CLINICAL PRACTICE

Alpha₁-Antitrypsin Deficiency

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This Journal *feature begins with a case vignette highlighting a common clinical problem.*
Evidence supporting various strategies is then presented, followed by a review of formal guidelines,
when they exist. The article ends with the authors' clinical recommendations.

A 60-year-old white man presents for evaluation of progressive dyspnea. He is a former smoker with a 20-pack-year smoking history and a 10-year history of diagnosed chronic obstructive pulmonary disease (COPD). There is no family history of COPD. Severe airflow obstruction is seen on spirometry, with a forced expiratory volume in 1 second (FEV₁) that is 40% of the predicted value. Should the patient be evaluated for alpha₁-antitrypsin (AAT) deficiency? If AAT deficiency is documented, how should his case be managed?

THE CLINICAL PROBLEM

AAT deficiency increases the risk of COPD, liver disease, and several other conditions. Although various definitions have been used, we define AAT deficiency as the inheritance of two severe deficiency alleles at the locus encoding AAT. AAT deficiency is relatively common in populations of European ancestry, with an estimated prevalence of 1 case per 3000 to 5000 persons in the United States.[1,2] The incidence of AAT deficiency in white newborns is similar to that of cystic fibrosis.[3] AAT is a serine protease inhibitor encoded by *SERPINA1* (also known as *PI*). AAT is a highly effective inhibitor of neutrophil elastase; an imbalance between levels of AAT and this elastase increases the risk of emphysema (Fig. 1A).

Most persons with AAT deficiency inherit two copies of the *PI*Z* allele (Table 1). Persons who inherit one of the heterogeneous group of *PI*Null* alleles, which result in the absence of AAT production, and one *PI*Z* allele (i.e., PI ZNull) are not readily distinguished from those who are homozygous for the *PI*Z* allele on the basis of serum AAT levels or protein phenotyping. Therefore, patients with the PI ZZ and PI ZNull genotypes are often clustered together as having the Z protein phenotype. The Z protein can form polymers that trap AAT within the rough endoplasmic reticulum of hepatocytes, the primary source of AAT synthesis, leading to reduced levels of circulating AAT in the bloodstream. Patients with the Z protein phenotype have approximately 15% of normal AAT levels. The accumulated AAT protein in hepatocytes appears to underlie the liver disease associated with AAT deficiency (Fig. 1B). The genetic, biochemical, and pathogenetic features of AAT deficiency have been reviewed previously.[4-11]

The natural history of AAT deficiency in adulthood remains poorly understood. AAT deficiency is recognized in less than 10% of persons in whom a diagnosis would be expected on the basis of screening studies in the general population. The diagnosis of AAT deficiency is generally made after the identification of COPD or liver disease or after the deficiency has been diagnosed in a family member. The health status of patients with undiagnosed AAT deficiency is uncertain, but many patients may not be substantially impaired. Cigarette smoking greatly increases the risk of COPD in patients with the Z protein phenotype.[12,13] Other risk factors for COPD in such patients are male sex and asthma.[14] Genetic modifiers of lung and liver disease

An audio version of this article is available at NEJM.org

A

Lung with predominantly
basilar panacinar
emphysema in AAT deficiency

Alveoli with panacinar destruction
and enlargement

Lung parenchyma viewed
with light microscopy

Enlarged
alveolar
airspaces

Destruction
of alveolar
septa

B

Liver affected by AAT

Hepatocytes with granules
representing aggregated AAT

Sinusoid

Polymerized AAT
molecules in a single granule

Granules

Hepatocyte

Polymerized AAT

Figure 1. Pathogenesis of Alpha$_1$-Antitrypsin (AAT) Deficiency.

Panel A shows a simplified representation of the mechanism for the development of emphysema in patients with AAT
deficiency. Gross pathological examination often reveals basilar panacinar emphysema, with alveolar septal destruc-
tion and airspace enlargement seen on light microscopy. Panel B provides an overview of liver disease in patients
with AAT deficiency. The liver has hepatocytes containing cytoplasmic globules, which are made up of polymerized
AAT molecules. The accumulation of these molecules appears to damage the liver, but there is no consensus re-
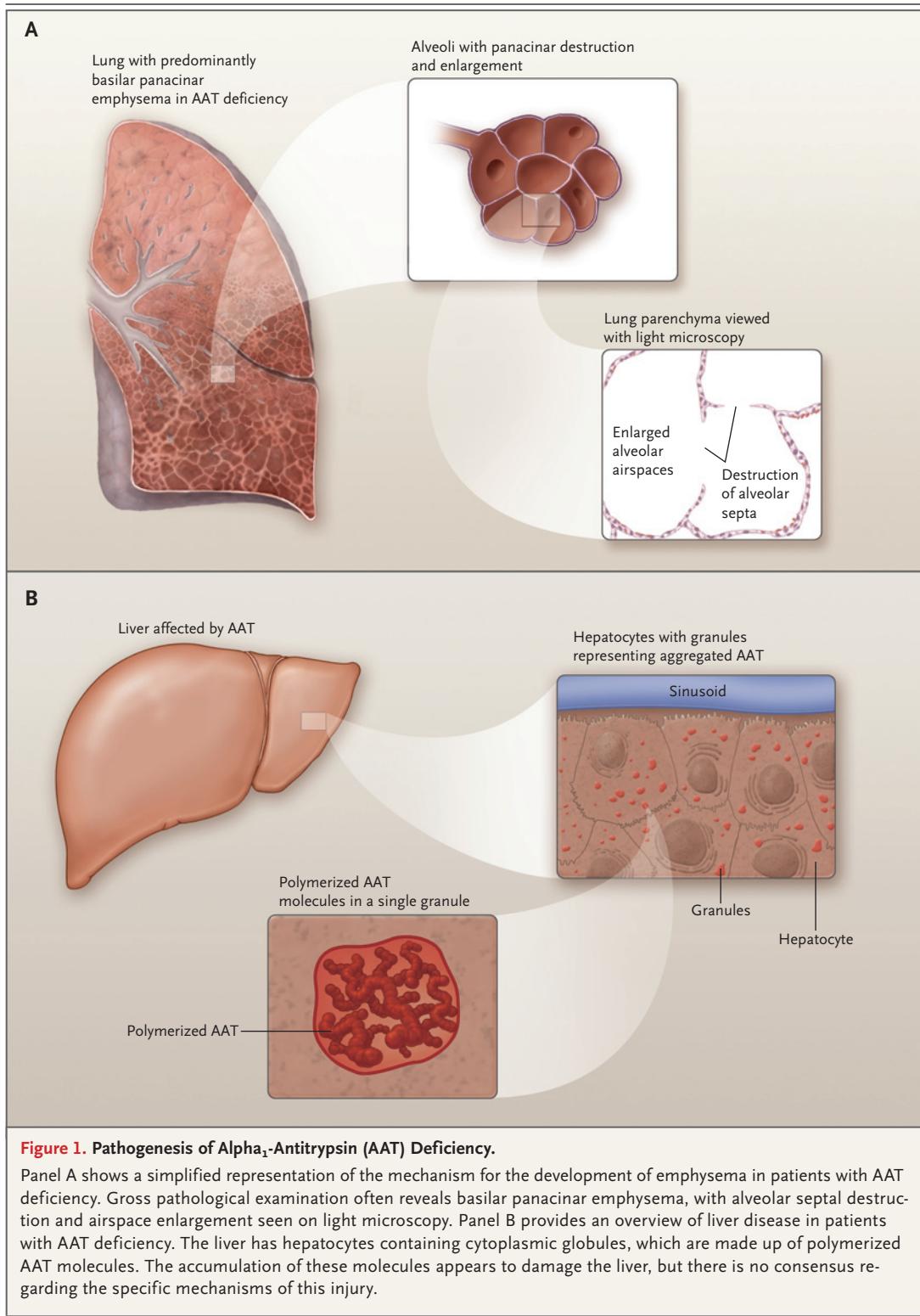garding the specific mechanisms of this injury.

Table 1. Diagnostic Tests for Alpha₁-Antitrypsin (AAT) Deficiency and Associated Disease Risks.*

Inherited Genetic Variants†	Protein Phenotype‡	Serum Protein Level§	Molecular Genotype¶	Risk of COPD	Risk of Liver Disease
ZZ	Z	Very low	ZZ	Very high	High
ZNull	Z	Very low	Z/non-S, non-Z	Very high	Unknown
MZ	MZ	Intermediate	Z/non-S, non-Z	Possibly increased	Possibly increased
MNull	M	Intermediate	Non-S, non-Z/non-S, non-Z	Unknown	None
SZ	SZ	Low	SZ	Increased	Possibly increased
NullNull	None	None	Non-S, non-Z/non-S, non-Z	Very high	None

* COPD denotes chronic obstructive pulmonary disease.
† Conventions for the description of AAT genotypes, protein phenotypes, and alleles are inconsistent. In this article, we have elected to use the convention of describing the genotype with the notation PI XX, in which X designates one of the two inherited *SERPINA1* (also called *PI*) alleles. For protein phenotypes, we have used X or XX, depending on whether one or two types of AAT protein are detected with isoelectric focusing, and we have used *PI*X* to describe a single allele of the *SERPINA1* gene.
‡ Among patients who are receiving AAT augmentation therapy, those with the PI ZZ and PI ZNull genotypes appear to have the MZ protein phenotype, and those with the PI NullNull genotype appear to have the M protein phenotype, since augmentation-therapy products are made up primarily of the M AAT protein.
§ Most hospital and commercial laboratories express their results in milligrams per deciliter in the United States and in grams per liter in Europe. The lower limit of the normal range for patients with the PI MM genotype is dependent on the laboratory but is generally 70 to 104 mg per deciliter (0.7 to 1.04 g per liter). Patients with the Z protein phenotype typically have AAT levels of 10 to 50 mg per deciliter (0.10 to 0.50 g per liter). A growing number of reference laboratories express AAT levels in micromoles per liter, with the lower limit of the normal range defined as 20 µmol per liter. Patients with the Z protein phenotype typically have levels of 2 to 10 µmol per liter. There is overlap between the levels seen in patients with a variety of heterozygous genotypes and in those with PI SS and PI MM genotypes. To convert the values for AAT from milligrams per deciliter to micromoles per liter, divide by 5.2 (based on the molecular weight of AAT of 52 kD).
¶ Molecular genotyping is typically performed with the use of allele-specific probes that detect *PI*S* and *PI*Z* alleles.

probably exist, although they remain largely undefined.[15,16]

The classic pulmonary presentation of AAT deficiency is severe, early-onset panacinar emphysema with a basilar predominance in adults (Fig. 1A and Fig. 2). However, emphysema may also occur in a diffuse distribution or predominantly in the upper lobes. Bronchiectasis, with or without concomitant emphysema, is less common.[17] Dyspnea is generally the prominent symptom, but chronic cough or wheezing may also occur.[18]

The majority of children with AAT deficiency with the Z protein phenotype who are identified through newborn screening have abnormal liver-function tests at some point during their first year of life. Approximately 10% of infants with the Z protein phenotype have prolonged obstructive jaundice, and about 2% present in childhood with liver failure requiring transplantation.[19,20] As these children age, there is an increasing risk of liver disease, including cirrhosis and hepatocellular carcinoma.[21] A postmortem study in Sweden suggested that adults with the Z protein phenotype who died from causes unrelated to AAT deficiency often had asymptomatic cirrhosis, and this risk increased with age.[22]

Most persons inherit two copies of the *PI*M* allele, which is associated with normal AAT levels. The *PI*S* allele is slightly more common than the *PI*Z* allele in most European populations and is associated with mildly reduced AAT levels. Available evidence suggests that patients with the PI MZ genotype may be at slightly increased risk for COPD and liver disease, but this association has not been proved.[23,24] Patients with the PI SZ genotype are at increased risk for COPD, especially if they smoke, as compared with those with the PI MM genotype, but they have a lower risk than those with the Z protein phenotype.[25]
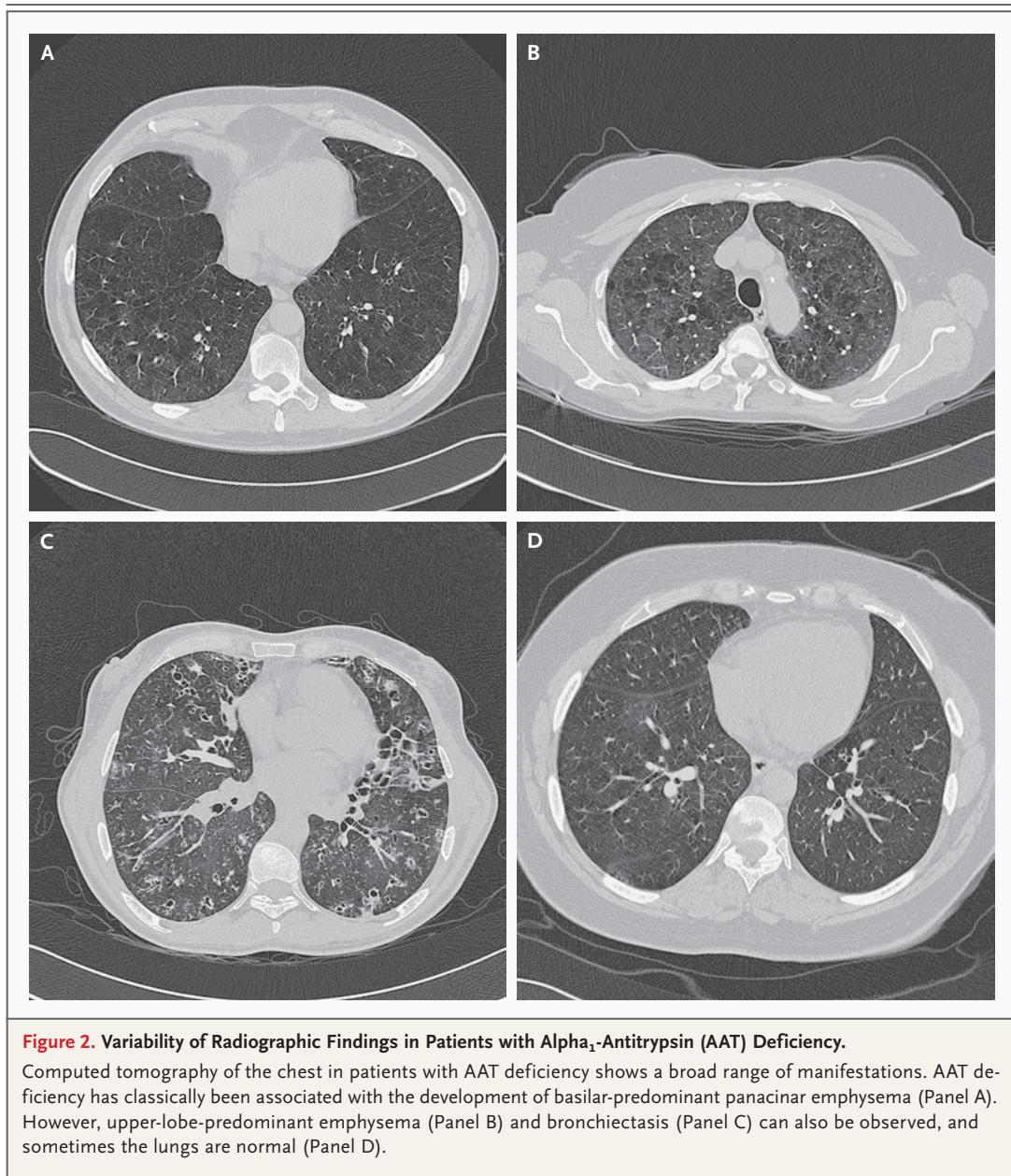
Figure 2. Variability of Radiographic Findings in Patients with Alpha$_1$-Antitrypsin (AAT) Deficiency.

Computed tomography of the chest in patients with AAT deficiency shows a broad range of manifestations. AAT deficiency has classically been associated with the development of basilar-predominant panacinar emphysema (Panel A). However, upper-lobe-predominant emphysema (Panel B) and bronchiectasis (Panel C) can also be observed, and sometimes the lungs are normal (Panel D).

STRATEGIES AND EVIDENCE

DIAGNOSIS

AAT deficiency remains undiagnosed in many patients, and there are often long delays between the onset of respiratory symptoms and diagnosis.[26,27] Approximately 1% of patients with COPD have AAT deficiency, and the condition is frequently not diagnosed. In some cases, the underdiagnosis of AAT deficiency may relate to perceived risks associated with testing for a genetic condition. It is recommended that patients be informed about risks of testing for AAT deficiency, including potential genetic discrimination, before testing is performed. The lack of studies demonstrating that increased AAT detection leads to improved health outcomes has led to varying approaches to AAT testing, but testing has been recommended for all patients with COPD, asthma with irreversible airflow obstruction, unexplained liver disease, or necrotizing panniculitis.[28]

Three strategies are commonly used to diag-

nose AAT deficiency: measurement of the serum or plasma protein level, AAT protein phenotyping of serum or plasma, and AAT genotyping (Table 1). The measurement of AAT levels is accurately performed in many laboratories and is a reasonable initial test,[29] but it has limitations. When an evaluation is performed on the basis of a family history of AAT deficiency, such testing may not detect persons who are heterozygous for a deficiency allele, who often have levels at or near the normal range. Since AAT is an acute-phase reactant, levels may rise substantially during illness or other types of inflammatory stress,[30,31] although they typically remain well below the normal range in AAT-deficient persons. A source of confusion in evaluating AAT levels is the variety of measurement units used to express the results. If the AAT protein level is below the normal range, further assessment with protein phenotyping or genotyping is recommended.

Protein phenotyping is performed at specialized laboratories by evaluating the isoform patterns of AAT protein with the use of an isoelectric focusing gel. One limitation of this approach is the inability to identify *PI*Null* alleles, since these variants produce no circulating protein.

Commercially available genotyping kits, which often use dried blood spots, are designed for the molecular identification of the most common abnormal AAT variants (*PI*S* and *PI*Z*). This approach can miss one of the more than 30 rare genetic variants that lead to reduced protein levels (e.g., *PI*M*$_{heerlen}$), absent protein levels (assorted *PI*Null* alleles), or normal levels of a dysfunctional protein (e.g., *PI*F*).[32] Uncommon genetic variants can also lead to confusion about paternity if they are not properly assessed. To overcome these limitations, the testing of levels or protein phenotyping should be performed with genotype testing.

EVALUATION AND FOLLOW-UP

The evaluation and treatment of AAT-deficient patients are summarized in Figure 3. The taking of a medical history and the physical examination should include assessment for COPD and signs of chronic liver disease, as well as less common manifestations of severe AAT deficiency: necrotizing panniculitis[33] and vasculitis, primarily anti–proteinase-3-positive vasculitis (e.g., Wegener's granulomatosis).[34] A detailed family history and assessment of environmental and occupational exposures (e.g., to smoking or occupational dust) is impor-

tant. After the diagnosis of AAT deficiency is confirmed, referral to specialists in lung and liver diseases with experience in managing AAT deficiency is recommended. Baseline evaluation should include assessment of liver and pulmonary function, including spirometry (both before and after bronchodilation) and testing of lung volumes and diffusing capacity of the lungs for carbon monoxide.[28]

COPD that is associated with AAT deficiency rarely develops before the age of 30 years.[35] To monitor for the development or progression of COPD in patients with AAT deficiency, annual pulmonary-function testing (spirometry and testing of lung volumes and diffusing capacity of the lungs for carbon monoxide) is recommended for patients over the age of 30 years or in younger patients with respiratory symptoms. Chest radiography may help to rule out other lung conditions but is not sensitive for the detection of emphysema. Chest computed tomography (CT) may identify bronchiectasis and provide details on the severity of emphysema, but the associated radiation exposure argues against the frequent use of CT. Evaluation of oxygenation should be performed in patients with COPD.

When a patient with the PI ZZ genotype presents with chronic liver disease, other causes should be considered. Liver biopsy is not typically required to diagnose AAT-related liver disease, but it may be helpful in certain cases to rule out other causes of liver disease and to assess severity. In addition to taking a medical history and performing a physical examination, varying strategies are used to assess for the development of liver disease in AAT-deficient patients. These strategies range from measuring liver function (generally on an annual basis) to obtaining a liver-biopsy specimen. Some hepatologists use abdominal ultrasonography and testing of alpha-fetoprotein levels to monitor patients for hepatocellular carcinoma, but the appropriate frequency and role of these tests are uncertain. AAT testing of relatives should be discussed with patients who have AAT deficiency. Testing of siblings is strongly recommended.[28]

TREATMENT

Lung Disease

All patients (including those without documented lung disease) should be counseled regarding smoking cessation; vaccination is warranted against
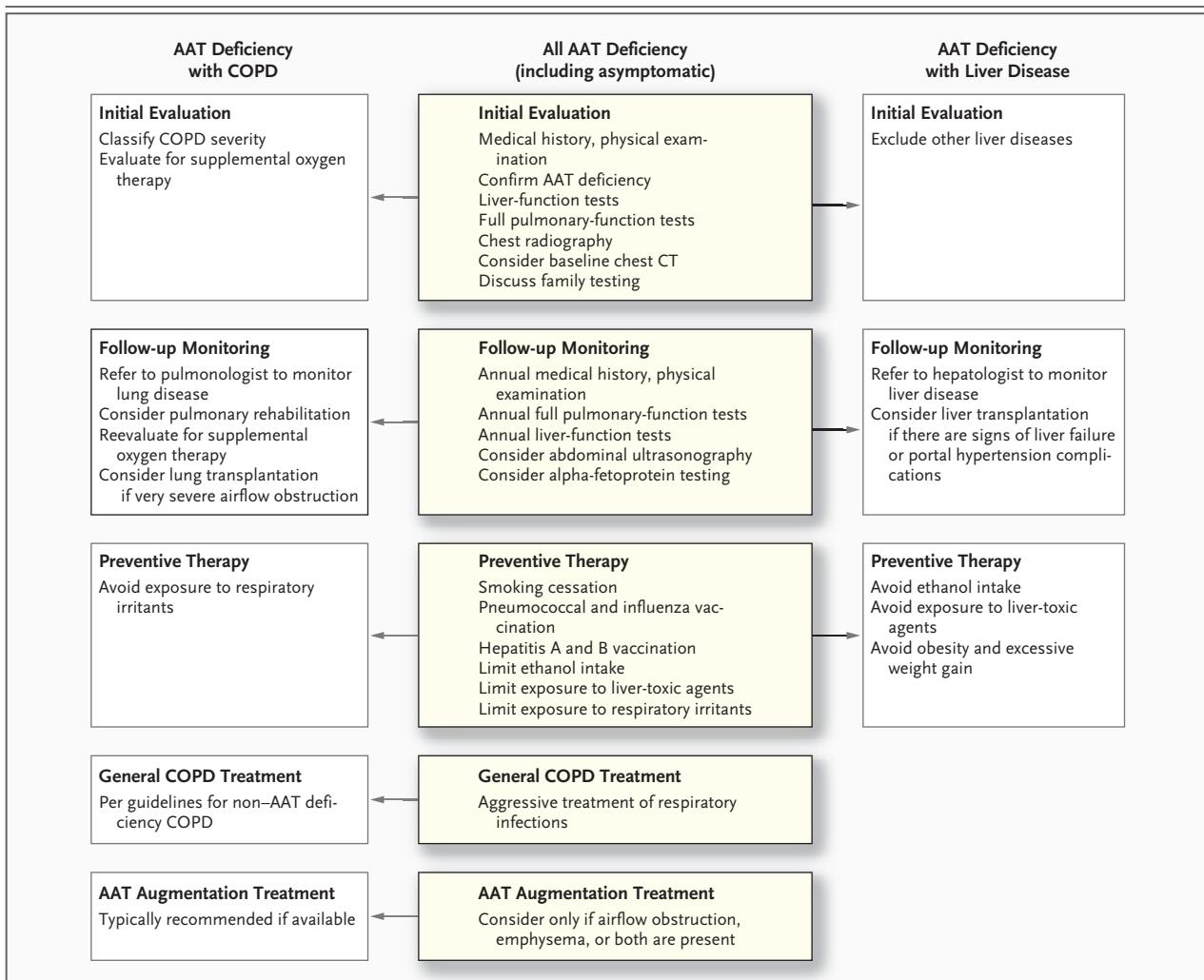
Figure 3. Evaluation and Management of Alpha₁-Antitrypsin (AAT) Deficiency.

Additional evaluation and management considerations recommended for patients with chronic obstructive pulmonary disease (COPD) or liver disease are shown. For children, chest computed tomography (CT) and annual testing of full pulmonary function are not typically recommended. The appropriate role and frequency of some follow-up monitoring tests, including alpha-fetoprotein testing and abdominal ultrasonography, have not been determined.

pneumococcal infection (despite the lack of compelling data for efficacy in COPD)[36] and influenza. Treatment with bronchodilators and inhaled-corticosteroid medications and pulmonary rehabilitation are recommended, as in cases of COPD unrelated to AAT deficiency, with increased intensity of therapy guided by disease severity.[37] However, the use of these guidelines specifically in AAT-deficient patients has not been formally assessed.

Surgical options for severe COPD include lung-volume reduction and lung transplantation. In the National Emphysema Treatment Trial,[38] a randomized trial of lung-volume reduction, the subgroup of patients with basilar-predominant emphysema, which is common in AAT deficiency, had no significant decrease in mortality or improvement in exercise capacity with surgery. In addition, in a small observational study involving AAT-deficient patients who underwent lung-volume reduction, improvements in pulmonary function were inconsistent, and any improvements were usually short-lived.[39] Because COPD often develops at an early age in AAT-deficient patients, they tend to be good candidates for lung transplantation. Case series suggest that AAT-deficient patients who have undergone bilateral lung transplantation have im-

proved rates of survival, as compared with those receiving single lung transplants,[40,41] but this finding remains controversial.[42]

Although definitive evidence is lacking, early antibiotic treatment is often recommended by experts in AAT deficiency for suspected bacterial respiratory infections, with the aim of minimizing the time that the lungs are exposed to an excessive neutrophil burden.[28]

Specific therapy for AAT deficiency–related lung disease is available as intravenous augmentation therapy[43] that uses a partially purified plasma preparation highly enriched for AAT. Several observational studies have suggested that AAT augmentation therapy may slow the rate of decline in lung function in the subgroup of AAT-deficient patients with moderate-to-severe airflow obstruction (variably defined in different studies),[44-46] although this subgroup analysis was not prespecified in those studies. In two randomized, controlled trials of augmentation therapy, patients had marginally significant reductions in the progression of emphysema, as assessed on quantitative CT densitometry ($P=0.07$ in one study[47] and $P=0.05$ to 0.08, depending on the analytical method, in the other study[48]). Neither study showed significant slowing in the decline in FEV_1, but both trials had limited statistical power to detect such differences.

AAT augmentation therapy has been approved by the Food and Drug Administration (FDA) for patients with AAT deficiency (defined as a protein level <11 μmol per liter) who have COPD, but this therapy is not available worldwide. The threshold level of AAT that is used to qualify patients for augmentation therapy is based on the plasma levels in patients with the PI SS genotype, who do not appear to be at increased risk for COPD, and in those with the PI SZ genotype, who appear to be at increased risk. The FDA-approved regimen of weekly intravenous infusions has been the most studied therapy, although biweekly and monthly regimens are sometimes used. Three plasma-derived drug products are available in the United States: Prolastin, Zemaira, and Aralast NP. There is no definitive evidence to suggest superiority of any one formulation; Zemaira and Aralast NP were approved for use on the basis of small noninferiority studies comparing them to Prolastin, the first approved AAT product. Adverse reactions to augmentation therapy (headache, dizziness, nausea, and dyspnea) are rare (<0.03 event per patient-month) and are generally mild.[49] Augmentation therapy is expensive ($60,000 to $150,000 per year, depending on body weight, pricing, and the cost of nursing care), involves infusing a blood product, and requires lifelong treatment.

Liver Disease

Early detection of liver disease in patients with AAT deficiency is difficult, and specific therapy is not currently available. AAT augmentation therapy is not intended to treat liver disease. Vaccination against hepatitis A and B is recommended for all AAT-deficient patients, who may be at increased risk for chronic liver disease after hepatitis virus infection.[50] Therapies for liver failure and portal hypertension related to AAT deficiency are the same as those for such diseases when they are associated with other factors: dietary modification (e.g., low-protein diet), medications, endoscopic and medical treatment of esophageal varices, and surgical approaches, including portosystemic shunting and (for end-stage liver failure) liver transplantation, which also cures AAT deficiency. Excessive weight gain and obesity should be avoided; nonalcoholic fatty liver disease has been shown to worsen many other forms of chronic liver disease. Ethanol intake should be avoided in patients with liver disease. Clinical experience indicates that elevations in liver enzymes in AAT-deficient patients may normalize after abstinence from ethanol.

Necrotizing panniculitis that is associated with AAT deficiency, a rare condition characterized by localized necrosis of the subcutaneous fat, presents as painful, discolored, suppurative lesions that often heal with scar formation.[51] Case reports suggest that AAT augmentation therapy (at the same doses used to treat lung disease) can be rapidly effective.[33] There is currently no evidence that AAT augmentation therapy is effective in the treatment of Wegener's granulomatosis associated with AAT deficiency.

AREAS OF UNCERTAINTY

The effectiveness of AAT augmentation therapy in slowing the progression of COPD related to AAT deficiency has not been conclusively shown. The role of augmentation therapy in patients with the SZ protein phenotype, who may be just above or just below the threshold of 11 μmol per liter for

AAT on any particular day, is highly controversial. Although widely used, this threshold may not be the optimal criterion for treatment. There is no evidence to support the use of augmentation therapy in patients with the MZ or MS protein phenotype[52] or in AAT-deficient patients with normal lung-function tests. The optimal dose of augmentation is uncertain.

Current methods for detecting early lung and liver disease and for assessing the progression of these diseases in patients with AAT deficiency are inadequate. Quantitative emphysema assessment on the basis of chest CT densitometry may help identify early emphysema and emphysema progression, but additional study is required before such a measure is used in routine care. It is plausible that earlier (and increased) detection of AAT deficiency may result in improved outcomes; however, studies are lacking to confirm this hypothesis. More research is needed to understand genetic and environmental factors that may modify clinical disease risks in AAT-deficient patients.

GUIDELINES

Guidelines of the American Thoracic Society and the European Respiratory Society recommend AAT testing for all patients with COPD, emphysema, or asthma with irreversible airflow obstruction,[28] although these recommendations are often not followed in practice. The Global Initiative for Chronic Obstructive Lung Disease recommends AAT testing specifically for patients with early-onset COPD (under the age of 45 years) or with a strong family history of COPD.[37] The guidelines of the American Thoracic Society and the European Respiratory Society recommend AAT augmentation therapy for patients with airflow obstruction related to AAT deficiency.[28]

CONCLUSIONS AND RECOMMENDATIONS

AAT deficiency is often unrecognized and may lead to COPD and severe liver disease. AAT deficiency can be readily diagnosed by measurement of the serum or plasma protein level, which should be confirmed by assessing the genotype or protein phenotype when AAT levels are below the normal range. According to professional guidelines, AAT testing is warranted in the patient in the vignette, given his diagnosis of COPD.[28] In patients with AAT deficiency, close monitoring for the development or progression of lung disease or liver disease (among those with at-risk genotypes) is required (Fig. 3). In addition to usual therapies for COPD in patients with AAT deficiency, AAT augmentation therapy should be considered (if available), although compelling evidence of benefit is lacking from randomized trials. Consultation with specialists in lung and liver diseases with experience in AAT deficiency is recommended. Additional information about AAT deficiency is available from the Alpha-1 Foundation (www.alphaone.org).

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