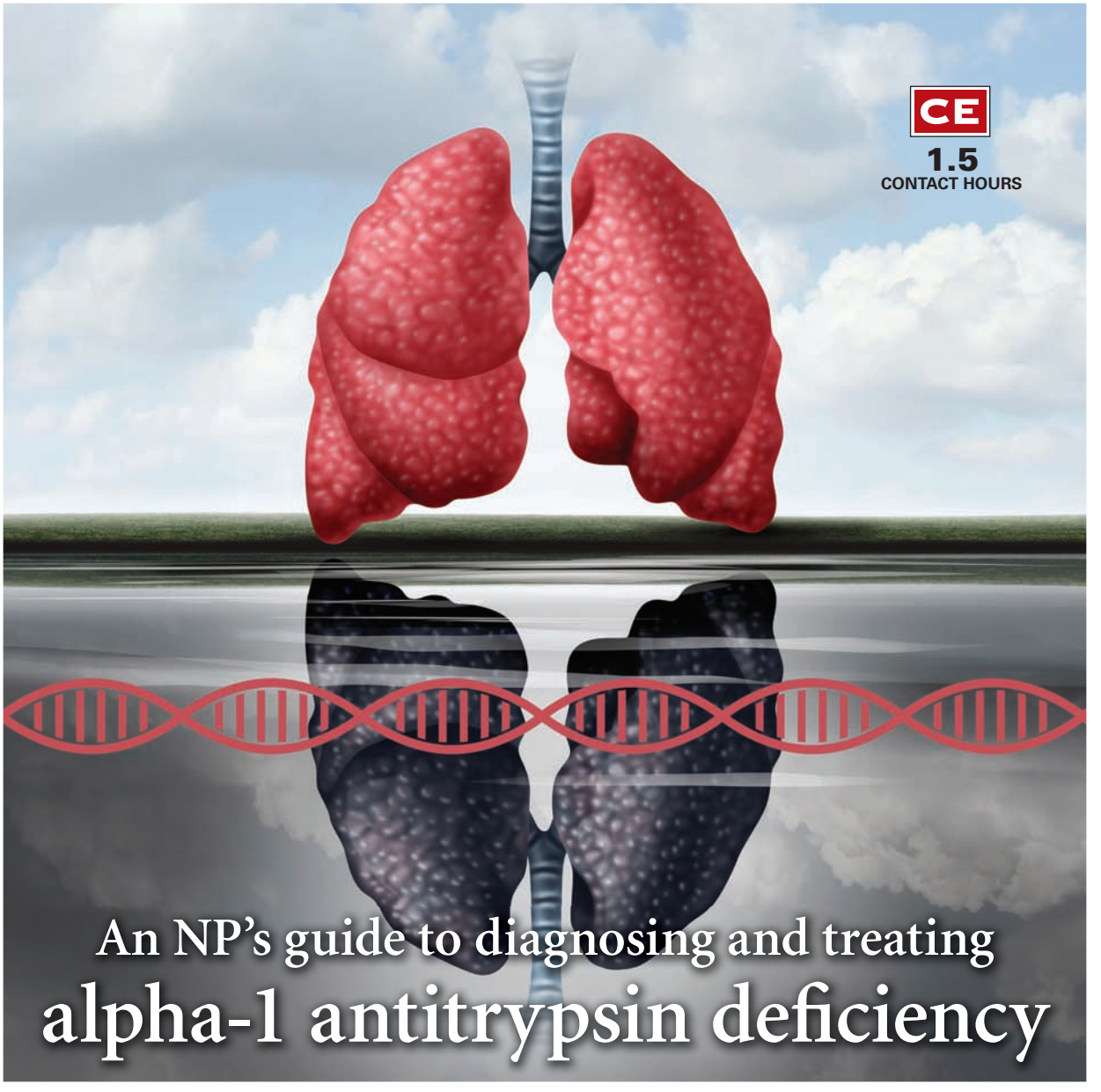

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An NP's guide to diagnosing and treating alpha-1 antitrypsin deficiency

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By Judith A. Newell, FNP-BC; Christine Donahue, MSN, NP; and D. Kyle Hogarth, MD, FCCP

Abstract: As NPs play an increasingly vital role in primary care, they must be well versed in a variety of conditions. Alpha-1 antitrypsin (AAT) deficiency is a respiratory disease for which there is particularly low awareness in both the nursing profession and the wider medical community. This article provides an overview of AAT deficiency and includes guidance for diagnosing the disease.

Alpha-1 antitrypsin (AAT) deficiency is a common genetic condition characterized by low serum levels of AAT, which is a major circulating serine protease inhibitor (PI).[1] AAT is synthesized in the liver, and has a key role in inhibiting neutrophil elastase, thereby protecting tissues, particularly the lungs, from degradation. AAT deficiency occurs as a result of mutations in the *SERPINA1* gene, which encodes AAT, and is inherited as an autosomal codominant condition.[1]

Absence or deficiency of AAT accelerates lung tissue degradation and increases an individual's risk for the development of chronic obstructive pulmonary disease (COPD) and early-onset emphysema, particularly in

Keywords: AAT, alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease, computed tomography, emphysema, genetic conditions, genetic testing

those who smoke.[2] AAT deficiency is also associated with extrapulmonary complications, primarily liver disease, the onset of which varies but can be as early as childhood. Other uncommon extrapulmonary symptoms can include granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis), vasculitis, and necrotizing panniculitis.[3,4]

There are approximately 1.5 million individuals worldwide with the more common severe AAT deficiency genotypes (PI*ZZ and PI*SZ); however, the condition remains underrecognized and underdiagnosed.[5] Data from 2005 suggest that only 5% of the 100,000 individuals thought to be affected by AAT deficiency in the US have been diagnosed.[6] Another study involving physicians in Europe found that few physicians routinely test for the condition. This can be attributed in part to a lack of awareness about the disease.[7] No unique clinical feature points to a definitive diagnosis of AAT deficiency, and significant delays exist between symptom onset and initial diagnosis, with patients often seeing multiple physicians before an accurate diagnosis is made.[6-8]

In the US, NPs are increasingly central to providing primary care, often serving as the first point of contact for patients, and thus are in a unique position to significantly impact patient care.[9,10] NPs in the US play a key role in educating patients about chronic diseases such as COPD. These types of patient interactions occur more commonly with NPs than with physicians.[11] This review aims to increase awareness of AAT deficiency and educate the advanced practice nursing and primary care communities about the disease, with an emphasis on identifying symptoms and diagnosing. In addition, case scenarios illustrating different presentations of AAT deficiency are provided to encourage integration of screening and testing into regular practice.

Suspected AAT deficiency: Identifying patients

As previously mentioned, no specific respiratory symptoms point to a definitive diagnosis of AAT deficiency. In a large registry study of patients with AAT deficiency, asthma-like symptoms, including dyspnea (84%), wheezing with and without upper respiratory tract infection (76% and 65%, respectively), cough (42%), and cough with mucus production (50%) were reported.[12] Overall, these pulmonary manifestations have been found to overlap the entire spectrum of disorders associated with COPD. A survey of patients with a diagnosis of AAT deficiency reported that the majority of participants (81%) had COPD with symptoms of asthma, chronic bronchitis, and emphysema, usually in combination, and a subset of patients (5.3%) developed liver disease in combination with lung manifestations.[13] The overall risk for the development of emphysema in severe AAT deficiency is not fully understood, although smoking is a particularly strong predictor of greater lung function decline in patients with AAT deficiency.[14] In individuals with severe AAT deficiency (PI*ZZ) who smoke, the forced expiratory volume in 1 second (FEV_1) percentage predicted value was found to be approximately half that of individuals who never smoked.[2]

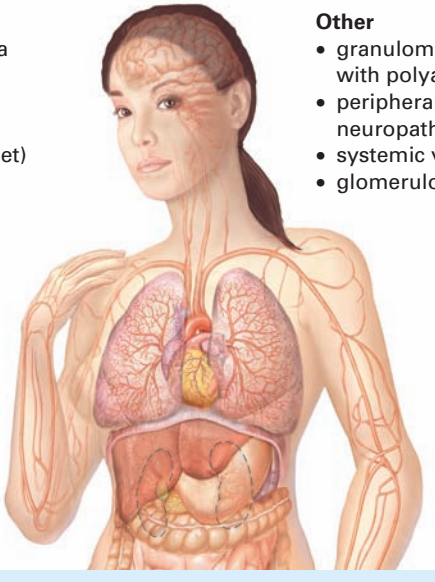
Given the heterogeneity in AAT deficiency presentation, the strategy for identification should be to rule out the disease based on a number of warning signs (see *Clinical presentations associated with AAT deficiency*).[15-17] Below are four theoretical scenarios based on the authors' expe-

Clinical presentations associated with AAT deficiency[15-17]

Lung
- COPD/emphysema
- bronchiectasis (without evident etiology)
- asthma (adult-onset)

Liver
- cirrhosis
- heptocarcinoma
- neonatal cholestasis

Skin
- nectrotizing panniculitis
- necrotizing vasculitis
- psoriasis
- chronic urticarial

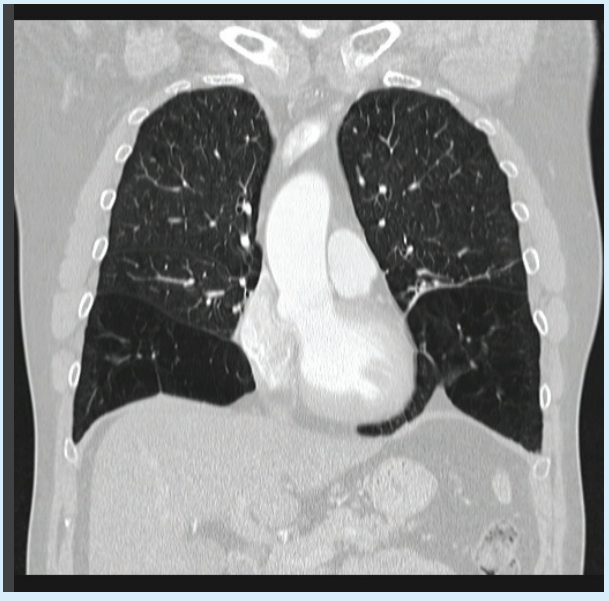


Other
- granulomatosis with polyangiitis
- peripheral neuropathy
- systemic vasculitis
- glomerulonephritis

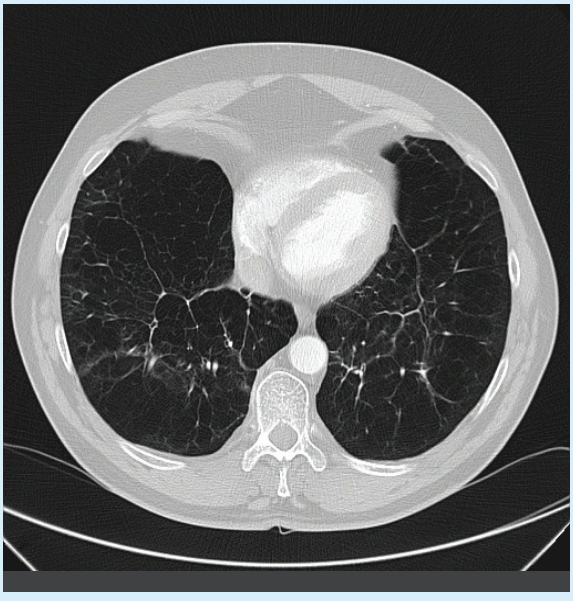
Art courtesy of the Anatomical Chart Company

Lung CT scan images of a patient with AAT deficiency and predominantly basal emphysema

A. Coronal cut of CT scan



B. Axial image from the same CT scan



Images courtesy of Prof. A. Rembert Koczulla, MD, Philips University, Marburg, Germany.
CT, computed tomography.

rience highlighting the diversity of symptom presentation in AAT deficiency.

Scenario 1

A 40-year-old male smoker (20 pack years) visited the ED twice in the past year with dyspnea. Asthma was suspected, and nebulized albuterol was administered on both occasions. The patient's symptoms improved, and he was discharged. However, the patient experienced a long recovery time and some limitations during strenuous exercise. He presented again at the ED and was found to have dyspnea and elevated temperature, C-reactive protein levels, and white blood cell count. The patient was prescribed antibiotics for suspected community-acquired pneumonia. His pulmonary function tests showed signs of obstructive lung disease, and investigation of medical history revealed no previous diagnosis of asthma and no allergies prior to earlier admissions. His radiologic assessment of the lungs by computed tomography (CT) scan showed signs of emphysema, predominately in the basal regions.

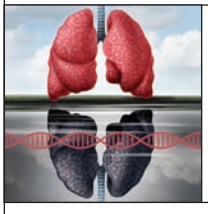
This case scenario describes the classic presentation of AAT deficiency. The disease most commonly affects white males around the age of 40 years who are smokers with wheezing and/or dyspnea.[18] In this scenario, the absence of childhood asthma and presence of frequent exacerbations point toward AAT deficiency. As previously discussed, epidemiologic data suggest that individuals with AAT deficiency who smoke are likely to develop signs and symptoms earlier in life.[19] The presence and extent of emphysema should be assessed by CT, although one-third of patients with AAT deficiency develop predominately apical disease. Predominant basal emphysema is the classic presentation.[20] (See *Lung CT scan images of a patient with AAT deficiency and predominantly basal emphysema*.) Radiologically confirmed emphysema, in addition to the symptoms described in scenario 1, means the patient may be eligible for AAT therapy. At this stage, referral to a pulmonologist and close monitoring should occur. These topics are discussed later in this article.

Scenario 2

A 30-year-old female long-distance runner (nonsmoker) observed a decline in her stamina in recent years, despite no change in training routines and no injuries or infections. The patient was followed up over the span of 2 years in an asthma clinic, and despite generally good health, a slight decline in spirometry measurements was

noted. She was referred to a respiratory center, and CT scans revealed early signs of emphysema.

The above case represents early detection of AAT deficiency. A longitudinal follow-up study of individuals in Sweden with AAT deficiency, who were identified by neonatal screening, found that at age 30, these individuals had largely normal lung function.[21] In contrast, data from the UK Antitrypsin Deficiency Assessment and Programme for Treatment registry suggest that CT scans can show signs of lung disease even at this early stage.[22] As above, the onset of symptoms in early-stage disease may be more noticeable to patients who regularly engage in strenuous aerobic activity, owing to greater self-monitoring of physical performance. In addition, a family history of COPD can also point toward AAT deficiency.



Any primary clinic can test for AAT deficiency; the most accessible diagnostic method is measurement of AAT levels.

Scenario 3

A 60-year-old male presented at a primary care center with mild dyspnea and a nonproductive cough. He was in otherwise good health, with no history of cardiovascular disease. He was a former smoker who stopped 30 years ago. Viral chest infection was suspected, and the patient was prescribed an albuterol inhaler. Three months later, the patient returned with no improvement of symptoms and no indication of bacterial infection. COPD was suspected, and he was prescribed a long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA).

This example represents a late diagnosis of AAT deficiency, with the onset of symptoms delayed by smoking cessation early in life. At the time of diagnosis, approximately 80% of patients with AAT deficiency have been found to be former or current smokers, with an average 23 pack years.[23] In individuals with AAT deficiency who never smoked, symptoms may never manifest or may develop at an advanced age.[24]

Scenario 4

A 55-year-old male (nonsmoker) presented at a primary care setting with generalized symptoms of fatigue and nausea. A full blood workup was ordered, and results revealed elevated alanine and aspartate aminotransferases in addition to moderately elevated bilirubin. The patient consumes alcohol moderately, with no previous history of alcohol abuse, and tested negative for viral hepatitis.

In the above example, liver disease may have been caused by the accumulation of abnormal AAT proteins within hepatocytes.[1] Some but not all patients with AAT deficiency will develop liver disease in addition to obstructive lung disease, whereas in a minority, liver disease may be the only clinical manifestation.[13,17] Severe liver disease in AAT deficiency usually develops later in life. Cirrhosis is a more common cause of death in patients older than age 50 who never smoked than in younger patients who smoke.[17] However, AAT deficiency-related liver dysfunction can also present in childhood, often as severe, prolonged jaundice in neonates.[17] For patients with AAT deficiency and severe liver disease, such as cirrhosis or liver failure, liver transplantation is the only treatment option.

Confirming AAT deficiency

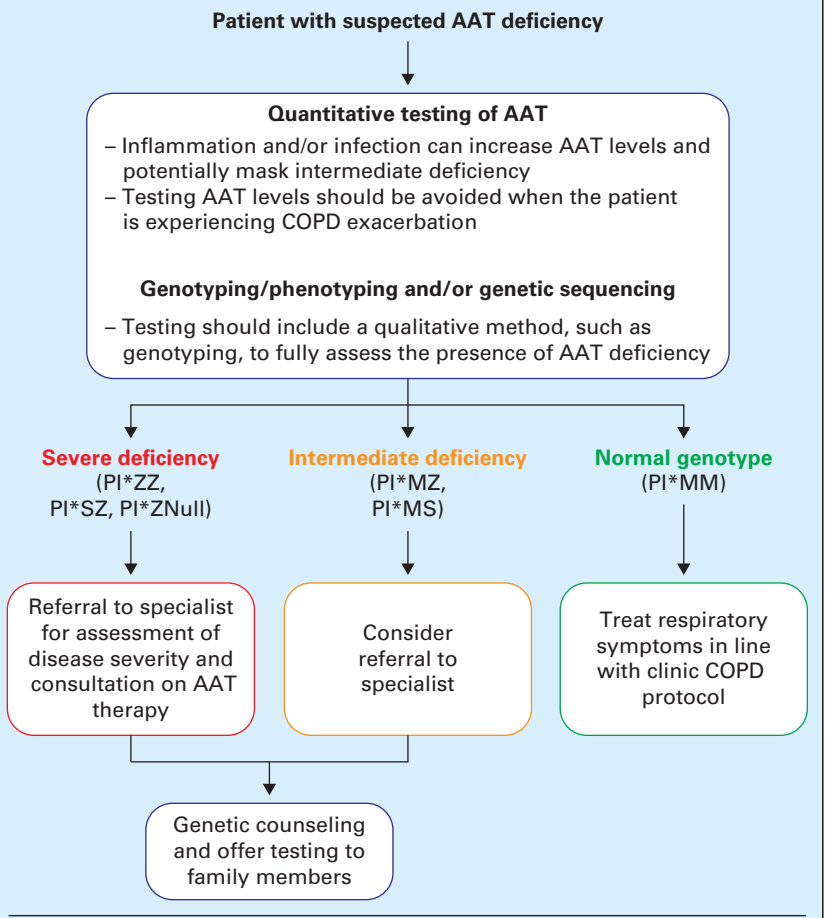
Testing. Patients presenting with any of the potential clinical manifestations *associated with AAT deficiency* should be tested for AAT deficiency. Particularly strong recommendations from recent guidelines are to test all individuals with COPD (regardless of age, ethnicity, or smoking history), emphysema, chronic obstructive asthma, unexplained liver disease, necrotizing panniculitis, and GPA for AAT deficiency.[1] A range of tests is available to confirm or rule out the diagnosis of AAT deficiency (see *AAT deficiency testing flow*).[25] Any primary clinic can test for AAT deficiency; the most accessible diagnostic method is measurement of AAT levels. The normal range for AAT levels is 83 to 220 mg/dL as measured by nephelometry, and individuals with the most common severe deficiency genotype (PI*ZZ) typically exhibit levels in the range 20 to 45 mg/dL.[17] However, testing levels should usually be accompanied by a form of qualitative assessment such as genotyping. To ensure comprehensive testing, several active national screening programs are available that provide finger-stick blood sampling kits, which can be submitted for free testing. Accurate diagnoses aid patient management and allow the impact a positive diagnosis has on both

patients and their family members to be assessed.[1]

Although genetic testing is essential to obtain an accurate diagnosis of AAT deficiency, several considerations relevant to any genetic assessment should be taken in account. First, it is essential that informed consent be obtained, and the potential wider ramifications of a positive test on family members should be discussed. Although a positive test result has the potential to cause anxiety and depression, a large survey of patients with AAT deficiency in the US revealed that, in general, the positives of a patient knowing their AAT deficiency status outweighed the negative psychological impact, and patients generally anticipated having an improved quality of life.[26] Nonetheless, NPs should be aware of the potential for false-positive or false-negative results from genetic testing, and ideally a second confirmatory test should be administered.

Patient follow-up and monitoring. Following a positive diagnosis, it is recommended that parents, children, siblings, and extended family members are provided with genetic counseling and offered testing. The initial clinical evaluation of diagnosed patients should focus on the early detection and follow-up of associated conditions, such as emphysema, bronchiectasis, and liver disease.[1] Complete lung function testing is recommended for all individuals with AAT deficiency, and adults with normal spirometry at baseline should be followed up annually.[1] In addition, referral for radiologic assessment is advisable to assess the presence of emphysema. A baseline CT scan, which has superseded the use of chest X-rays, is recommended to assess the extent of emphysema in newly diagnosed symptomatic patients.[1] Serial CT scanning is not currently recommended because of concerns regarding radiation dosage and uncertainty surrounding the clinical utility of the data.[1] Progression of lung disease in patients with AAT deficiency is largely monitored by spirometry, and recording the frequency and severity of exacerbations is also useful.[1,16] When available, diffusing capacity of the lungs for carbon monoxide assessment can provide more in-depth detail on the progression of emphysema in patients with AAT deficiency.[1]

AAT deficiency testing flow[25]



AAT, Alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease.

Treatment guidelines

When a diagnosis of AAT deficiency is confirmed, both nonpharmacologic and pharmacologic approaches to treatment are recommended.

Nonpharmacologic treatment options. In line with recommended treatment for general COPD, a crucial aspect to managing AAT deficiency is smoking cessation.[1] It is known that respiratory symptoms manifest earlier in patients with AAT deficiency who smoke as opposed to those who do not smoke.[17] Furthermore, data suggest patients have substantial reductions in their

rate of lung function decline following smoking cessation and that ex-smokers have similar lung function to those who never smoked.[2,27] Patients with AAT deficiency should also be advised to avoid environmental exposure to pollutants and to seek appropriate immunization against influenza, hepatitis, and pneumonia.[17,28] Maintaining an appropriate nutrition status and getting moderate exercise are important aspects of patient care and can help reduce exacerbations, morbidity, and mortality.[29] Patients may also wish to consider pulmonary rehabilitation as a treatment option, an intervention that has been shown to reduce symptoms, and improve exercise capacity and health-related quality of life in patients with COPD.[30]

The key differentiator between symptomatic AAT deficiency and general COPD is the use of AAT therapy.

A key strategy to encourage self-care for patients with AAT deficiency is through the use of targeted disease management programs, which have been shown to improve overall quality of life.[23] Recently, AlphaNet, a US advocacy group for patients with AAT deficiency, published results of a nationwide Alpha-1 Disease Management and Prevention Program. Data indicate that those who adhered to the program were more informed about their condition and more likely to implement self-care strategies, including regular exercise, smoking cessation, and staying up to date on appropriate immunizations.[28]

Pharmacologic treatment options. The pharmacologic management of symptomatic AAT deficiency involves three key areas: symptomatic management with bronchodilators and inhaled corticosteroids, AAT therapy, and management of exacerbations (see *Clinical management of symptomatic patients with AAT deficiency*).[1,31] In general, symptom management and treatment of exacerbations is in line with that for general COPD, and NPs should follow general COPD clinical guidelines, such as those issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[31]

The key differentiator between symptomatic AAT deficiency and general COPD is the use of AAT therapy. AAT replacement is the only treatment to influence disease progression by administering the protein that is missing. The feasibility of AAT therapy for the treatment of AAT deficiency-related emphysema was first demonstrated in the 1980s.[32,33] Infusion of AAT was shown to reverse the biochemical abnormalities in serum and lung fluid that characterize the disorder. More recently, the RAPID (Randomized, placebo-controlled trial of augmentation therapy in Alpha 1-Proteinase Inhibitor Deficiency) clinical trial program, the largest randomized clinical trial of AAT therapy in patients with AAT deficiency completed to date, definitively confirmed the efficacy of therapy in slowing disease progression, as measured by CT densitometry.[34,35] Furthermore, a post-hoc analysis, which investigated the time to respiratory crisis (defined as death, lung transplant, or a crippling respiratory

Clinical management of symptomatic patients with AAT deficiency[1,31]

Symptomatic management	• LABA/LAMA and inhaled corticosteroids • Oxygen therapy may be required in severe/late-stage disease
AAT therapy (Specialist involvement required)	• AAT therapy initiation implemented on case-by-case basis, requiring discussion between treating physician and patient • Symptomatic patients with a severe AAT deficiency genotype (PI*ZZ, PI*SZ, PI*ZNull, and PI*ZNullNull) can be considered for treatment • Historically most evidence for efficacy between FEV1>30 and ≤65% predicted, new recommendations state that treatment can be considered outside of this range • Patients with AAT deficiency and rapidly declining lung function should be treated with AAT as a priority
Management of exacerbations	• Oral antibiotics (amoxicillin, macrolides) in patients with purulent sputum • Consider short course of oral corticosteroids (prednisolone) • Referral to critical care setting when patients present with acute respiratory distress

AAT, alpha-1 antitrypsin; FEV1, forced expiratory volume in one second; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist

condition) for progressive emphysema, projected a gain of 5.6 life-years in patients treated with AAT compared with placebo.[34,35]

When initiating AAT therapy with an I.V. infusion of alpha$_1$-proteinase inhibitor, consultation between a specialist physician and the patient is required. Many factors contribute to the decision to commence treatment. For example, severe genetic deficiency must be confirmed, and the extent of disease progression should also be considered. The strongest recommendation for AAT therapy provision is for patients with moderate disease, defined as FEV$_1$ in the range of 30% to 65% predicted.[17] However, more recent recommendations support treatment outside of this range on a case-by-case basis, and evidence from the RAPID clinical trial program suggests that earlier intervention may help to prolong the time to terminal respiratory failure.[1,36] Therapy may also be effective in treating other AAT deficiency-related conditions such as panniculitis and GPA, but is not currently recommended for individuals without symptoms of emphysema, and is not effective or recommended for the treatment of liver disease in AAT deficiency.[1,4,37]

The NP role in patient care

Diagnosis and monitoring AAT deficiency. NPs can help facilitate the earlier detection of AAT deficiency and improve rates of diagnosis. Within primary care settings, symptoms and pathologies associated with COPD and adult-onset asthma should prompt AAT deficiency testing, which is essential for accurate diagnosis. In addition, it is crucial that NPs conduct standard spirometric assessments on all patients with respiratory symptoms, as recommended in the latest GOLD guidelines.[31] This is central to determining whether a patient has airflow obstruction indicative of COPD or asthma and for providing baseline measurements for future comparison. Additionally, referral for radiologic assessment is advisable to assess the presence of lung pathology. Identification of patients with early-stage lung disease allows for earlier treatment initiation, which can improve patient outcomes. Currently, AAT deficiency is often diagnosed in patients with late-stage disease suggesting that, in the primary care setting, barriers to referring patients for testing may exist. These may include a lack of knowledge and awareness about the disease, perceived costs associated with testing, and administrative workflow barriers that are not conducive to testing referral. To help minimize potential barriers, measures such as including alerts within electronic medical records have been shown to improve referral for testing.[38]

Once diagnosed, monitoring patients with AAT deficiency is similar to that of patients with general COPD. NPs should be observant of changes in overall health status and lung function, and mindful that patients with AAT deficiency can experience periods of rapid decline in lung function, including an annual reduction in FEV$_1$ of 200 to 300 mL. If this is observed, it is essential to relay this information to the treating pulmonologist, as these patients should be treated with AAT therapy as a priority. In addition, NPs should be vigilant for symptoms associated with other clinical manifestations of AAT deficiency. Referral for specialist assessment is essential in patients with signs of unexplained fatigue, abdominal pain, and jaundice, which could indicate the presence of AAT deficiency-associated liver disease. In addition, skin nodules or areas of inflammation could point toward AAT deficiency-related panniculitis, a rare but potentially serious complication.[17] Panniculitis cases necessitate involving both the treating pulmonologist and a dermatologist. In the recent European Respiratory Society statement on AAT deficiency, the importance of identifying patients' personal risk is highlighted, and links to multidisciplinary teams are encouraged to ensure the best quality of care.[39]

Within primary care settings, symptoms and pathologies associated with COPD and adult-onset asthma should prompt AAT deficiency testing.

Treatment of AAT deficiency. Some patients with AAT deficiency will receive weekly I.V. infusions of alpha$_1$-proteinase inhibitor. In the US, these infusions are typically administered by representatives of home nursing agencies, with AAT products supplied by specialty pharmacies. Although AAT therapy has a generally positive safety profile, issues related to I.V. infusion, such as infusion site reactions and bruising, may occur.[40] NPs should be vigilant for these eventualities and maintain effective communication with the home nursing team. A minority of patients may choose to self-administer their AAT

therapy at home and NPs should ensure that these patients are able to self-administer effectively. If patients become increasingly frail or have worsening dexterity issues, the option to refer back to a home nursing team or a local treatment center for AAT infusions should be discussed. Furthermore, NPs will be involved in the wider treatment decisions for patients with AAT deficiency, including conducting regular respiratory medication reviews and checking inhaler technique.

Educational programs and patient networking. NPs can further contribute to the effective care of patients with AAT deficiency by conducting educational programs or by directing patients to programs such as those conducted by AlphaNet. These programs can improve patient knowledge of AAT deficiency, and in turn support essential self-care initiatives such as smoking cessation. NPs can also encourage patient networking and general engagement with patient groups, which have been shown to improve quality of life and medication adherence, and reduce healthcare-related expenditure.[41] Support networks, such as the Alpha 1 Foundation, can provide emotional support and a pathway into research studies for interested patients.[42,43]

Conclusion

AAT deficiency is not a rare disease, but is rarely diagnosed, and NPs are in a key position to help improve awareness, testing, referral, and diagnosis. Early and accurate diagnosis of AAT deficiency can lead to earlier intervention with AAT therapy, encourage lifestyle changes, and allow appropriate monitoring of disease progression. NP

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Judith A. Newell is an NP at HonorHealth, Phoenix, Ariz.

Christine Donahue is a senior medical science liaison at CSL Behring, King of Prussia, Pa.

D. Kyle Hogarth is an associate professor of medicine at the University of Chicago Medicine, Chicago, Ill.

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