevalence is higher in northern and western European countries, whereas the PI*S prevalence is higher in southwestern European countries (36). Isolated areas with lower genetic diversity and confined populations, such as islands or alpine valleys, appear to have

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a higher prevalence of Z and S deficiency phenotypes (Table E2) (33, 34).

The high prevalence of AATD prompts the question as to why so few AAT-deficient patients have been detected. As one indication of underrecognition, fewer than 10,000 individuals in the United States with severe AATD (of the estimated 33,000–70,000) are currently receiving intravenous augmentation therapy.

Other studies confirm that individuals with severe AATD frequently go unrecognized. For example, Silverman and colleagues sampled 20,000 blood specimens donated to the St. Louis blood bank, among which seven were from individuals with PI*ZZ AATD (9). On the assumption that donating blood is unassociated with having severe AATD, this analysis suggested a prevalence of 700 PI*ZZ individuals in St. Louis. Yet, the investigators' attempt to account for all known PI*ZZ individuals by contacting local physicians identified only 28 PI*ZZ patients, suggesting that only a small minority (4%) of the AATD individuals in St. Louis were medically recognized. Similarly, in a survey of eight countries (Canada, Italy, Holland, New Zealand, Australia, Spain, Sweden, and the United Kingdom), Luisetti and Seersholm estimated that only 0.35% of the expected 305,009 PI*ZZ and PI*SZ individuals were detected (36).

Finally, that underrecognition occurs frequently has been demonstrated in a survey of 300 self-reported PI*ZZ individuals (37). When given a questionnaire addressing the number of physicians seen for attributable symptoms and the time of onset of AATD-related symptoms, the group reported a mean delay between first symptom and initial AATD diagnosis of 7.2 ($\pm$ 8.3) years. Furthermore, 44% of these respondents reported seeing at least three physicians with attributable symptoms before the initial diagnosis of AATD was made (37). Later studies confirm this long diagnostic delay and continuing underrecognition; two separate 2003 surveys showed that the mean intervals between first symptom and initial diagnosis were 8.3 $\pm$ 6.9 years and 5.6 $\pm$ 8.5 years, respectively (38, 39).

Because adverse sequelae of delayed diagnosis of AATD may include slowed opportunities to offer specific counseling and therapy as well as adverse psychosocial effects, expanded efforts to enhance clinicians' diagnostic recognition of AATD are warranted and are ongoing worldwide. Most recently, when physician alerts to test for AATD in guideline-recommended at-risk individuals were attached to hard copy of pulmonary function reports or within the electronic medical record (40, 41), the frequency of testing for AATD increased. Whether such strategies enhance detection of affected individuals requires further investigation, perhaps especially in settings where vigilance for AATD has not already been heightened (42).

THE GENETICS OF AATD

AATD is inherited as an autosomal codominant condition for which more than 120 alleles have been identified (Table E3) (43). The responsible gene, SERPINA1, is located on the long arm of chromosome 14 (14q31–32.3), where it spans 12.2 kb and is organized into four coding (2–4, and 5) and three noncoding (1a, 1b, and 1c) exons. Phenotypes are classified by a PI (for protease inhibitor) coding system, in which the names of the inherited alleles follow (usually letters to denote the migration of the molecule in an isoelectric pH gradient from "A" for anodal variants to "Z" for slower migrating variants; e.g., PI*MM for individuals homozygous for the normal "M" allele and PI*ZZ for individuals homozygous for the Z allele). By convention, the phenotype refers to the AAT protein expression, as demonstrated by isoelectric focusing, and the genotype reflects the specific allelic combination (e.g., as demonstrated by allele-specific amplification).

AAT variants are categorized into four groups (Table E3). Common alleles are (*1*) normal variants, characterized by normal serum AAT (20–53 μM, or $\sim$80–220 mg/dl by nephelometry) and (*2*) deficient variants, characterized by serum levels of AAT less than 20 μM and, for some alleles (e.g., Z), concomitant decreased functional activity of the AAT molecule. The Z allele, characterized by a single amino acid substitution of lysine for glutamic acid at position 342, is the most common, accounting for approximately 95% of cases of clinically recognized AATD. Rare alleles include (*1*) null variants, which are characterized by absent circulating AAT due to transcriptional or translational errors that interrupt protein synthesis, and (*2*) dysfunctional variants, which are characterized by abnormal function of AAT (e.g., with decreased binding to neutrophil elastase, as in the F variant, or with thrombin inhibitory activity, as in Pittsburgh variant) (Figure 1) (44).

In the context of this classification scheme, testing for AATD often begins with determining the serum level of AAT (e.g., most commonly performed by nephelometry). When serum levels are low (i.e., $<$100 mg/dl) or when pedigree analysis is needed to clarify familial patterns, phenotyping by isolectric focusing or genotyping is commonly used. Genotyping can be performed by allele-specific amplification (currently for the S and Z alleles) or by extracting genomic DNA from circulating mononuclear cells or from mouth swabs for direct analysis. The presence of rare null alleles can be inferred from genotyping but not from phenotyping by isoelectric focusing because null alleles do not produce protein that can be identified by a band on the isoelectric focusing field. Many clinicians advocate simultaneously assessing AAT serum levels and genotyping, which is available through some commercial dried blood spot kits and also in a free, confidential home-testing kit (http://www.alpha-1foundation.org/alphas/?c=02-Get-Tested).

Pathophysiology of AATD

AAT is the prototypic member of the serine protease inhibitor (serpin) superfamily of proteins, which includes α-1 antichymotrypsin, C1 inhibitor, antithrombin, and neuroserpin (45). Conformational instability of the β-sheet structure of serpins underlies their susceptibility to mutations and polymerization, leading to the serpinopathies (46). These conditions may reflect a gain-of-toxic-function defect (i.e., due to the accumulation of protein), such as liver cirrhosis or dementia (with AAT and neuroserpin, respectively), or a loss-of-function defect, such as emphysema, angioedema, or thrombosis (with AAT, C1 inhibitor, and antithrombin, respectively) (Figure 1) (45). In the case of PI*ZZ AATD, polymerization results in retention of aggregates of AAT in hepatocytes, leading to liver cirrhosis. Also, loss of the natural antiprotease screen against neutrophil elastase (and other proteases), as well as the loss of the antiinflammatory effects of AAT, predispose to emphysema. The proinflammatory effects of AATD have been proposed to confer a survival advantage against infectious diseases in affected individuals (47). Other studies have suggested that decreased protease inhibition may increase fertility, ovulation, sperm migration, and twinning (48–50). For instance, compared with control subjects, higher frequencies of the S and Z alleles and of the S allele have been observed in dizygotic twins and in mothers of monozygotic twins, respectively (48). Enhanced defense against infection and fertility may explain the persistently high frequency of AAT gene mutations in certain countries.

Normal Physiology of AAT

AAT is mainly produced in the liver and reaches the lungs by diffusion from the circulation (51) and by local production in

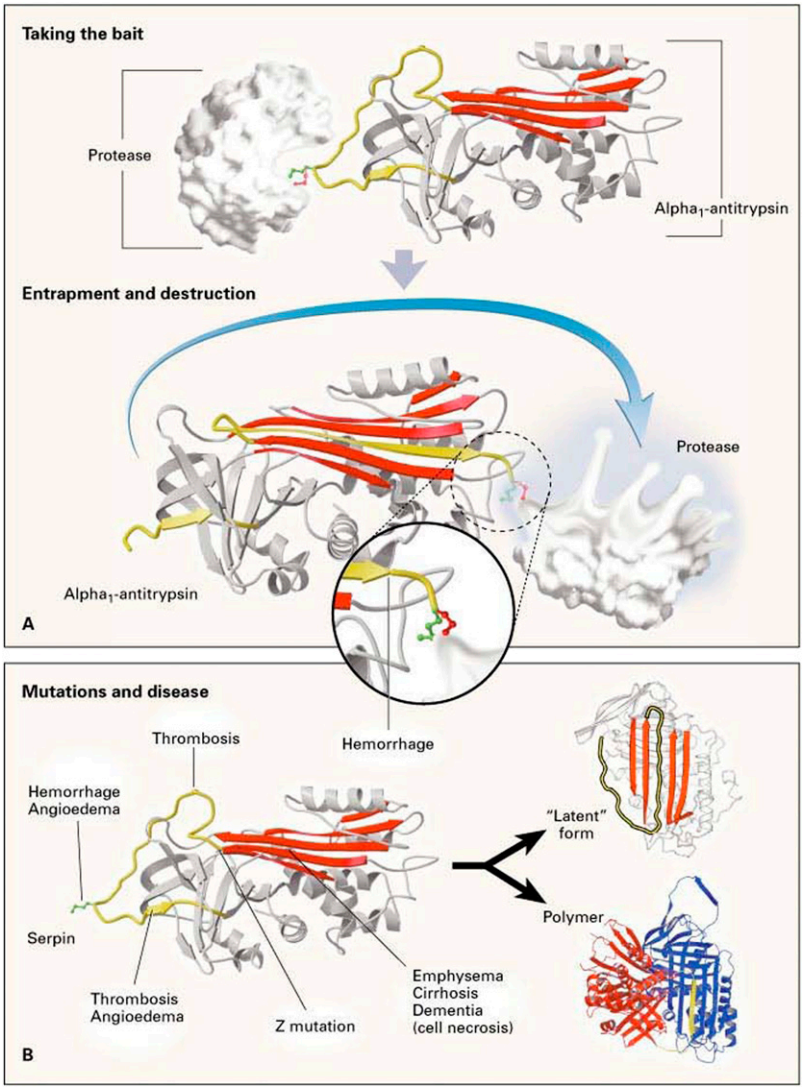

Figure 1. Mechanism of inhibition of proteases by α-1 antitrypsin (AAT) and of polymerization in serpinopathies. (*A*) *Top*: Docking of the protease to the reactive center loop of AAT. *Bottom*: The protease has cleaved the reactive center loop, releasing it from its metastable high-energy state. The reactive loop swings with the protease in tow into a more stable conformation within the main β sheet. The process distorts and alters the structure of the protease. (*B*) Mutations of serpins can result in several diseases. In the case of AAT deficiency caused by a Z mutation, a substitution of lysine for glutamic acid at position 342 widens the β-sheet A. The gap in the β-sheet A can accept its own loop to form a latent conformation or proceed to polymerization in an irreversible process (from Ref. 188).

macrophages and bronchial epithelial cells (52–55). Despite its name, AAT reacts with neutrophil elastase much more avidly than with trypsin (56) and provides greater than 90% of the defense against the elastolytic burden in the lower airways posed by neutrophil elastase, which is contained within the azurophilic granules of neutrophils (57). Other neutrophil- and macrophage-derived elastolytic enzymes have been implicated in the pathogenesis of emphysema (e.g., matrix metalloproteinases 9 and 12) (58).

Serpins have been likened to mousetraps complete with bait, a loaded high-energy but unstable state, and a swinging arm. In the specific case of AAT (Figure 1), the bait is a methionine amino acid side chain in the reactive center of the serpin. Docking of the neutrophil elastase on that residue cleaves the reactive center, releases the AAT protein from its metastable high energy state, and allows the cleaved reactive loop to snap back, with the protease attached, to the opposite pole of the molecule. Because that arm remains relatively short, it distorts and inactivates the elastase molecule by squeezing it on the other end of the AAT molecule (59). Although this process is mutually suicidal to both molecules, there is normally an excess of AAT in the lung, thereby providing an adequate protective screen against the elastolytic burden of neutrophil elastase (60).

Mechanisms of Polymerization

Two mechanisms of polymerization have been proposed: so-called "loop-sheet" polymerization (61–66) and "domain-swapping" polymerization (67). According to the former model, in Z-type AATD, the substitution of lysine for glutamic acid at position 342 widens the β-sheet A and allows polymerization, which links the reactive loop of one AAT molecule to the β-sheet A of another molecule in an irreversible process (Figure 1) (61–63). Factors that encourage polymerization include increased temperature and Z protein concentration (64) and decreased pH to <6 or increased pH to >8 (61). Because polymerization within the hepatocyte prevents its secretion, only about 15% of Z protein is secreted into the plasma (53, 64).

Mechanism of Liver Disease

Polymers of Z-type protein have been identified on electron microscopy and stain as periodic acid-Schiff stain–positive, diastase-resistant inclusions within the endoplasmic reticulum (ER) of hepatocytes (64). Intracellular liver inclusions have been seen with other AATD phenotypes characterized by polymer formation, including S_{iiyama} (65) and M_{malton} (66). Although most PI*ZZ individuals appear to escape clinically evident liver disease and factors affecting clinical disease expression remain

incompletely understood, the available evidence suggests that a lag in intracellular degradation of Z-type protein from the ER is associated with clinical liver disease (68).

Retention of the polymers in the ER may be due to an impaired interaction between Z-type protein and its molecular chaperone, calnexin (69), perhaps involving calnexin phosphorylation (70). Other mechanistic studies suggest that AAT accumulation is due to a derangement of the unfolded protein response (71), perhaps because the ordered polymeric structures are not recognized as misfolded (72), and impaired autophagy (73).

Potential liver-directed treatment strategies targeting intrahepatocyte accumulation include the use of peptides and small molecules to block polymerization (74, 75), chaperones to stabilize monomeric proteins (76), and drugs to promote autophagy as a means to clear the pathologic inclusions (77).

Mechanisms of Lung Disease

Emphysema in AATD has been ascribed to several pathogenetic mechanisms, including protease–antiprotease imbalance, inflammation fueled by enhanced chemotaxis, and mechanical damage, as reviewed below.

Protease–antiprotease imbalance. The protease–antiprotease model posits an imbalance between the reduced AAT-protective screen (due to retention of polymers in the endoplasmic reticulum of liver cells) and the neutrophil elastase burden, causing unchecked proteolytic activity that leads to emphysema. Cigarette smoking and lung infections increase the elastase burden and may further tip the elastase–antielastase balance toward accelerated lung breakdown (78).

Inflammation fueled by enhanced chemotaxis. Enhanced recruitment of neutrophils to the lung (e.g., by cytokines or AAT polymers) can fuel inflammation in AATD. For example, patients with AATD have increased release of leukotriene (LT) B4 by alveolar macrophages (79–81), with levels that correlate with exacerbation frequency (82) and decline with augmentation therapy (83). Binding of free neutrophil elastase to alveolar macrophages causes their release of LTB4, which has been estimated to contribute about 47% of the neutrophil chemotactic activity in the sputum of patients with COPD (81). Similarly, human neutrophil peptide is neutralized by AAT, and elevated bronchoalveolar concentrations in AATD are proinflammatory (e.g., by releasing macrophage LTB4 synergistically with neutrophil elastase and IL-8) (84). IL-8, a ligand for CXCR1 (which is a receptor expressed on the surface of neutrophils), has been estimated to contribute about 31% of the neutrophil chemotactic activity in the sputum of AATD individuals with COPD (81).

Z-type AAT polymers, which may be produced within the lung, also appear to fuel inflammation in AATD. Specifically, Z-type polymers colocalize with neutrophils in the alveoli of patients with AATD (85), are chemotactic for human neutrophils in *in vitro* studies (54, 85, 86), and stimulate myeloperoxidase release and neutrophil adhesion (86). These findings help explain the prominent interstitial neutrophilia seen in the lungs of patients with Z-type AATD (85, 86) and, given the role of neutrophils and neutrophil elastase in the pathogenesis of emphysema, help to explain why lung disease in PI*ZZ AATD can progress during augmentation therapy. For instance, augmentation reduces sputum elastase and LTB4 but does not significantly reduce myeloperoxidase, which is a marker of neutrophil activity (83). Also, in a mouse model, oxidation of Z-type AAT by cigarette smoke can promote polymerization within the lung (87).

Finally, in a murine model of emphysema, elastin fragments have been found to drive chemotactic activity and monocyte recruitment in response to cigarette smoke. In support of this notion, use of a monoclonal antibody against elastin fragments interrupts the chemotaxis (88).

Mechanical damage. Biomechanical stresses imposed by the cyclic strain on the alveolar wall tissue may contribute to the development and progression of emphysema (89). It has been speculated that the persistently accelerated loss of FEV_1 after lung volume reduction surgery (e.g., up to 255 ml/yr) (90) relates to the additional load of biomechanical stresses imposed by expansion of the remaining lung tissue (89). Also, in a mouse model, mechanical tissue strain is increased in lungs with low levels of elastin and may worsen emphysema after experimental cigarette smoke exposure (91).

In summary, although neutrophil elastase appears to be the primary substrate of AAT, the reduction or absence of AAT decreases binding of AAT to human neutrophil peptide and IL-8. The release of human neutrophil peptide, neutrophil elastase, and IL-8 promotes a cascade of events that lead to unchecked proteolytic breakdown, compounded by the macrophage and neutrophil chemotactic effects of elastin fragments, LTB4, and IL-8. Mechanical lung tissue strain may further accelerate the lung injury. In most cases of AATD associated with polymerization, lung polymers also effect chemotaxis and provide a mechanism of lung injury that would not be expected to respond to augmentation therapy. Active smoking further compounds the elastolytic burden by increasing neutrophils and neutrophil elastase and by promoting polymerization.

Clinical Manifestations and Diagnosis

AATD can clearly predispose to lung disease (e.g., emphysema and bronchiectasis) (92), liver disease (e.g., chronic hepatitis, cirrhosis and hepatoma) (93, 94), and skin disease (i.e., panniculitis) (95) and is associated with vasculitis (especially anticytoplasmic antibody-positive vasculitis such as Wegener's granulomatosis [WG]) (96–98). Although other disease associations have been suggested, they are less well established (99), including glomerulonephritis (100); celiac disease (101); lung, colorectal, and bladder cancers (102); intracranial and intraabdominal aneurysms (103); fibromuscular dysplasia (104); and pancreatitis (105).

Lung disease. Distinctive and suggestive features of the emphysema associated with AATD may include early onset (i.e., in the fourth and fifth decades), panacinar pathology, and disproportionate emphysematous involvement of the lung bases (vs. the more apical distribution seen in usual, AAT-replete COPD) (Figure 2) (92, 106, 107). Still, restricting testing for AATD to circumstances in which "classic" features are present fosters underrecognition (108) because most patients with AATD present with more usual signs and symptoms of COPD. For example, symptoms in the 1,129 participants in the NHLBI Registry of Individuals with Severe Deficiency of AAT included dyspnea (84%), usual cough (42%), usual phlegm (46%), and wheezing with upper respiratory infections (76%) (109). In a series of 165 plain chest radiographs from PI*ZZ individuals, Gishen and colleagues observed that 15% of the films were normal and that only 20% demonstrated the distinctive pattern of emphysema changes confined to the lung bases (107). Also, among 102 PI*ZZ individuals with evidence of emphysema on computed tomography (CT), Parr and colleagues reported that 64% had basal-predominant emphysema but that 36% had predominantly apical emphysema (110).

As in most patients with COPD (111), partial reversibility of airflow obstruction is common in individuals with AATD; for example, a significant reversible component (e.g., as indicated by a 12% and 200-ml rise in the FEV_1 or FVC postbronchodilator) was evident in approximately 61% of NHLBI Registry

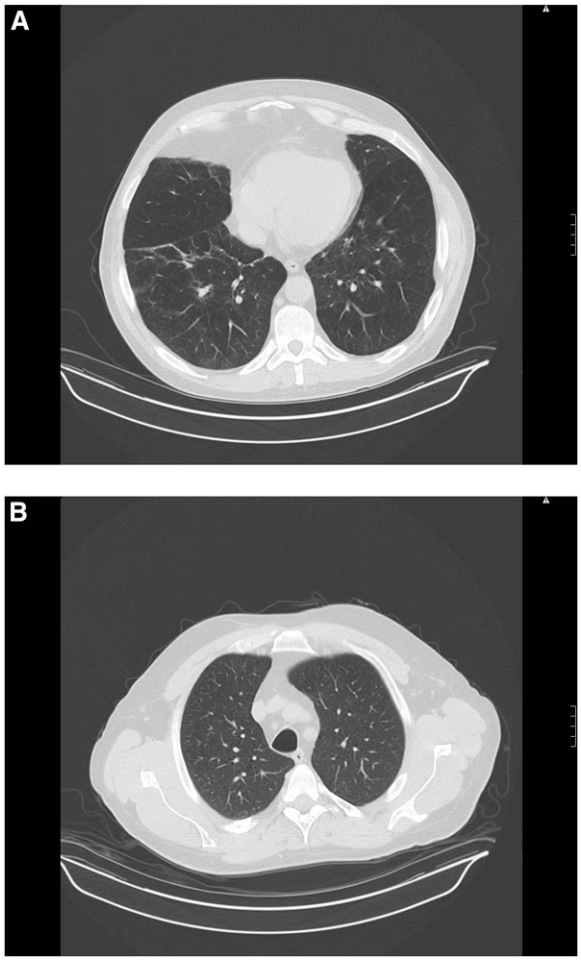

Figure 2. Sections from a chest computed tomographic scan of a patient with PI*ZZ AATD, demonstrating the basilar distribution pattern. The basal cut (*A*) shows more pronounced emphysematous change than the more apical section of the lung (*B*).

participants tested with up to three serial spirometries (109). In keeping with this high frequency of partial reversibility of airflow obstruction, 35% of the NHLBI Registry participants reported having asthma (109).

Evidence regarding the association of bronchiectasis with AATD is mixed. Larsson originally observed bronchiectasis in 11.3% of 246 PI*ZZ individuals (112), whereas the NHLBI Registry reported clinically evident bronchiectasis in only 2% of 1,129 participants (113), and, in a case-control study, Cuvelier and colleagues observed no excess frequency of AATD in patients with bronchiectasis versus those without bronchiectasis (114). In a series of 74 PI*Z individuals undergoing chest CT scans, Parr and colleagues reported radiographic evidence of bronchiectasis in 95%; 27% had "clinically significant" bronchiectasis (115). In the context of the mixed results reported in the literature, current recommendations are to test for AATD when the cause of bronchiectasis remains unknown after consideration of the usual etiologies (e.g., cystic fibrosis, hypogammaglobulinemia, ciliary dysfunction, etc.) (116).

Liver disease. Liver disease, including hepatitis, cirrhosis, and hepatoma, represents another clinical manifestation of AATD, at least for individuals with phenotypes characterized by intrahepatocyte polymerization (e.g., with Z, M_{malton}, and S_{iiyama} alleles) (4). Several studies have assessed the prevalence of liver disease in individuals with AATD. Specifically, in the Swedish population-based screening study of 200,000 newborns, 22 of the 120 PI*Z newborns (18%) had evidence of some liver dysfunction over follow-up, including obstructive jaundice (12%) and minor laboratory abnormalities (7%) (8). The risk of developing cirrhosis among those with liver dysfunction was estimated to be 50%; 25% died within the first decade of life, and 2% developed cirrhosis later in childhood (94). Follow-up of 70% of the Swedish PI*Z neonatal screenees at age 30 showed that 3 to 5% had elevated transaminases but that none had clinically evident liver disease (117). In a second study in which 246 PI*Z individuals were followed for up to 11 years, Larsson observed liver disease in 12% (cirrhosis in 11.8%, neonatal hepatitis in 0.4%, and hepatoma in 3.3%) (112). Finally, in an analysis of 38 postmortem examinations from among the 58 expected AATD decedents in Malmo, Sweden, Eriksson observed cirrhosis in 34% (n = 14). Cirrhosis had been suspected in 64% (n = 9) (118), and hepatocellular carcinoma was observed in 34% of those with cirrhosis (118).

The strong association between the PI*ZZ phenotype and liver disease has prompted the recommendation to test for AATD in all individuals "with unexplained liver disease, including neonates, children, and adults, especially the elderly" (116).

Panniculitis. First described by Warter and colleagues in 1972 (119), the association of panniculitis with AATD has been established on the basis of approximately 50 reported cases (116, 120). However, panniculitis occurs infrequently, with an estimated prevalence of approximately 1 per 1,000 AAT-deficient individuals (109). The panniculitis is characterized by painful, weepy cutaneous nodules that can sometimes necrose (Figure 3). Panniculitis occurs at the site of trauma in one third of individuals and may accompany several phenotypes, including PI*ZZ (121), PI*SZ (122), PI*SS (123), and PI*MS (124). Diagnosis often requires deep excisional biopsy, which shows areas of fat necrosis interspersed among normal-appearing areas. That the cause of panniculitis is unopposed proteolysis is suggested by the finding of Z-type polymers in the skin of a PI*ZZ patient with panniculitis (125) and by the dramatic clinical response to intravenous augmentation therapy (126, 127). Prescribing augmentation therapy for panniculitis is an off-label use. Furthermore, Blanco and colleagues reported that higher-than-conventional doses of intravenous augmentation therapy (i.e., up to 90 mg/kg) conferred benefit in refractory AATD-related panniculitis (128).

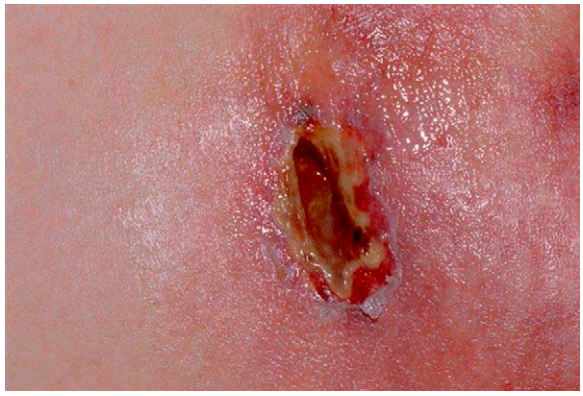

Figure 3. Skin lesion of panniculitis associated with α-1 antitrypsin deficiency. Note the necrotic weeping nature of the inflammatory cutaneous nodules.

Vasculitis. An association between antiproteinase 3 (PR3) antibody-positive vasculitis (i.e., usually c-ANCA positive) and AATD was first reported in 1993 (129, 130) Since then, several series have established an overrepresentation of abnormal AAT phenotypes among individuals with anti-PR3 positive vasculitis. Specifically, prevalence estimates of the Z allele among anti-PR3 positive individuals of 5.6 to 17.6% among six series exceeds by 3- to 9-fold the frequency in normal individuals (116, 129). In a recent analysis of 433 patients with WG compared with non-WG control subjects, the frequency of PI*ZZ was 0.9% (vs. 0), and the frequency of PI*SZ was 0.5% (vs. 0); the odds ratio for PI*ZZ, SZ, or SS was 14.58 (98). In a study of patients with anti-PR3 positive vasculitis, the mortality rate was increased in those who were heterozygous for the Z-allele compared with non-PI*Z carriers (39 vs. 16%, respectively) (131).

Concerning the association of vasculitis with different AATD alleles, one study showed an increased frequency of the PI*Z but not PI*S alleles in c-ANCA patients, whereas an increased frequency of the PI*S allele was seen in p-ANCA patients with a trend toward increased PI*Z allele frequency (132).

Although the specific pathogenesis of AATD-associated vasculitis remains poorly understood, four potential mechanisms have been proposed: (*1*) AATD may prolong the half-life of proteinase-3 because AAT is a major substrate for PR-3. The increased immune exposure of PR-3 could prompt development of PR-3 antibodies (132, 133). (*2*) Decreased AAT levels may allow proteinase-3 that has been released by neutrophils to effect proteolytic vessel damage. (*3*) The polymerization of Z-type AAT protein may prompt an autoimmune vasculitic response. (*4*) Linkage disequilibrium may have promoted the inheritance of important autoimmunity genes accompanying abnormal AAT phenotypes (132).

Overall, the strength of the association between c-ANCA–positive vasculitis and AATD has prompted the recommendation that testing for AATD should be done in all adults with c-ANCA–positive vasculitis (116). Phenotyping or genotypic identification may be required because AAT is an acute phase reactant (131, 132) and AAT levels could rise during active vasculitis.

Natural History of Emphysema in AATD

Although the precise risk of developing emphysema in individuals with severe AAT deficiency is incompletely understood and it is clear that some PI*ZZ individuals may escape developing emphysema, several studies suggest a high likelihood of developing emphysema. For example, Tobin and colleagues assessed the risk of emphysema in PI*ZZ siblings of index cases and found radiographically confirmed emphysema in 90% of PI*ZZ smokers compared with 65% of nonsmokers (108). Also, postmortem series from Sweden (60) and CT imaging studies (110) suggested that only 14 to 20% of PI*Z homozygotes were free of COPD.

Estimates of the annual rate of decline of FEV_1 in PI*Z homozygotes varies from 23 to 316 ml (Table 1) (134–146). Important predictors of an increased rate of FEV_1 decline include smoking status (i.e., current vs. ever vs. never), male sex, age 30 to 44 years, FEV_1 between 35 and 79% of predicted value, decreased serum AAT level, and bronchodilator responsiveness (134, 136, 147). In one model, age, sex, pack-years of smoking, bronchodilator responsiveness, chronic bronchitis symptoms, and index case status accounted for 50% of the variance in FEV_1 (148). Single-nucleotide polymorphisms of IL-10 have also been associated with COPD in patients with severe AAT deficiency (149). Occupational and environmental hazards as may occur in firefighters (150) or with exposure to pollution, including ozone and particulate matter less than 10 μm in diameter (151), have also been associated with an accelerated rate of lung function decline in AATD.

The most common cause of death in patients with AATD is respiratory failure (accounting for 45–72% of deaths), followed by liver cirrhosis (accounting for 10–13% of deaths) (112, 134, 152). Among PI*ZZ never smokers, emphysema accounted for fewer deaths (45%) and cirrhosis more deaths (28%) than in series including both smokers and nonsmokers (153). Also, how individuals come to clinical attention affects prognosis. Asymptomatic never-smoking PI*ZZ subjects ascertained as family members of probands had no higher expected mortality than normal subjects (154). In many available series, the observed overall yearly mortality rate has been found to range from 1.7 to 3.5% (112, 134, 145, 152, 155). In the NHLBI Registry, factors

TABLE 1. RATE OF FEV_1 DECLINE AMONG INDIVIDUALS WITH α-1 ANTITRYPSIN DEFICIENCY

Reference	*n*	Ever Smokers (%)	Months of Follow-up*	FEV_1 Slope (*ml/yr*)*			
				Overall	Never Smokers	Ex-smokers	Current Smokers
Buist, 1983 (135)†	30	97	62 (36)	111 (102)			
Buist, 1983 (135)‡	41	83	74 (47)	104 (94)			
Janus, 1985 (140)	21	67	72 (10)§		80 (38)§	61 (43)§	316 (80)§
Hutchison, 1987 (139)	82				66 (55)	44 (56)	67 (46)
Wu, 1988 (145)	80	58	71		61 (100)	81 (70)	61 (170)
Seersholm, 1995 (142)	161	89			86 (107)	52 (80)	132 (105)
Seersholm *et al.*, 1997 ‖ (143)	97	100	70 (41)			75 (60) (95% CI, 63–87)	
NHLBI, 1998 (134)	927	79	52 (12–86)¶	56 (4)§	67 (95% CI, 56–78)	55 (95% CI, 46–63)	109 (95% CI, 81–137)
Piitulainen, 1999 (141)	608	65	66 (12–372) ¶	48 (79)	47 (95% CI, 41–53)	41 (95% CI, 36–48)	70 (95% CI, 58–82)
Dirksen, 1999 (137)	56	100	36**			59 (12)§	
Wencker, 2001 (144)	96	88	48 (28)	49 (61)			
Dawkins, 2009 (136)	101	82	36**	50 (7)			
Dirksen, 2009 (138)	77	90	24**	23 (10)§			
Tonelli, 2009 (146)	40	79	42	37 (12)§	38 (12.12)§	41 (22.47)§	

* Values are mean (SD) unless otherwise indicated.
† United States patients.
‡ Swedish patients.
§ Parentheses indicate SEM.
‖ Danish patients not on augmentation therapy,
¶ Median (range).
** Minimum follow-up.

associated with increased mortality included older age, lower education, lower FEV_1% predicted, lung transplant, and not receiving augmentation therapy (134). In another study, only age and the CT assessment of proportion of emphysema were found to predict respiratory and all-cause mortality (152).

Treatment of AATD

Treatment for individuals with COPD due to AATD should include the usual therapy for COPD (e.g., smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen when indicated, rehabilitation, etc.) (156, 157), with the possible exception of lung volume reduction surgery. In the small available series examining AAT-deficient individuals, lung volume reduction surgery has generally conferred shorter-lived benefits (158, 159) than has been observed in individuals with AAT-replete COPD (160).

Beyond the usual treatment of COPD, specific treatment of AATD is available and consists of the infusion of purified pooled human plasma AAT, known as intravenous augmentation therapy. The goal of augmentation therapy in AATD is to raise and maintain serum AAT levels above the protective threshold value. Six different preparations of purified AAT from pooled human plasma are available in the United States, of which two are modifications of earlier preparations (Table 2).

Two types of criteria—biochemical and clinical—have been used to assess the efficacy of augmentation therapy. Biochemical efficacy criteria include: (*1*) Does the drug produce serum levels that exceed the protective threshold value, ideally over the entire interdose interval? and (*2*) Is the functional capacity of the infused α-1 antiprotease preserved?

Criteria regarding the clinical efficacy and usefulness of augmentation therapy include: (*1*) Does augmentation therapy slow the rate of decline of lung function or the rate of emphysema progression? (*2*) Does augmentation therapy enhance functional status, ameliorate symptoms, or prolong life? (*3*) Is augmentation therapy safe? and (*4*) Is augmentation therapy cost-effective?

Biochemical efficacy criteria have formed the primary basis for approval of all currently available products for augmentation therapy in the United States. For example, Wewers and colleagues showed that the infusion of 60 mg/kg once weekly of purified AAT derived from normal donors raised serum levels above the protective threshold of 11 μM over the entire dosing interval, along with increases in the antielastase activity within the bronchoalveolar lavage fluid of drug recipients (161). Studies of alternate dose regimens, such as 120 mg/kg once every 2 weeks or 250 mg/kg once a month, are less promising biochemically because serum levels were maintained above the protective threshold for only part of the 2- and 4-week interdose intervals, respectively (137, 162, 163).

Available studies of the clinical efficacy of augmentation therapy (Table 3) represent various designs, including several observational cohort studies and two relatively small randomized controlled clinical trials (83, 134, 137, 138, 143, 144, 146, 164–166). Various outcome measures have been studied, including the rate of FEV_1 decline, change in lung density by CT, frequency of exacerbations, and functional measures.

The largest observational cohort study, the NHLBI Registry for Individuals with Severe Deficiency of AAT, evaluated 1,129 enrollees, of whom 747 received augmentation therapy at some point over Registry follow-up (134). Augmentation therapy

TABLE 2. AVAILABLE PREPARATIONS OF PURIFIED α-1 ANTITRYPSIN IN THE UNITED STATES*

Drug	Purification Method†	Comments
Prolastin‡	Cold ethanol fractionation	25 mg/ml after reconstitution
	PEG precipitation	Infusion time of 30 min (min) for 60 mg/kg dose
	Depth filtration	Older preparation
	Pasteurization	
Prolastin-C‡	Cold ethanol fractionation	Compared with Prolastin
	PEG precipitation	More concentrated (50 mg/ml) after reconstitution
	Chromatography	More purified
	Depth filtration	Infusion time of 15 min for 60 mg/kg dose
	Solvent detergent purification	
	Nanofiltration	
Aralast§	Cold ethanol fractionation	20 mg/ml after reconstitution
	PEG precipitation	Infusion time of 37.5 min for 60 mg/kg dose
	Zn Cl precipitation	Older preparation
	Chromatography	
	Solvent detergent purification	
	Nanofiltration	
Aralast NP§	Cold ethanol fractionation	20 mg/ml after reconstitution
	PEG precipitation	Infusion time of 37.5 min for 60 mg/kg dose
	Zn Cl precipitation	Compared with Aralast:
	Chromatography	Removal of most of C-terminal lysine (lys 394)
	Solvent detergent purification	
	Nanofiltration	
Zemaira‖	Cold ethanol fractionation	50 mg/ml after reconstitution
	Pasteurization	Infusion time of 15 min for 60 mg/kg dose
	Nanofiltration	Room temperature storage and transport
Glassia¶	Cold ethanol fractionation	20 mg/ml comes as liquid formulation
	Chromatography	No reconstitution needed
	Solvent detergent purification	Infusion time of 60–80 min for 60 mg/kg dose
	Nanofiltration	

* Source for all preparations is pooled human plasma.
† Information obtained from package inserts.
‡ Talecris (Research Triangle Park, NC).
§ Baxter (Deerfield, IL).
‖ CSL-Behring (Kankakee, IL).
¶ Kamada (Beit Kama, Israel).

TABLE 3. AVAILABLE STUDIES ON CLINICAL EFFICACY OF AUGMENTATION THERAPY*

Reference	Date	Design	Infusion Interval	Main Results
Stone *et al.*, 1995 (166)	1995	Observational cohort	Monthly	Urine desmosine level fell while on treatment.
Seersholm *et al.* 1997 (143)	1997	Observational cohort, concurrent controls	Weekly	In patients with FEV_1 31–65% predicted, augmentation slowed the decline of FEV_1 by 21 ml/yr ($P = 0.04$).
NHLBI Registry (134)	1998	Observational cohort, concurrent controls	51% weekly	In patients with FEV_1 35–49% predicted, augmentation slowed the decline of FEV_1 by 27 ml/yr ($P = 0.03$). In the whole group, the risk ratio of death was 0.64 compared with nonrecipients ($P = 0.02$).
			25% biweekly 22% monthly	
Dirksen (137)	1999	Randomized controlled trial	Every 28 d	Loss of lung tissue (by CT densitometry) was 1.5 g/L/yr with augmentation and 2.6 g/L/yr with placebo ($P = 0.07$). FEV_1 decline was not significantly reduced.
Gottlieb (164)	2000	Descriptive	Weekly	Augmentation did not reduce elastin degradation rate.
Lieberman (165)	2000	Observational (web-based survey)	56% weekly	The number of lung infections per year decreased from 3–5 preaugmentation to 0–1 postaugmentation.
			36% biweekly 7% monthly	
Wencker (144)	2001	Observational (before-after)	Weekly	Rates of FEV_1 decline pre- and postaugmentation were 49.2 vs. 34.2 ml/yr, respectively ($P = 0.019$).
Stockley (83)	2002	Descriptive	Weekly	Augmentation reduced sputum leukotriene B4.
Dirksen (138)	2009	Randomized controlled trial	Weekly	Using the first and last CT scans with covariates adjustment, loss of lung tissue was 2.9 g/L with augmentation therapy vs. 4.1 g/L in placebo ($P < 0.05$).
Tonelli (146)	2009	Observational	Weekly	In augmentation therapy recipients, rate of FEV_1 change was +10.6 + 21.4 ml/yr vs. −39.96 + 12.1 ml/yr in nonrecipients ($P = 0.05$).

*Adapted with permission from Reference 187.

recipients showed a decreased mortality rate (relative risk of death, 0.64; $P = 0.02$) (134). Differences between augmentation therapy recipients and nonrecipients in the rate of FEV_1 decline did not achieve statistical significance for the group overall. Subgroup analysis in prespecified groups showed that FEV_1 decline slowed significantly in augmentation therapy recipients (by 27 ml/yr; $P = 0.03$), with values of FEV_1 between 35 and 49% predicted (134). As emphasized in available observational reports (83, 134, 143, 144, 146, 164–166) (Table 3), cautious interpretation of these results is warranted because of the risk of bias when comparing outcomes of cohorts in observational studies. At the same time, concordant results regarding slowed rates of FEV_1 decline in augmentation therapy recipients were observed in other observational studies (143, 144, 167).

In the first of two randomized, double-blind, placebo-controlled trials of augmentation therapy, Dirksen and colleagues randomly allocated 56 PI*ZZ subjects to active treatment (250 mg/kg of a French AAT augmentation therapy preparation administered every 4 wk) or to a placebo control group that received monthly albumin infusions (137). Over at least 3 years of follow-up, the primary outcome of FEV_1 decline showed no significant difference between augmentation and placebo recipients, although a trend toward slower loss of lung tissue (by CT scan) was observed in augmentation therapy recipients ($P = 0.07$) (137).

In the second randomized controlled trial, called EXACTLE (EXacerbations And CT As Lung Endpoints), 77 PI*Z subjects in three countries were allocated to once weekly augmentation therapy (60 mg/kg) for 24 to 30 months versus an intravenous albumin placebo. The primary outcome measure was the change in lung density on CT as measured by the 15th percentile for density using four different analytic methods (i.e., either correcting for lung volume or not or using all scans versus only the first and last). A significant P value (0.049) was achieved for one of the four methods. No significant differences between augmentation versus placebo recipients were observed regarding overall exacerbation frequency, St. George Respiratory Questionnaire ratings, or rates of decline of FEV_1 or diffusing capacity (138).

Pooled analyses and metaanalyses of augmentation therapy have also tended to support efficacy while drawing inquiry regarding the "poolability" of results from the two available randomized trials. Notwithstanding the use of different augmentation therapy preparations in the two trials, different dosing frequencies, and including an hypothesis-generating study in an outcome analysis, a pooled analysis of the two available randomized controlled trials reported that augmentation therapy was associated with a slowed rate of loss of lung density (−2.74 vs. −1.73 g/l/yr; $P = 0.006$) but not with a slowed rate of FEV_1 loss (13 ml/yr; $P = 0.321$) (168). A metaanalysis of five studies and 1,509 total subjects showed that augmentation therapy use conferred a 23% slower rate of FEV_1 decline (13.4 ml/yr difference; 95% CI, 1.5–25.3 ml/yr) than non-use and that the effect was greatest in subjects with FEV_1 30 to 65% predicted (169). Finally, a Cochrane Database report suggested that augmentation therapy lacked efficacy but has been challenged on questions of poolability of the data, on the lack of independence of the pooled data sets, and on a discordance between the study analyses and stated conclusions in the report (170).

Overall, in the context that definitive data are not available and that the metaanalyses have drawn debate, we believe the biochemical evidence supporting augmentation therapy is clear and that the evidence supports clinical efficacy (116) (Table 3). In keeping with this view, available standards documents endorsed by the Canadian Thoracic Society (171) and by a group

TABLE 4. SUMMARY OF ADVERSE EXPERIENCES ASSOCIATED WITH INTRAVENOUS AUGMENTATION THERAPY*

	Study	
Adverse Effect	Wencker *et al.* (167) (*n* = *443*)	Stoller *et al.* (174) (*n* = *747*)
Anaphylaxis	0.9%†	0%‡
Dyspnea	3.0%	8.5%
Wheezing	NR	1.9%
Hypotension	NR	0.3%
Headache	NR	47.1%
Dizziness (fainting)	NR	16.8%
Chills	NR	7.5%
Fever	3.8%	7.4%
Rash	NR	5.1%
Chest tightness	NR	5.1%
Hives/itching	4.1%	3.2%
Tachycardia	NR	2.8%
Moderate chest pain	NR	2.2%
Emesis/nausea	4.7%	1.7%
Flushing	NR	6.5%
Anxiety	NR	4.4%
Mild pain	NR	4.3%
Muscle cramps	NR	3.8%
Fatigue	1.6%	NR

Definition of abbreviation: NR = not reported.
* Adapted with permission from Reference 187.
† Percentage of patients.
‡ Percentage of total of 720 adverse events.

of organizations, including the American Thoracic Society, the European Respiratory Society, the American College of Chest Physicians, and the American Association for Respiratory Care, support the selected use of augmentation therapy (116). Specifically, the latter 2003 international, evidence-based standards document states, "Recognizing that support of efficacy comes from concordant observational studies but not from a randomized controlled clinical trial, the Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AATD. Evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV_1 decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV_1 35–60% predicted) than for those with severe airflow obstruction. Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (e.g., $FEV_1 < 35\%$ predicted) or mild (e.g., $FEV_1 > 50$–60% predicted) airflow obstruction are less clear" (116).

The role of augmentation therapy for Z heterozygotes (e.g., PI*MZ and PI*SZ) has been the source of confusion for clinicians and so merits comment. Augmentation therapy is not recommended for PI*MZ heterozygotes who may have COPD (172), based on the absence of supportive evidence of efficacy for heterozygotes and the fact that the target nadir serum levels of augmentation therapy for PI*ZZ homozygotes is below the usual AAT serum levels for PI*MZ individuals; PI*MZ heterozygotes rarely have serum levels below the protective threshold value of 11 μM. For PI*SZ heterozygotes, approximately 10% of such individuals may have serum levels below 11 μM (173). Although no studies specifically address the issue, symptomatic PI*SZ individuals with COPD may be candidates for augmentation therapy.

Regarding the safety of augmentation therapy, available data over more than 20 years of use suggest that the treatment is generally well tolerated (167, 174). In the first of two large studies addressing this issue (Table 4), Wencker and colleagues reported the experience of 443 augmentation therapy recipients, of whom 65 experienced a total of 124 adverse events (167). The most common adverse reactions were fever and chills (17 patients), urticaria (18 patients), nausea and vomiting (21 patients), and fatigue (7 patients). No deaths or instances of viral transmission (i.e., HIV or hepatitis) were observed (167).

In the second large study, among 747 augmentation therapy recipients in the NHLBI Registry, 174 subjects reported 720 adverse events, the most common of which were dyspnea (47%) and dizziness/fainting (17%) (134). The overall incidence of adverse events was very low ($\sim$ 0.02 events per patient-month) (174). Augmentation therapy recipients experienced on average fewer than two adverse events over 5 years of continuous therapy. Also, no instance of hepatitis, HIV, or prion disease transmission has been ascribed to intravenous augmentation therapy (167, 174, 175).

In the context that augmentation therapy is expensive (i.e., with estimated 2011 average annual wholesale prices of $93,000 to $120,000) (176), the question of cost-effectiveness has been addressed by several studies (177–179). Methodologic variation among these studies likely accounts for the substantial difference in cost-effectiveness estimates (Table E4) (177–179). In brief, available estimates of cost-effectiveness of intravenous pooled human plasma AAT have been $28,000 to $128,000 for the cost per year of life saved (179), $13,971 as the incremental cost per year of life saved (177), and $207,841 to $312,511 per quality-adjusted life-year, depending on whether augmentation therapy was modeled to lifelong use or to be discontinued when FEV_1 fell below 35% predicted (178). All estimates of the incremental cost-effectiveness ratios for augmentation therapy exceed the conventional criterion for cost-effectiveness (i.e., $50,000 per quality-adjusted life-year), indicating the need for more cost-effective treatment.

Future treatment prospects for AATD show promise along many lines of investigation, including gene therapy by injecting adeno-associated virus carrying the human AAT gene (180, 181), preparation of recombinant AAT, inhibiting intrahepatic polymerization of AAT (74, 75), promoting hepatic secretion of AAT (76, 182), inhibiting of neutrophil elastase by small-molecule inhibitors, prolonging the serum half-life of AAT (e.g., by pegylation) (183), delivery of AAT by inhalation, and dose-ranging studies of intravenous augmentation therapy. A recent dose escalation trial of recombinant adeno-associated virus expressing normal human AAT in nine PI*ZZ AAT–deficient subjects showed that the highest expression was 200-fold lower than the protective threshold value of 11 μM (184). Murine studies with the autophagy-enhancing drugs carbamazepine and rapamycin have shown a decreased load of Z-type AAT and may prompt human studies to explore ways to lower the risk of liver disease (185, 186). Results of a European study of inhaled pooled human plasma AAT are awaited (www.clinicaltrials.gov).

In summary, AATD remains an important challenge for clinicians for which emerging treatments show great promise in the future. Enhanced recognition is needed to avail affected individuals of current and future treatment.

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