

**KOŚCIOLEK, Dawid, URBAŚ, Michał, KEPCZYK, Martyna, KOŚCIOLEK, Aleksandra, SUROWIECKA, Kaja, MISIAK, Jakub, OJDANA, Miłosz, SZALBOT, Konrad, TOKARSKI, Mikołaj and MARCZAK, Natalia. The Alpha 1 antitrypsin deficiency - etiology, symptoms in various organs, diagnosis, treatment, prognosis. Journal of Education, Health and Sport. 2024;61:200-213. eISSN 2391-8306. <https://dx.doi.org/10.12775/JEHS.2024.61.013>
<https://apcz.umk.pl/JEHS/article/view/48340>
<https://zenodo.org/records/10682310>**

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). © The Authors 2024.
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.01.2024. Revised: 15.02.2024. Accepted: 20.02.2024. Published: 20.02.2024.

The alpha 1 antitrypsin deficiency - etiology, symptoms in various organs, diagnosis, treatment, prognosis

Dawid Kościółek, Medical University of Lodz, al. Tadeusza Kosciuszki 4, 90-419 Lodz, Poland

<https://orcid.org/0009-0001-7946-753X>, d.d.kosciolek@gmail.com

Michał Urbaś, Stefan Zeromski Specialist Hospital, ul. Osiedle Na Skarpie 66, 31-913 Krakow, Poland

<https://orcid.org/0009-0005-2762-4723>, michal.urbas97@gmail.com

Martyna Kępczyk, Medical University of Lodz, al. Tadeusza Kosciuszki 4, 90-419 Lodz, Poland

<https://orcid.org/0009-0004-3556-6925>, martyna.kepczyk@wp.pl

Aleksandra Kościółek, Medical University of Lodz, al. Tadeusza Kosciuszki 4, 90-419 Lodz, Poland

<https://orcid.org/0009-0000-1307-8438>, a.kosciolekk@gmail.com

Kaja Surowiecka, Student Research Club of Orthopedics and Traumatology, Medical University of Lublin, ul. Aleje Raclawickie 1, 20-059 Lublin, Poland

<https://orcid.org/0009-0009-7951-5448>, kajasuro@gmail.com

Jakub Misiak, Department of Pathology, Chair of Oncology, Medical University of Lodz, ul. Pabianicka 62, 93-513 Lodz, Poland

<https://orcid.org/0009-0003-1176-3994>, misiakj98@gmail.com

Milosz Ojdana, Military Medical Academy Memorial Teaching Hospital – Central Veterans' Hospital, ul. Zeromskiego 113, 90-549 Lodz, Poland

<https://orcid.org/0009-0002-4901-7252>, miloszojdana77@gmail.com

Konrad Szalbot, Medical University of Lodz, al. Tadeusza Kosciuszki 4, 90-419 Lodz, Poland

<https://orcid.org/0009-0007-2210-0386>, konradshalbot.md@gmail.com

Mikołaj Tokarski, Medical University of Lodz, al. Tadeusza Kosciuszki 4, 90-419 Lodz, Poland

<https://orcid.org/0009-0005-9301-6267>, mikolaj.tokarski.md@outlook.com

Natalia Marczak, Poznan University of Medical Sciences Collegium Maius, Fredry 10 Street 61-701 Poznań

<https://orcid.org/0009-0006-4716-8187>, 00nat.aliaa@gmail.com

Corresponding author:

Dawid Kościółek

Medical University of Lodz,

al. Tadeusza Kosciuszki 4,

90-419 Lodz, Poland

d.d.kosciolek@gmail.com

Abstract:**Introduction:**

Alpha-1 antitrypsin (AAT) is a glycoprotein produced by liver, belonging to the serine protease inhibitor family. Alpha-1 antitrypsin deficiency (AATD) is very common autosomal recessive genetic disease caused by point mutation in SERPINA1 gene. Mutations in the alpha-1 antitrypsin gene lead to production of misfolded AAT resulting in impaired release into the blood. This disorder leads to destruction of connecting tissue especially in lungs and to accumulation of retarded protein in the liver.

Purpose:

Most studies addressing AAT deficiency focus on presenting symptoms related to the lungs and liver. We want to take a broader look at this issue, so we have closely examined scientific reports on the presentation of the disease in organs other than the lungs and liver. The goal is to gather holistic knowledge about the disease to enhance awareness and treatment.

Material and methods:

In our paper, we endeavored to address the issue of AAT deficiency comprehensively. We explored symptoms with an emphasis on organs beyond the liver and lungs. We also delved into the etiology, diagnosis, treatment, and prognosis of this disease.

Discussion:

The clinical symptoms of alpha 1 antitrypsin deficiency extending beyond the liver and lungs remain inadequately described. We know that AAT deficiency can lead to excessive destruction of connective tissue in any organ, not just the lungs and liver. Unfortunately, this condition continues to go undiagnosed, and the number of scientific publications on symptoms from other organs is too limited. This affects the insufficient attention given by doctors to tissue destruction in organs other than the lungs and liver.

Keywords: Alpha-1-antitrypsin; Alpha-1-antitrypsin deficiency; COPD; cirrhosis;

Introduction:

Alpha-1 antitrypsin deficiency (AATD) is one of the most common genetically inherited disorders caused by homozygous substitution of one amino acid, Glu342Lys in SERPINA1 gene. The prevalence is estimated to be 1 in 1500 to 1 in 3000 live births in the European and American populations. The disease follows an autosomal recessive inheritance pattern, meaning it is not linked to gender, and symptoms only manifest in individuals who are homozygous.(1–3)

So far, over 150 gene variants for alpha-1 antitrypsin have been identified. The concentration of alpha-1 antitrypsin in the blood and the degree of impairment in its activity depend on the gene variant. Normal variants of the alpha-1 antitrypsin gene are present in approximately 95% of the population.(2,4,5)

The most common deficient variants, "Z" and "S," are associated with a reduction in the concentration of alpha-1 antitrypsin in blood serum. In the "ZZ" variant, the concentration of alpha-1 antitrypsin is about 10-15% of the normal concentration. In asymptomatic heterozygotes with one abnormal gene, the concentration of alpha-1 antitrypsin is 50%-60% of the level found in healthy individuals. (6–8)

Alpha-1 antitrypsin is a glycoprotein belonging to the serine protease inhibitor family. It is produced by the liver and released into the blood. Mutations in the alpha-1 antitrypsin gene lead to changes in the structure of the produced protein, resulting in impaired release into the blood. It is not a rare disorder but grossly under-recognized or misdiagnosed as asthma, chronic obstructive pulmonary disease (COPD) or cryptogenic liver disease. The altered protein accumulates in liver cells, leading to the development of liver diseases. In the respiratory system, alpha-1 antitrypsin deficiency causes the destruction of elastic fibers by neutrophil-secreted elastases, leading to lung destruction.(1,9)

Purpose:

Most studies addressing AAT deficiency focus on presenting symptoms related to the lungs and liver. In our opinion, there is a lack of research that portrays the problem comprehensively, highlighting manifestations from other organs. In line with the spirit of holistic medicine, we should not concentrate on a single disease entity, one organ, or one group of symptoms. The approach to the patient must be comprehensive, and expanding knowledge about symptoms from other tissues in AAT deficiency can help doctors better understand the patient's experiences and respond more effectively to their needs with treatment.

Material and methods:

In our paper, we endeavored to address the issue of AAT deficiency comprehensively. We conducted a thorough search of available literature on Google Scholar and PubMed, focusing on exploring symptoms with an emphasis on organs beyond the liver and lungs. We also delved into the etiology, diagnosis, treatment, and prognosis of this disease.

Etiology:

Alpha 1 antitrypsin is a protease inhibitor produced and secreted by the liver, originating as a product of the SERPINA1 gene. It prevents neutrophil elastase from breaking down connecting tissue.(1,10,11)

Deficiency of AAT(AATD) is autosomal codominant condition caused by point mutation in SERPINA1. The most commonly mutation causing AAT deficiency include the S and the Z alleles leading to missfolded α 1-antitrypsin accumulation in hepatocytes and low circulating level of this protein. The Z mutation leads to the degradation of the enzyme through endoplasmic reticulum-associated degradation (ERAD) or its retention within hepatocytes as polymers forming periodic acid-Schiff (PAS)-positive, diastase-resistant inclusions. These inclusions are associated with neonatal hepatitis, liver cirrhosis, and hepatocellular carcinoma. Only 10-15% of Z 1-AT is folded and released into circulation, leaving the lungs vulnerable to enzymatic damage by neutrophil elastase, predisposing Z homozygotes to early-onset emphysema. Systemic AAT deficiency leads to excessive damage to connective tissue by

elastase released from neutrophils in response to bacterial infection.(1,2,12) The most vulnerable organs are lungs and liver. The most frequent disease entities caused by AATD are chronic obstructive pulmonary disease (COPD) liver cirrhosis, pulmonary dilatation and emphysema.(6)

Symptoms:

Alpha-1-antitrypsin deficiency may contribute to many diseases, which have early onset. (13) The main clinical manifestation of AAT deficiency is related to the lung, the liver, and, rarely, the skin. (13) (14) (15) There are also cases related to other organs, but they occur less frequently than the previous ones.(7,8,15) Clinical presentation of lung diseases is emphysema and rarely bronchiectasis. It has many features in common with usual COPD. The patient can present symptoms like: dyspnea, cough, and wheezing with upper respiratory infections. (13) (15) (16) Liver disease associated with AATD include hepatitis, cirrhosis, and hepatocellular carcinoma. Even newborns can present symptoms like obstructive jaundice and minor laboratory abnormalities. The symptoms correspond with the degree of liver damage. (13) (15) (17)The major dermatologic manifestation of AAT deficiency is necrotizing panniculitis. It is characterized by hot, painful, erythematous nodules, or plaques on the thigh or buttocks. (13) (15) (14) It is also described as an association between AATD and vasculitis. The multisystemic nature of vasculitis is the cause of many symptoms. A detailed history and physical examination are key to diagnosis of vasculitis. (13) (18)Other reasons may cause these diseases. The hereditary nature should be indicated by early onset, most often without other risk factors. (13,19)

Diagnosis:

The initial examination performed in individuals suspected of having a deficiency of this inhibitor involves measuring the concentration of AAT in serum/plasma using immunologic or colorimetric methods.(20) Normal AAT concentration values in the serum of healthy individuals range from 83-220 mg/dL for immunoephelometric methods and 150-330 mg/dL for rocket immunoelectrophoresis. Identification of AAT concentration below 130 mg/dL should prompt further qualitative examinations. The protective threshold concentration for AAT is 11 $\mu\text{mol/L}$, corresponding to 50 mg/dL for immunoephelometric methods and 80

mg/dL for rocket immunoelectrophoresis. Further diagnostics include phenotypic, genotypic, and DNA sequencing studies.(4,21,22)

Treatment:

Emphysema and COPD management mostly include symptomatic treatment such as use of inhaled bronchodilators in the event of bronchospastic symptoms, as well as respiratory rehabilitation and oxygen therapy in case of respiratory failure. (23) The patients should cease smoking and avoid exposure to tobacco smoke. Emphasis should also be made to avoid irritants in home and work environments. Early prevention like vaccinations and treatment of respiratory system infections should also be recommended. In severely progressed cases of lung disease the recommended treatment of last resort is lung transplantation. (6,22)

Infusions of intravenous alpha-1 antitrypsin, is a treatment derived from donated human plasma from healthy donors. The augmentation therapy is thought to arrest the course of the disease and halt any further damage to the lungs, though so far it has produced only vague evidence. It has demonstrated reduction of the lung density loss measured by computer tomography, but it failed to show improvement in lung function, exacerbation frequency or quality of life. (6,9,23) Although the therapy remains controversial, it has been approved by many national authorities and drug administrations(11,24–26)

In liver disease promising results were found with use of Fazirsiran - a RNA-interfering drug, which is able to reduce the production of abnormal alpha-1 antitrypsin. The drug appears to be very well-tolerated with no adverse effects. In AROAAT-2002 study, fazirsiran was given to patients with Alpha-1 Antitrypsin Deficiency (AATD)- associated liver disease complicated by liver fibrosis. After 48 weeks of treatment all participants showed reduced accumulation of abnormal protein in the liver with median reduction of 83%, as well as serum concentration by 90% and decrease in liver enzyme levels. Seven out of fifteen patients exhibited a regression of liver fibrosis. (7). Scientists currently examine various compounds that have shown promising results in stopping liver injury in mouse models. One study in mice showed that rapamycin, a macrolide antibiotic which is also an immunosuppressant, reduced liver injury by promoting phagocytosis.(27) Patients should avoid consumption of alcohol, nonsteroidal antiinflammatory drugs to slow progression and

further damage. Regular screenings for esophageal varices are also recommended. In end-stage cirrhosis, liver transplantation is the only viable option. (22,28)

Finding the right pharmacological treatment to neutrophilic panniculitis poses a challenge as it is an extremely rare condition, which effectively hinders from conducting meaningful therapeutic trials. The treatment for years remained empiric, with little to no scientific basis for usage of antibiotics, steroids and nonsteroidal anti-inflammatory drugs. Currently, in the first line clinicians recommend the usage of dapsone, a drug with anti-inflammatory properties which prevents neutrophil adhesion and migration. (29,30) Though, its usage has significant disadvantages with frequent failure to achieve remissions. (31) In treatment of neutrophilic panniculitis good response has been shown with intravenous alpha-1 antitrypsin augmentation therapy. (31–33) One report showed impressive response to anakinra, an interleukin-1 agonist in treatment resistant panniculitis. (34)

Prognosis:

Alpha-1 antitrypsin deficiency is a disease burdened with an increased risk of death due to organ complications it induces, particularly associated with adverse effects on the lungs and liver. In a study by Paul Dawkins et al., researchers focused on assessing the mortality of the mentioned condition in a cohort of 488 patients from the United Kingdom presenting this disease. Over a 9-year period, during which the average length of patient observation was 4.45 years, 56 patients died, with the majority of cases (30 patients, 54%) showing a direct link between death and pulmonary emphysema. The cause of death for 6 patients (10.7%) was liver disease. 5 patients died due to malignant tumors of other organs (1 patient each due to lung, esophageal, gastric, brain, and lymphatic cancer). The remaining deaths comprised a miscellaneous group, including causes such as strokes, heart diseases, thromboembolic events, and others, including pancreatitis, pulmonary hemorrhage, and after partial lung resection. However, this article does not cover prognoses for patients presenting with symptoms beyond the lungs and liver directly associated with alpha-1 antitrypsin deficiency. Therefore, we will address a review of these issues.(35,36)

Panniculitis

According to Franciosi AN et al., the deficiency of alpha-1 antitrypsin among patients presenting with subcutaneous tissue inflammation is more prevalent than previously thought, although, following data from the National Heart, Lung, and Blood Institute, it affected approximately 0.1-0.9% of individuals with AATD. Additionally, the occurrence of panniculitis in patients with AAT1 deficiency was associated with higher mortality. It was observed that the cutaneous presentation of alpha-1 antitrypsin deficiency occurred not only among patients with the ZZ genotype, which is associated with a worse prognosis, but also among patients with genotypes not predisposing to a severe course of AATD. In the further part of the study, Franciosi AN et al. focused on the prognosis among patients with skin changes in the mentioned disease unit. Following Franciosi AN, no case has been reported where subcutaneous tissue inflammation caused by AATD resolved spontaneously. Patients were treated with antibiotics, glucocorticoids, and immunosuppressants, but effectiveness was demonstrated only in the case of plasma exchange, liver transplantation, the use of dapson, and intravenous infusions of purified human alpha-1 antitrypsin. This effectiveness was determined to be above 50%.(34)

In a study conducted by Pedram Geraminejad et al. on 41 reported cases of subcutaneous tissue inflammation, 3 resulted in death due to complications involving other organs affected by alpha-1 antitrypsin deficiency (such as cardiovascular complications, pulmonary complications) during the follow-up period.(37)

However, it should be noted that the vast majority of cases of subcutaneous tissue inflammation in AATD present at an advanced stage of the disease, where skin ulcers occur, also having other conditions resulting from the involvement of other organs such as the lungs and liver. Therefore, the prognosis for individuals developing cutaneous complications is difficult to assess in isolation from the overall underlying disease. It is worth noting that there are no available randomized controlled trials of therapies, and the evidence is limited to case histories and one meta-analysis, making a precise prognosis evaluation challenging. Consequently, the prognosis for patients, especially those with ZZ-AATD, may be uncertain and requires further clinical research.(34,38)

Other localisations

Prognosis among patients who develop clinical manifestations of alpha-1 antitrypsin deficiency from other locations is difficult to determine due to the limited literature

addressing this issue. Focusing on other organs, we can only state that the condition of patients affected by alpha-1 antitrypsin deficiency is characterized by progressive organ failure and tissue dysfunction. Although disorders resulting from the underlying disease, such as nephropathies, glomerulonephritis, vasculitis, aneurysmal disease, and various dermatological manifestations have been described, prognosis for individual manifestations of the disease has not yet been addressed in the literature. Determining prognosis in these patients requires further research and observation.

Discussion:

Clinical manifestations of AATD beyond the liver and lungs remain inadequately described. We know that AAT deficiency can lead to excessive destruction of connective tissue in any organ, not just the lungs and liver. Unfortunately, this medical condition still tends to go undiagnosed, and the number of scientific publications on symptoms in other organs is too limited. This impacts the insufficient attention given by physicians to tissue destruction in organs other than the lungs and liver.

The reasons for this situation should be sought in the significant predominance of the destructive impact on the lungs and liver due to AAT deficiency. Involvement of these two organs is crucial in determining the prognosis for the patient and remains the most common cause of misdiagnosis. The clinical manifestation of AAT deficiency in the lungs and liver often resembles other frequently occurring conditions, leading to delayed diagnosis and appropriate treatment. This contributes to further progression of the pathological changes.

So far, only the biochemical efficacy of AAT (Alpha-1 Antitrypsin) therapy has been assessed. The reinforcing therapy has been appropriately evaluated and there are still no conclusive data regarding its parameters of clinical efficacy or biomarkers associated with the development of pulmonary emphysema. The low frequency of AAT deficiency, along with a general lack of collaboration among physicians regarding international AAT registries, has hindered the development of new therapeutic alternatives more quickly. With the establishment and development of national and international AAT registries, this could be an unfavorable scenario that is changed. AATD is a slowly progressing disease with clinical symptoms that may manifest after decades, and recruiting a sufficient number of patients for prolonged, placebo-controlled studies remains a significant obstacle. Initiating treatment

early in patients with severe AATD associated with pulmonary emphysema may delay the time to death, lung transplantation, or debilitating respiratory conditions. Further research is needed to assess long-term outcomes.

Conclusion:

AATD remains underdiagnosed. New strategies to enhance detectability are needed, especially since available evidence confirms the clinical effectiveness of supportive therapies. Currently, promising new alternative therapies are being investigated, which may change the landscape of treatment and diseases in the coming years. Evidence is beginning to suggest an improvement in survival among patients with AATD receiving augmentation therapy. It is also suggested that slowing the progression of emphysema through supportive therapy may limit health deterioration. In the study, patients in the delayed start group who transitioned to active treatment did not regain lost lung tissue compared to the placebo phase. This emphasizes the importance of early intervention with augmentation therapy to minimize the occurrence of adverse health consequences associated with AATD.

Additionally, appropriate biomarkers are still needed for patient stratification to better predict the disease progression or monitor response to treatment. A holistic approach to patient needs and attention to the diversity of clinical manifestations of AATD remain extremely helpful in both therapy and diagnosis of this condition.

DISCLOSURE

Author's contribution

Conceptualization, Dawid Kościółek, and Michał Urbaś; methodology, Martyna Kępczyk.; software, Mikołaj Tokarski; check, Michał Urbaś, Jakub Misiak and Mikołaj Tokarski; formal analysis, Kaja Surowiecka and Michał Urbaś; investigation, Konrad Szalbot and Aleksandra Kościółek; resources, Aleksandra Kościółek and Natalia Marczak; data curation, Michał Urbaś ; writing - rough preparation, Kaja Surowiecka and Dawid Kościółek; writing - review and editing, Miłosz Ojdana and Jakub Misiak; visualization, Natalia Marczak; supervision, Mikołaj Tokarski and Konrad Szalbot; project administration, Michał Urbaś and Dawid Kościółek; receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing statement

The study received no specific funding

Institutional Review Board Statement

Not applicable – Not required

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Not applicable

Conflict of interest

The authors deny any conflict of interest

References:

1. Strnad P, McElvaney NG, Lomas DA. Alpha₁-Antitrypsin Deficiency. Longo DL, editor. *N Engl J Med*. 2020 Apr 9;382(15):1443–55.
2. Stoller JK, Aboussouan LS. A Review of α_1 -Antitrypsin Deficiency. *Am J Respir Crit Care Med*. 2012 Feb 1;185(3):246–59.
3. Köhnlein T, Welte T. Alpha-1 Antitrypsin Deficiency: Pathogenesis, Clinical Presentation, Diagnosis, and Treatment. *The American Journal of Medicine*. 2008 Jan;121(1):3–9.
4. Valiulis A, Utkus A, Stukas R, Valiulis A, Siderius L, Leonardo da Vinci Alfa-1-Qual No. LLP-LdV-PRT-2011-LT-0300 project group. Introducing standards of the best medical practice for patients with inherited alpha-1-antitrypsin deficiency in Central Eastern Europe. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2014;35(1):107–14.
5. Mornex JF. [Alpha-1 antitrypsin deficiency 50 years later]. *Bull Acad Natl Med*. 2014;198(4–5):757–66.
6. Edgar R, Patel M, Bayliss S, Crossley D, Sapey E, Turner A. Treatment of lung disease in alpha-1 antitrypsin deficiency: a systematic review. *COPD*. 2017 May;Volume 12:1295–308.
7. Strnad P, Mandorfer M, Choudhury G, Griffiths W, Trautwein C, Loomba R, et al. Fazirsiran for Liver Disease Associated with Alpha₁-Antitrypsin Deficiency. *N Engl J Med*. 2022 Aug 11;387(6):514–24.
8. Lachaux A, Dumortier J. Atteinte hépatique du déficit héréditaire en alpha-1-antitrypsine. *Revue des Maladies Respiratoires*. 2014 Apr;31(4):357–64.
9. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *Cochrane Airways Group*, editor.

- Cochrane Database of Systematic Reviews [Internet]. 2016 Sep 20 [cited 2024 Jan 23];2016(9). Available from: <http://doi.wiley.com/10.1002/14651858.CD007851.pub3>
10. Patel D, Teckman JH. Alpha-1-Antitrypsin Deficiency Liver Disease. *Clinics in Liver Disease*. 2018 Nov;22(4):643–55.
 11. Bouche-careilh M. Le déficit en alpha-1-antitrypsine. *Med Sci (Paris)*. 2014 Oct;30(10):889–95.
 12. Duvoix A, Roussel BD, Lomas DA. Molecular pathogenesis of alpha-1-antitrypsin deficiency. *Revue des Maladies Respiratoires*. 2014 Dec;31(10):992–1002.
 13. Stoller JK, Aboussouan LS. A Review of α_1 -Antitrypsin Deficiency. *Am J Respir Crit Care Med*. 2012 Feb 1;185(3):246–59.
 14. Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. *Orphanet J Rare Dis*. 2008 Dec;3(1):16.
 15. Stoller JK, Aboussouan LS. α_1 -antitrypsin deficiency. *The Lancet*. 2005 Jun;365(9478):2225–36.
 16. Nuñez A, Barrecheguren M, Rodríguez E, Miravittles M, Esquinas C. Diagnosis of alpha-1-antitrypsin deficiency not just in severe COPD. *Pulmonology*. 2018 Nov;24(6):351–3.
 17. Teckman JH. Liver Disease in Alpha-1 Antitrypsin Deficiency: Current Understanding and Future Therapy. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2013 Mar 7;10(sup1):35–43.
 18. Deshayes S, Martin Silva N, Grandhomme F, Khoy K, Mariotte D, Boutemy J, et al. Clinical Effect of Alpha-1 Antitrypsin Deficiency in Antineutrophil Cytoplasmic Antibody-associated Vasculitis: Results from a French Retrospective Monocentric Cohort. *J Rheumatol*. 2019 Nov;46(11):1502–8.
 19. Henao MP, Craig TJ. Understanding alpha-1 antitrypsin deficiency: A review with an allergist's outlook. *allergy asthma proc*. 2017 Mar 1;38(2):98–107.
 20. Balduyck M, Odou MF, Zerimech F, Porchet N, Lafitte JJ, Maitre B. Diagnosis of alpha-1 antitrypsin deficiency: Modalities, indications and diagnosis strategy. *Revue des Maladies Respiratoires*. 2014 Oct;31(8):729–45.
 21. Nelson DR, Teckman J, Di Bisceglie AM, Brenner DA. Diagnosis and Management of Patients With α_1 -Antitrypsin (A1AT) Deficiency. *Clinical Gastroenterology and Hepatology*. 2012 Jun;10(6):575–80.
 22. Santangelo S, Scarlata S, Poeta M, Bialas A, Paone G, Incalzi R. Alpha-1 Antitrypsin Deficiency: Current Perspective from Genetics to Diagnosis and Therapeutic Approaches. *CMC*. 2017 Jan 16;24(1):65–90.
 23. Dummer J, Dobler CC, Holmes M, Chambers D, Yang IA, Parkin L, et al. Diagnosis and treatment of lung disease associated with alpha one-antitrypsin deficiency: A position statement from the Thoracic Society of Australia and New Zealand*. *Respirology*. 2020 Mar;25(3):321–35.
 24. Brantly M. Treatment for Alpha-1 Antitrypsin Deficiency: Does Augmentation Therapy Work? *Am J Respir Crit Care Med*. 2023 Nov 1;208(9):948–9.
 25. Strange C. Anti-Proteases and Alpha-1 Antitrypsin Augmentation Therapy. *Respir Care*. 2018 Jun;63(6):690–8.
 26. Rahaghi FF, Miravittles M. Long-term clinical outcomes following treatment with alpha 1-proteinase inhibitor for COPD associated with alpha-1 antitrypsin deficiency: a look at the evidence. *Respir Res*. 2017 Dec;18(1):105.
 27. Kaushal S, Annamali M, Blomenkamp K, Rudnick D, Halloran D, Brunt EM, et al. Rapamycin reduces intrahepatic alpha-1-antitrypsin mutant Z protein polymers and liver injury in a mouse model. *Exp Biol Med (Maywood)*. 2010 Jun;235(6):700–9.
 28. Jaspers E, Van Dijck I, Hoffman I, Knops N, Stéphenne X, Witters P, et al. Cystic fibrosis and alpha-1 antitrypsin deficiency: case report and review of literature. *BMC Pediatr*. 2022 Dec;22(1):247.
 29. Blanco I, Lipsker D, Lara B, Janciauskiene S. Neutrophilic panniculitis associated with alpha-1-antitrypsin deficiency: an update. *Br J Dermatol*. 2016 Apr;174(4):753–62.
 30. Valverde R, Rosales B, Ortiz-de Frutos FJ, Rodríguez-Peralto JL, Ortiz-Romero PL. Alpha-1-Antitrypsin Deficiency Panniculitis. *Dermatologic Clinics*. 2008 Oct;26(4):447–51.

31. Smith KC, Pittelkow MR, Su WP. Panniculitis associated with severe alpha 1-antitrypsin deficiency. Treatment and review of the literature. *Arch Dermatol.* 1987 Dec;123(12):1655–61.
32. Al-Niaini F, Lyon C. Severe ulcerative panniculitis caused by alpha 1-antitrypsin deficiency: Remission induced and maintained with intravenous alpha 1-antitrypsin. *Journal of the American Academy of Dermatology.* 2011 Jul;65(1):227–9.
33. O’Riordan K, Blei A, Rao MS, Abecassis M. α 1-ANTITRYPSIN DEFICIENCY-ASSOCIATED PANNICULITIS: Resolution with Intravenous α 1-Antitrypsin Administration and Liver Transplantation. *Transplantation.* 1997 Feb;63(3):480–2.
34. Lipsker D, Perrigouard C, Foubert A, Cribier B. Anakinra for Difficult-to-Treat Neutrophilic Panniculitis: IL-1 Blockade as a Promising Treatment Option for Neutrophil-Mediated Inflammatory Skin Disease. *Dermatology.* 2010;220(3):264–7.
35. Dawkins P, Wood A, Nightingale P, Stockley R. Mortality in alpha-1-antitrypsin deficiency in the United Kingdom. *Respiratory Medicine.* 2009 Oct;103(10):1540–7.
36. Stockley RA, Turner AM. α -1-Antitrypsin deficiency: clinical variability, assessment, and treatment. *Trends in Molecular Medicine.* 2014 Feb;20(2):105–15.
37. Geraminejad P, DeBloom JR, Walling HW, Sontheimer RD, VanBeek M. Alpha-1-antitrypsin associated panniculitis: The MS variant. *Journal of the American Academy of Dermatology.* 2004 Oct;51(4):645–55.
38. Perlmutter D. Alpha-1-Antitrypsin Deficiency. *Semin Liver Dis.* 1998;18(03):217–25.