GUIDANCE FOR TESTING, DIAGNOSIS, AND TREATMENT OF ALPHA-1 ANTITRYPSIN (AAT) DEFICIENCY

From the GOLD 2019 Report[1]
and ATS-ERS 2003 Standards[2]

GOLD 2019 Report[1]

In 2019, the Global Initiative for Chronic Obstructive Lung Disease released a consensus report, Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD 2019 Report). The aim of this report is to provide a nonbiased review of the current evidence for the assessment, diagnosis, and treatment of patients with COPD that can aid clinicians. The recommendations are based on the best scientific information and important literature in COPD research and care available through July 2018.

ATS-ERS 2003 Standards[2]

The American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals With Alpha-1 Antitrypsin Deficiency (ATS-ERS 2003 Standards) presented the views of a large international group of experts regarding the diagnosis and management of individuals with AAT deficiency, using a systematic review and evidence-based approach. The Standards were approved in 2003.

Interpreting test results

The severity of a patient's alpha-1 antitrypsin (AAT) deficiency is based on AAT serum levels and the phenotypes of altered alleles.[2] Understanding the clinical relevance of each phenotype helps identify potential candidates for treatment.

- Quantitative AAT levels help to identify at-risk individuals but it is important to note that AAT levels may change with inflammatory conditions[2]
- To provide a confirmatory qualitative evaluation of their AAT deficiency, subjects with abnormal AAT serum levels should be investigated further[2]
- Qualitative testing includes phenotyping (PI-typing) using isoelectric focusing to identify AAT variants, and AAT genotyping for molecular diagnosis[2]

RANGE OF AAT SERUM LEVELS ACCORDING TO PHENOTYPE*[2,3]

Patient phenotype	Status of AAT alleles	AAT serum levels	
		Purified standard	Typical commercial standard*
MM	Normal	20-48 μM	150-350 mg/dL
MNull	1 normal allele	<11 μM	<80 mg/dL
MS	1 mildly deficient allele	18-52 μM	110-340 mg/dL
MZ	1 severely deficient allele	17-33 μM	90-210 mg/dL
SS	2 mildly deficient alleles	15-33 μM	100-200 mg/dL
SZ	2 different deficient alleles	8-16 μM	75-120 mg/dL
ZZ	2 severely deficient alleles	2.5-7 μM	20-45 mg/dL
Null/Null	Mutated AAT alleles	No AAT produced	

This list is not inclusive of all possible AAT genetic variants.

*Serum levels given are measured using a typical commercial standard (mg/dL) and the purified standard (μM) used in the US Registry. A level of <11 μM is associated with an increased risk for emphysema.[2]

The GOLD 2019 Report and ATS-ERS Standards recommend alpha-1 testing for all COPD patients[1,2]

Testing is recommended for:

- Adults with symptomatic emphysema[2] or COPD[1,2]
- Adults with asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators[2]
- Individuals with unexplained liver disease[2]
- Siblings of an individual with AAT deficiency[2]
- Adults with necrotizing panniculitis[2]
- Asymptomatic individuals with persistent obstruction on pulmonary function tests with identifiable risk factors (eg, cigarette smoking, occupational exposure)[2]

Testing should be discussed for:

- Adults with bronchiectasis without evident etiology[2]
- Asymptomatic individuals with persistent airflow obstruction and no risk factors[2]
- Adults with C-ANCA-positive (anti-proteinase 3-positive)[2]

Considerations for augmentation therapy

AAT serum levels and pulmonary function of an AAT-deficient patient help determine whether the patient is an appropriate candidate to receive augmentation therapy and when.[1,2]

ACCORDING TO ATS-ERS STANDARDS[2]:

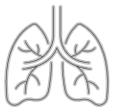
Consider augmentation therapy if:

- **AAT serum level <11.0 μM (level of evidence II-2*):** Consideration for treatment is independent of the phenotype and based on level and presence of obstructive lung disease[2]
- **FEV_1 (postbronchodilation) 30%-65% predicted (level of evidence II-2*):** Subjects with normal or nearly normal pulmonary function can be treated if they experience a rapid decline in lung function (change in FEV_1 >120 mL/year). Patients with very poor lung function, already treated, should be kept on treatment[2]
- In the 2003 ATS-ERS Standards, recommendations regarding the impact of augmentation therapy on progression of emphysema were based on limited evidence available from observational studies and only a single randomized placebo-controlled trial[2]

Recommendations against augmentation therapy:

- Augmentation therapy is not currently recommended for individuals without emphysema, and benefits in individuals with severe (eg, FEV_1 ≤35% predicted) or mild (eg, FEV_1 ≥50%-60% predicted) airflow obstruction are less clear
- Insufficient evidence regarding augmentation therapy in patients who have undergone lung transplantation precludes a firm recommendation†

*Grade of evidence II-2: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one center or research group.
†However, it has been observed that inflammation results in free elastase activity in epithelial lining fluid in individuals who have undergone lung transplantation (eg, during acute rejection and infection). ATS-ERS Standards favor augmentation therapy for lung transplant recipients during such episodes.[2]



ACCORDING TO THE GOLD 2019 REPORT[1]:

Considerations for augmentation therapy:

- Never or ex-smokers with an FEV_1 of 35%-60% predicted have been suggested as those most suitable for augmentation therapy (Evidence B‡)[1]
- The evidence for augmentation therapy efficacy varies according to the outcome studied. IV augmentation therapy has been recommended for individuals with AAT deficiency and FEV_1 of ≤65% based on previous observational studies. A recent study based on CT scan as an outcome has recommended consideration for patients with progressive lung disease and FEV_1 >65%. Individual discussion is recommended based on the cost of therapy and lack of evidence for significant benefit
- Because AAT deficiency is rare, formal clinical trials to assess efficacy with conventional spirometric outcome have never been undertaken

Recommendation against augmentation therapy:

- Individuals without evidence of continued and rapid emphysema progression following smoking cessation

‡Evidence Category B: Evidence is from randomized clinical trials (RCTs) with important limitations or when there is limited body of evidence.

Additional examinations for patients with AAT deficiency

- **Full lung function testing:** Assess spirometry, static lung volumes, arterial blood gas analysis, and gas transfer at baseline; perform spirometry annually[2]
- **Chest CT scan:** Consider as a definitive technique to detect and quantify emphysema and to monitor progression[2]
- **Liver disease monitoring:** Regular assessment by physical exam, liver function tests, and ultrasound examination[2]

Initiating augmentation therapy

Manage the risk factors[2]

Advise patients on techniques to prevent further lung damage:

- Early smoking cessation, including pharmacologic aids as appropriate, to slow FEV_1 decline
- Control of respiratory infection and bronchial hyperreactivity
- Minimizing exposure to respiratory irritants (eg, secondhand smoke, dust, and fumes), including change of job if necessary
- Influenza and pneumococcal vaccination; hepatitis B vaccination in patients with overt liver disease

Consider additional medical treatment options[2]

Consider use of bronchodilators, physical activity as tolerated, inhaled steroids, antibiotics, oxygen, oral corticosteroids, treatment for depression and panic, and pulmonary rehabilitation.

Rare expertise

Our Takeda team of dedicated experts is committed to working with clinicians to advance the management of AAT for the good of the alpha-1 community.

References: 1. Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J.* 2019;53(5):1900164. doi:10.1183/13993003.00164-2019. **2.** American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. The Alpha-1 Antitrypsin Deficiency Task Force. *Am J Respir Crit Care Med.* 2003;168(7):818-900. **3.** Exeter Clinical Laboratory International. Alpha-1-Antitrypsin Blood Sciences Test. https://www.exeterlaboratory.com/test/alpha-1-antitrypsin/. Accessed August 7, 2019.