Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Perspective

Designing Clinical Trials in "Regular" COPD Versus Alpha-1 Antitrypsin Deficiency-Associated COPD: "More Alike Than Unalike?"

James K. Stoller, MD, MS[1]

Abstract

Alpha-1 antitrypsin deficiency (AATD) predisposes to emphysema, liver disease, and panniculitis. This emphysema risk naturally invites a comparison between "regular" chronic obstructive pulmonary disease (COPD) (i.e., unrelated to AATD) and AATD-associated emphysema.

Several features characterize both conditions. Both can be life-limiting and highly debilitating. Both are highly under-recognized.

An important corollary of this comparison between "regular" COPD and AATD-associated COPD is whether both should be treated similarly and whether clinical trials to assess new therapies can be conducted similarly in both. Here, the distinctions between "regular" COPD and AATD-associated COPD are quite pronounced. Therapeutically, sparse available data suggest that lung volume reduction surgery confers less improvement in forced expiratory volume in 1 second (FEV_1) in AATD and that such benefits are shorter-lived. Perhaps the most striking contrast between the 2 conditions is that clinical trial designs and conduct are necessarily very different. The relative scarcity of diagnosed individuals with AATD hampers recruitment to trials. Furthermore, primary outcome measures in trials of "regular" COPD must differ markedly from those of AATD-associated emphysema. Specifically, power calculations show that FEV_1 and exacerbation frequency, which are amply represented as endpoints in large COPD trials, are infeasible in studies of AATD-associated emphysema. Rather, in the 3 available randomized controlled trials of intravenous augmentation therapy, the rate of emphysema progression based on serial computed tomography densitometry measurements has been the only feasible primary outcome measure.

These considerations underscore the distinctive challenges and needs of conducting treatment trials in AATD-associated emphysema and emphasize that, with regard to clinical study design, the 2 conditions are "more unalike than alike."

Abbreviations: alpha-1 antitrypsin deficiency, **AATD**; forced expiratory volume in 1 second, **FEV1**; Efficacy and Safety of Triple Therapy in Obstructive Lung Disease study, **ETHOS**; Body-mass index-airflow Obstruction-Dyspnea-Exercise capacity, **BODE**; National Heart, Lung and Blood Institute, **NHLBI**; computed tomography, **CT**; Long-term Oxygen Treatment Trial, **LOTT**; randomized controlled trials, **RCTs**; long-volume reduction surgery, **LVRS**; relative risk, **RR**; salmeterol, **SAL**; fluticasone propionate, **FP**; hazard rate, **HR**; tiotropium, **TIO**; azithromycin, **AZITHRO**; oxygen, **O_2**; flucticasone furoate, **FF**; vilanteral, **VII**; glycopyrrolate, **GLYCO**; Intravenous Augmentation Treatment in Severe Alpha-1 Antitrypsin Deficiency, **RAPID**; Towards a Revolution in COPD Health, **TORCH**; Understanding Long-term Impact on Function with Tiotropium, **UPLIFT**; St George's Respiratory Questionnaire, **SGRQ**; total lung capacity, **TLC**

Funding Support: The author received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Date of Acceptance: October 26, 2021 | **Published Online Date:** November 3, 2021
Citation: Stoller JK. Designing clinical trials in "regular" COPD versus alpha-1 antitrypsin deficiency-associated COPD: "more alike than unalike?" *Chronic Obstr Pulm Dis.* 2022;9(1):95-102. doi: https://doi.org/10.15326/jcopdf.2021.0261

1. Education Institute, Cleveland Clinic Foundation, Cleveland, Ohio, United States

Address correspondence to:

James K. Stoller, MD, MS
Education Institute
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195
Phone: (216) 444-1960
Email: stollej@ccf.org

Keywords:

alpha-1 antitrypsin deficiency; COPD; endotype, clinical trials

Introduction

Alpha-1 antitrypsin deficiency (AATD) predisposes to chronic obstructive pulmonary disease (COPD),[1] which naturally prompts the question about "lumping" versus "splitting" the 2 entities: COPD associated with AATD versus "regular" (i.e., alpha-1 antitrypsin-replete) COPD. Do the 2 conditions have different clinical implications? Should they be treated differently? Should clinical trials in both conditions be conducted similarly? These issues have been especially topical in the ongoing dialog between the patient and clinical/scientific communities and regulatory agencies regarding endpoints for registrational trials of new therapies for AATD.

In this context, the current perspective considers the common and discordant features of both conditions, with a special focus on issues regarding clinical trial design. In her poem, *Human Family*, Maya Angelou, the Pulitzer Prize-nominated poet, states: "I note the obvious differences between each sort and type. But we are more alike my friends then we are unalike."[2] The question here is whether regular COPD and AATD-associated COPD are "more alike than unalike," especially regarding the design of clinical trials to assess treatment.

Common Features of Regular COPD and COPD Associated with Alpha-1 Antitrypsin Deficiency

Regular COPD and AATD-associated COPD bear important similarities. Both conditions are life-threatening. Regular COPD is currently the fourth leading cause of death in the United States with 38.2 deaths per 100,000.[3,4] Similarly, data from the recent Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial in regular COPD[5] show a 1-year mortality rate of 2.5% in study participants. Also, regular COPD individuals with the highest Body mass index-airflow Obstruction-Dyspnea-Exercise capacity (BODE) index quartile (BODE 4) demonstrated only a 20% 1-year survival rate.[6] In AATD, data from the National Heart Lung and Blood Institute (NHLBI) Registry for Individuals with Severe Deficiency of Alpha-1 Antitrypsin[7] showed a similar 18.6% mortality rate at 5 years or approximately 3%/year mortality rate.

Another similarity is that both conditions are severely debilitating. Combining death and disability, regular COPD is the fourth leading cause in the United States. Based on data from the NHLBI AATD Registry, 30% of participants whose mean age was 46 years reported being retired or medically unemployed,[8] a reminder of the disability burden associated with AATD.

Similarly, both regular COPD and AATD are severely under-recognized.[9-13] Specifically, 2020 estimates suggest that >25 million Americans have regular COPD, of whom 12 million are currently undiagnosed.[3,4] Regarding AATD, estimates suggest that there are approximately 100,000 severely deficient Americans, of whom the vast majority – perhaps ~90,000 – are currently unrecognized.[1] Under-recognition of AATD has regrettably been longstanding. In a 1989 study sampling 20,000 St. Louis blood bank specimens, Silverman et al[12] identified 7 PI*Z genotype individuals, for a prevalence of 1 in 2900. Reasoning that donated blood bank specimens were representative of the overall population of St. Louis (2 million), this prevalence estimate predicted 700 PI*Z St. Louis individuals. However, when the investigators subsequently polled all the pulmonary practices in St. Louis, only 28 (4%) of the expected 700 individuals were reported.[12] More recently but similarly, an analysis of 458,164 participants in the U.K. Biobank showed that only 6.4% of the 140 PI*ZZ genotype individuals in the Biobank had been previously identified as having AATD.[13] These observations show that AATD is persistently and severely under-recognized.

Further evidence of under-recognition of AATD is the long diagnostic delay commonly experienced by

AATD individuals.[14-17] A 1994 survey[10] of 300 self-reported severely AAT-deficient individuals showed that the mean age of onset of lung symptoms, most frequently dyspnea, was 35 years but that individuals reported a mean 7.2-year interval between first onset of dyspnea and first diagnosis of AATD. Furthermore, when asked about the number of physicians they saw between first symptom and first diagnosis of AATD, 25% reported having the diagnosis made on the first physician visit but 12.5% reported seeing 6-10 physicians before initial diagnosis; 44% reported seeing >3 physicians before the initial diagnosis of AATD.

This prolonged diagnostic delay interval has persisted over time (Table 1), i.e., was estimated to be 6 years[17] in 2019 versus 7 years[9] in 1994. The inescapable conclusion is that, like regular COPD, AATD remains severely under-recognized currently.

Table 1. Diagnostic Delay Interval Estimates for Alpha-1 Antitrypsin Deficiency

Authors and Reference	Publication Year	Country	Diagnostic Delay (Years±SD)
Stoller et al[9]	1994	USA	7.2 years±8.3
Stoller et al[10]	2005	USA	5.6 years±8.5
Campos et al[14]	2005	USA	8.3 years±6.9
Kohnlein et al[15]	2010	Germany	6 years
Greulich et al[16]	2013	Germany	7 years (0–73, IQR 13)
		Italy	6 years (0–40, IQR 11)
Tejwani et al[17]	2019	USA	Median 6 years (25%–75% CI=2.9–15.4 yrs) for participants with symptoms

SD=standard deviation; CI=confidence interval

Discordant Features of Regular COPD and COPD Associated with Alpha-1 Antitrypsin Deficiency

Notwithstanding these considerable similarities between both regular COPD and AATD-associated COPD, there are substantial differences. First, regular COPD demonstrates polygenic inheritance with a strong environmental/lifestyle component. In contrast, AATD is inherited as an autosomal codominant condition where the risk is also amplified by smoking and occupational exposures.[1]

AATD is also a distinctive endotype of COPD, with different pathogenesis than regular COPD, a characteristically different distribution of emphysema, and a markedly higher prevalence of associated bronchiectasis. Pathogenetically, McDonough et al[18] proposed that inflammation and subsequent disappearance of small airways leads to the loss of alveolar walls in regular COPD. In contrast, in AATD, emphysema results from unopposed proteolytic damage to lung matrix like elastin, causing the destruction of alveolar walls and resultant emphysema.

Radiographically, the craniocaudal distribution of emphysema between regular COPD and AATD differs markedly;[19-21] lower lobe predominance is more frequent in AATD, and homogeneous or upper lobe emphysema is more prevalent in regular COPD. Specifically, in PI*ZZ genotype individuals, 96% demonstrated lower lobe predominant COPD in contrast to individuals with regular COPD, in whom homogeneous or upper lobe emphysema was evident in 84%. Data from Parr et al[21] confirm the distinctively lower lobe predominance of emphysema in AATD; specifically, 64% of 102 PI*ZZ genotype individuals undergoing computed tomography (CT) chest scans demonstrated predominantly basilar hyperlucency.

The prevalence of bronchiectasis associated with COPD can also differentiate the 2 entities. The frequency of bronchiectasis in regular COPD ranged from 4% to 69% with a mean of 38.5% in 16 available studies.[22] While prevalence estimates of bronchiectasis in AATD vary,[23] one series showed that 95% of PI*ZZ genotype individuals had radiographic evidence of bronchiectasis,[24] with 31% of individuals demonstrating clinical bronchiectasis, e.g., copious phlegm, with exacerbations, hemoptysis, etc. In the UK Biobank study,[13] though only 4.3% of AATD participants carried the clinical diagnosis of bronchiectasis, the odds ratio for having bronchiectasis in PI*ZZ genotype AATD compared with AAT-replete participants was 7.3.

Treatment differences also underscore the distinctiveness of these 2 entities. Absent specific studies in AATD, mainstay treatment of COPD in both conditions – e.g., bronchodilators, supplemental oxygen, rehabilitation – is often similar. Yet, when AATD has been specifically studied, important

treatment differences are noteworthy. For example, in a subset analysis from the National Emphysema Treatment Trial,[25] lung volume reduction surgery conferred smaller and shorter improvements in FEV_1 in individuals with AATD-associated COPD than with regular COPD. Similarly, in a subset analysis from the Long-term Oxygen Treatment Trial (LOTT[26]), individuals with AATD-associated COPD demonstrated earlier and more profound desaturation than matched individuals with regular COPD.

Perhaps the most important dissimilarity between the 2 conditions involves the feasibility and conduct of clinical trials regarding treatments. While regular COPD is common, allowing large-scale recruitment for a large number of clinical trials of various treatments (Table 2),[5,25,27-33] relatively few randomized controlled trials (RCTs) in AATD are available.[34-38] For example, only 3 published RCTs have examined the efficacy of intravenous augmentation therapy,[34-36] and 1 each has examined the efficacy of inhaled AAT[38] and the efficacy of the retinoid agonist, palovarotene.[37] The largest of the available RCTs of augmentation therapy in AATD, called RAPID for "Intravenous Augmentation Treatment in Severe Alpha-1 Antitrypsin Deficiency," recruited a total of only 180 individuals.[36] Notably, recruitment of these 180 individuals took 56 months in 28 centers across 13 countries and actually even longer from study inception to recruitment close (approximately 7 years). The number of participants in the palovarotene and inhaled AAT RCTs were 262 and 168 respectively, underscoring the challenge of recruiting large numbers of participants in RCTs regarding AATD.

In contrast to the experience with AATD, sample sizes from some of the many recent RCTs in regular COPD are summarized in Table 2 and indicate large-scale recruitment success.[5,25,27-33] In some instances,

Table 2. Summary of Selected Key Trials in "Regular" COPD

Trial/Author (Reference and Date)	Intervention	Primary Outcome	Number of Participants	Summary of Results
NETT[25] (2003)	LVRS vs. Usual Care	Survival	N=1218 (of 3777 assessed)	Long-term survival with LVRS>usual care, RR death with LVRS 0.85 (p=0.02)
TORCH[27] (2007)	Salmeterol (SAL)+Fluticasone Propionate (FP) vs. Placebo or Single Agents	Time to death over 3 years	N=6184 (of 8555 recruited)	2.6% reduction in death risk with SAL+FP, HR 0.825, p=0.052)
UPLIFT[28] (2008)	Tiotropium vs. Placebo	Rate of FEV_1 decline over 4 years	N=5993 (N=2987 TIO vs. N=3006 Placebo)	No difference in FEV_1 slope after 30 days (2ml/yr, p=0.21)
Calverley et al[29] (2009)	Roflumilast vs. Placebo	Time to first COPD exacerbation	N=3296 (2 trials combined, individually N=1525 and 1571)	Roflumilast better than placebo, HR 0.89, p=0.0185
Albert et al[30] (2011)	Azithromycin vs. Placebo	Time to first exacerbation	N=1142	Longer time to 1st exacerbation with AZITHRO, p<0.0001
POET[31] (2011)	Tiotropium vs. Salmeterol	COPD exacerbation	N=7376	TIO>SAL, HR 0.72, p<0.001
LOTT[32] (2016)	Supplemental O_2 vs. No Supplemental O_2	Death and/or time to first hospitalization (any cause)	N=738	No effect, HR 0.94, p=0.52
IMPACT[33] (2018)	Fluticasone Furoate (FF)+Vilanterol (VII)+ Umeclidinium vs. Double vs. Placebo	Annual rate of mod/severe COPD exacerbation	N=10,355	Triple vs. FF+VII, rate ratio 0.85, p< 0.001
ETHOS[5] (2020)	Budesonide/Glycopyrrolate (GLYCO)/ Fluticasone Furoate vs. Double vs. Placebo	Annual rate of mod/severe COPD exacerbation	N=8572	Triple vs. GLYCO+FF, rate ratio 0.76, p<0.001

LVRS=lung-volume reduction surgery; RR=relative risk; SAL=salmeterol; FP=fluticasone propionate; HR=hazard rate; TIO=tiotropium; FEV_1=forced expiratory volume in 1 second; AZITHRO=azithromycin; O_2=oxygen; FF=fluticasone furoate; VII=vilanterol; GLYCO=glycopyrrolate

as in the TOwards a Revolution in COPD Health (TORCH) study[27] and the Understanding Long-term Impact on Function with Tiotropium (UPLIFT) study,[28] where 6184 and 5993 patients respectively participated, differences between treatment and placebo arms were still inapparent, even in the face of very large numbers of participants. As noted, recruitment experience in studies regarding AATD are orders of magnitude smaller given the infrequency of AATD[1,11] and its under-recognition. In this context, regular COPD and COPD associated with AATD are distinctly "more unalike than alike."

Compounding this recruitment challenge, sample size estimates for various primary outcome measures in studies regarding AATD suggest the infeasibility of using many of the conventional outcome measures employed in studies of regular COPD, including mortality, spirometry measures, St George's Respiratory Questionnaire (SGRQ), and exacerbation frequency. For example, Idell and Cohen[39] estimated the sample size required to detect a reduction in mortality in AATD. The smallest estimated number of participants in a study with mortality as a primary endpoint and an effect size (i.e., mortality benefit) of 50% in individuals followed over 5 years was 192 patients per treatment arm. For less dramatic reductions in mortality related to augmentation therapy and shorter follow-up (e.g., 30% mortality reduction studied over 2 years), the estimated number of participants necessary to show power increased (e.g., to 1757 per treatment arm). The infeasibility of such recruitment numbers led to the recommendation to defer an RCT of augmentation therapy and have the NHLBI assemble a registry for individuals with AATD. On the basis of observed mortality data from the resultant NHLBI registry, Schluchter et al[40] estimated that 208 patients would be required in each treatment arm for an RCT of augmentation therapy showing a 50% reduction in mortality in the subset of individuals whose FEV_1 was between 35% and 49% predicted at baseline. With a smaller effect size, i.e., a 30% reduction in mortality, the required sample size rose to 648, which is clearly infeasible (Table 3). Power calculations using SGRQ as a possible primary outcome measure in studies of AATD show similar infeasibility. Even using an enriched population with rapid decline in FEV_1, Stockley et al[41] estimated that 5039 participants would be needed per treatment arm to show a

Table 3. Sample Size Estimates for Trials of Augmentation Therapy Using Forced Expiratory Volume in 1 Second as Primary Outcome

Number of Participants Needed per Treatment Arm by Follow-up Duration			
Author(s) and Reference	3 Years	4 Years	5 Years
[a]Idell S and Cohen AM[39]	377	352	344
[b]Schluchter et al[40]	213	164	143
[c]Dirksen et al[34]	275		

[a]For individuals with FEV_1 30%-65% predicted, calculations assume 90% power, untreated FEV_1 decline -89ml/yr, and 4 measurements/year.
[b]For individuals with FEV_1 30%-65% predicted, calculations assumed one-sided test, 90% power, a=0.05 with FEV_1ml/year and treatment effect=24%
[c]To achieve a 50% reduction in FEV_1 slope

FEV_1=forced expiratory volume in 1 second

25% decrement in decline. The message is clear. As with mortality and SGRQ as endpoints, recruitment requirements based on these estimates make a trial of therapy for AATD using FEV_1 or exacerbation frequency as a primary outcome measure infeasible. Indeed, none of the 3 available RCTs of intravenous augmentation therapy has shown significant benefits regarding FEV_1 slope or exacerbation frequency.[34-36] While other endpoints like degree of inflammation in exacerbations or duration of exacerbation could be considered, inexperience with their use as primary outcomes in pivotal trials and the lack of power calculations have blunted enthusiasm for their use. Also, some have advocated using FEV_1% predicted or % predicted transfer factor in trials in which the participant pool is enhanced by including participants screened for rapid FEV_1 decline. While the proposed numbers of participants for such trials (86 and 77 per treatment arm, respectively)[41] have appeal for feasibility, it bears emphasizing that such rapid decliners comprise a small minority of all AATD individuals, which compounds the recruitment challenge by limiting inclusion to a small subset of an already limited population. For example, in the study by Wencker et al,[42] rapid decliners comprised only 7.3% of the overall population of 96 AATD participants in that study.

The only primary outcome measure for which recruitment goals for an RCT of augmentation therapy for AATD have proven feasible, to date, is CT densitometry.[43] Based on the first available RCT,[34] an observed effect of size of loss of lung density

at 1.07g/L/year over a 3-year trial estimated the need for 130 total participants in an RCT using CT densitometry as the primary outcome measure. In the subsequent RAPID trial,[36] although challenging and, as discussed above, requiring protracted recruitment to accrue only 180 participants, the study demonstrated a significant difference between the rate of loss of lung density among augmentation versus placebo recipients over 2 years using CT densitometry at total lung capacity (TLC) (but not either TLC or functional residual capacity) as the outcome measure. The effect size of 0.74g/L/year using CT densitometry (measured at TLC alone) achieved statistical significance at p=0.03. Finally, data from the RAPID trial have been used to estimate sample size requirements for FEV_1 %predicted, exacerbation frequency, and the SGRQ data as primary outcome measures in a randomized trial of augmentation therapy in AATD. As suggested above, these estimates (Table 4) suggest a minimum of 1525 participants per treatment arm, again, clearly infeasible in AATD based on the prevalence estimates and under-recognition challenges noted.

In conclusion, as to applying Maya Angelou's question of "more alike than unalike" to the entities of regular COPD and COPD associated with AATD the response is while they share commonalities of being under-recognized and very debilitating, they are distinctly unalike in important ways, perhaps most pronouncedly regarding the possibility and needs for clinical trial design. The infeasibility of conducting clinical trials in AATD using conventional outcome measures for regular COPD requires innovative thought and design, especially considering CT densitometry as a primary outcome measure. The appeal of CT densitometry as a primary outcome measure is based on its measuring lung integrity[43] and, importantly, on the demonstrated feasibility of using it as an outcome in trials regarding treatment of AATD.

Declaration of Interest

Dr. Stoller serves as a member of the Board of Directors of the Alpha-1 Foundation and as a consultant to: 23andMe, Grifols, Takeda, CSL-Behring, InhibRx, Arrowhead Pharmaceuticals, Dicerna, Insmed, Vertex, 4DMT, Korro, and Bridgebio.

Table 4. Sample Size Estimates to Show Outcome Differences[29] Based on the Data from the RAPID Trial[a]

Outcome Measure	Observed Difference Between Aug and Placebo in RAPID at 24 Months	Sample Size (per Group) Needed for Observed Difference to Achieve Statistical Significance
FEV_1% Predicted	0.8% predicted (-3.1% predicted vs. -2.3% predicted), p=0.21	N=3510 per group (Total N=7020)
Exacerbation Frequency	0.28 per year (1.70 vs. 1.42 at 24 months)	N=1525 –1929 per group (Total N=3050–3858)
SGRQ	0.8-unit benefit in August recipients, p=0.91	N=3191 per group (Total N=6382)

[a]Thanks to Amy Nowacki, PhD

FEV_1=forced expiratory volume in 1 second; SGRQ=St George's Respiratory Questionnaire

References

1. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Stoller JK, Snider GL, Brantly ML, Fallat RJ, Stockley RA. ***Am J Respir Crit Care Med.*** 2003;168(7):816-900. doi: https://doi.org/10.1164/rccm.168.7.818

2. Angelou M. *Human Family*. All Poetry website. Accessed May 2021. https://allpoetry.com/Human-Family

3. Centers for Disease Control and Prevention (CDC). COPD. CDC website. Updated July 29, 2021. Accessed May 20, 2021. https://www.cdc.gov/dotw/copd/index.html#:~:text=Chronic%20lower%20respiratory%20disease%2C%20mainly,genetics%20can%20also%20cause%20COPD

4. HealthyPeople.gov. COPD mortality. HealthyPeople.gov website. Published 2020. Accessed May 20, 2021. https://www.healthypeople.gov/2020

5. Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced all-cause mortality in the ETHOS trial of budesonide/glycopyrrolate/formoterol for chronic obstructive pulmonary disease. A randomized, double-blind, multicenter, parallel-group study. ***Am J Respir Crit Care Med.*** 2021;203(5):553-564. doi: https://doi.org/10.1164/rccm.202006-2618OC

6. Celli B, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. ***N Engl J Med.*** 2004;350(10):1005-1012. doi: https://doi.org/10.1056/NEJMoa021322

7. Stoller JK, Tomashefski J Jr, Crystal RG, et al. Mortality in individuals with severe deficiency of alpha-1 antitrypsin: findings from the National Heart, Lung, and Blood Institute Registry. ***Chest.*** 2005;127(4):1196-1204. doi: https://doi.org/10.1016/S0012-3692(15)34467-6

8. McElvaney NG, Stoller JK, Buist AS, et al; Alpha-1 Antitrypsin Deficiency Registry Study Group. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of alpha 1-antitrypsin deficiency. ***Chest.*** 1997;111(2):394-403. doi: https://doi.org/10.1378/chest.111.2.394

9. Stoller JK, Smith P, Yang P. Physical and social impact of alpha-1 antitrypsin deficiency: results of a mail survey of the readership of a national newsletter. ***Cleve Clin J Med.*** 1994;61(6):461-467. doi: https://doi.org/10.3949/ccjm.61.6.461

10. Stoller JK, Sandhaus RA, Turino G, Dickson R, Rodgers K, Strange C. Delay in diagnosis of alpha-1 antitrypsin deficiency: a continuing problem. ***Chest.*** 2005;128(4):1989-1994. doi: https://doi.org/10.1378/chest.128.4.1989

11. Stoller JK, Brantly M. The challenge of detecting alpha-1 antitrypsin deficiency. ***COPD.*** 2013;10(sup 1):26-34. doi: https://doi.org/10.3109/15412555.2013.763782

12. Silverman EK, Miletich JP, Pierce JA, et al. Alpha-1 antitrypsin deficiency. High prevalence in the St. Louis area determined by direct population screening. ***Am Rev Respir Dis.*** 1989;140(4):961-966. doi: https://doi.org/10.1164/ajrccm/140.4.961

13. Nakanishi T, Forgetta V, Handa T, et al. The undiagnosed disease burden associated with alpha-1 antitrypsin deficiency genotypes. ***Eur Respir J.*** 2020;56(6):2001441. doi: https://doi.org/10.1183/13993003.01441-2020

14. Campos MA, Wanner A, Zhang G, Sandhaus R. Trends in the diagnosis of symptomatic patients with alpha-1 antitrypsin deficiency between 1968 and 2003. ***Chest.*** 2005;128(3):1179-1186. doi: https://doi.org/10.1378/chest.128.3.1179

15. Kohnlein T, Janciauskiene S, Welte T. Diagnostic delay and clinical modifiers in alpha-1 antitrypsin deficiency. ***Ther Adv Respir Dis.*** 2010;4(5):279-287. doi: https://doi.org/10.1177/1753465810376407

16. Greulich T, Ottaviani S, Bals R, et al. Alpha-1 antitrypsin deficiency - diagnostic testing and disease awareness in Germany and Italy. ***Respir Med.*** 2013;107(9):1400-1408. doi: https://doi.org/10.1016/j.rmed.2013.04.023

17. Tejwani V, Nowacki A, Fye E, Sanders C, Stoller JK. The impact of delayed diagnosis of alpha-1 antitrypsin deficiency: the association between diagnostic delay and worsened clinical status. ***Respir Care.*** 2019;64(8):915-922. doi: https://doi.org/10.4187/respcare.06555

18. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. ***N Engl J Med.*** 2011;365(17):1567-1575. doi: https://doi.org/10.1056/NEJMoa1106955

19. Strnad P, McElvaney N, Lomas D. Alpha-1 antitrypsin deficiency. ***N Engl J Med.*** 2020;382:1447-1455. doi: https://doi.org/10.1056/NEJMra1910234

20. Stavngaard T, Shaker SB, Dirksen A. Quantitative assessment of emphysema distribution in smokers and patients with alpha-1 antitrypsin deficiency. ***Respir Med.*** 2006;100(1):94-100. doi: https://doi.org/10.1016/j.rmed.2005.04.001

21. Parr D, Stoel B, Stolk J, Stockley R. Pattern of emphysema distribution in alpha1-antitrypsin deficiency influences lung function impairment. ***Am J Respir Crit Care Med.*** 2004;170(11):1172-1178. doi: https://doi.org/10.1164/rccm.200406-761OC

22. Martinez-Garcia M, Miravitlles M. Bronchiectasis in COPD patients: more than a comorbidity? ***Int J Chron Obstruct Pulmon Dis.*** 2017;12:1401-1411. doi: https://doi.org/10.2147/COPD.S132961

23. Sanduzzi A, Ciasullo E, Capitelli L, et al. Alpha-1 antitrypsin deficiency and bronchiectasis: a concomitance or a real association? ***Int J Environ Res Public Health.*** 2020;17:2294-2301. doi: https://doi.org/10.3390/ijerph17072294

24. Parr D, Guest PG, Reynolds JH, Dowson L, Stockley R. Prevalence and impact of bronchiectasis in alpha-1 antitrypsin deficiency. ***Am J Respir Crit Care Med.*** 2007;176(12):1215-1221. doi: https://doi.org/10.1164/rccm.200703-489OC

25. National Emphysema Treatment Trial. Randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. ***N Engl J Med.*** 2003;348(21):2059-2073. doi: https://doi.org/10.1056/NEJMoa030287

26. Stoller JK, Aboussouan L, Kanner R, et al. Characteristics of alpha-1 antitrypsin deficient individuals in the long-term oxygen treatment trial (LOTT) and comparison with other subjects with chronic obstructive pulmonary disease. ***Ann Am Thorac Soc.*** 2015;12(12):1796-1804. doi: https://doi.org/10.15131/AnnalsATS.201506-389OC

27. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. ***N Engl J Med.*** 2007;356(8):775-789. doi: https://doi.org/10.1056/NEJMoa063070

28. Tashkin DP, UPLIFT Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. ***N Engl J Med.*** 2008;359(15):1543-1554. doi: https://doi.org/10.1056/NEJMoa0805800

29. Calverley PM, Rabe KF, Goehring U, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomized clinical trials. ***Lancet.*** 2009;374(9691):685-694. doi: https://doi.org/10.1016/S0140-6736(09)61255-1

30. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. ***N Engl J Med.*** 2011;365(8):689-698. doi: https://doi.org/10.1056/NEJMoa1104623

31. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. ***N Engl J Med.*** 2011;364(12):1093-1103. doi: https://doi.org/10.1056/NEJMoa1008378

32. Albert RK, Au DH, Blackford AL, et al. A randomized trial of long-term oxygen for COPD with moderate desaturation. ***N Engl J Med.*** 2016;375(17):1617-1627. doi: https://doi.org/10.1056/NEJMoa1604344

33. Ismaila AS, Risebrough N, Schroeder M, et al. Cost-effectiveness of once-daily single-inhaler triple therapy in COPD: the IMPACT trial. ***Int J Chron Obstruct Pulmon Dis.*** 2019;14:2681-2695. doi: https://doi.org/10.2147/COPD.S216072

34. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha-1 antitrypsin augmentation therapy. ***Am J Respir Crit Care Med.*** 1999;160(5):1468-1472. doi: https://doi.org/10.1164/ajrccm.160.5.9901055

35. Dirksen A, Piitulainen E, Parr DG, et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha-1 antitrypsin deficiency. ***Eur Respir J.*** 2009;33(6):1345-1353. doi: https://doi.org/10.1183/09031936.00159408

36. Chapman K, Burdon JGW, Piitulainen E, et al. Intravenous augmentation treatment in severe alpha-1 antitrypsin deficiency (RAPID): a randomized, double-blind, placebo-controlled trial. ***Lancet.*** 2015;386(9991):360-368. doi: https://doi.org/10.1016/S0140-6736(15)60860-1

37. Stolk J, Stockley RA, Stoel BC, et al. Randomised controlled trial for emphysema with a selective agonist of the gamma-type retinoic acid receptor. ***Eur Respir J.*** 2012;40(2):306-312. doi: https://doi.org/10.1183/09031936.00161911

38. Stolk J, Tov N, Chapman KR, et al. Efficacy and safety of inhaled alpha-1 antitrypsin in patients with severe alpha-1 antitrypsin deficiency and frequent exacerbations of COPD. ***Eur Respir J.*** 2019;54(5):1900673. doi: https://doi.org/10.1183/13993003.00673-2019

39. Idell S, Cohen AB. Alpha-1 antitrypsin deficiency. ***Clin Chest Med.*** 1983;4(3):359-375. doi: https://doi.org/10.1016/S0272-5231(21)00213-6

40. Schluchter MD, Stoller JK, Barker AF, et al. Feasibility of a clinical trial of augmentation therapy for alpha-1 antitrypsin deficiency. ***Am J Respir Crit Care Med.*** 2000;161(3):796-801. doi: https://doi.org/10.1164/ajrccm.161.3.9906011

41. Stockley RA, Edgar RG, Starkey S, Turner AM. Health status decline in alpha-1 antitrypsin deficiency: a feasible outcome for disease modifying therapies? ***Respir Res.*** 2018;19:137-146. doi: https://doi.org/10.1186/s12931-018-0844-6

42. Wencker M, Fuhrmann B, Banik N, et al. Longitudinal follow-up of patients with alpha 1-protease inhibitor deficiency before and during therapy with IV alpha 1-protease inhibitor. ***Chest.*** 2001;119(3):737-744. doi: https://doi.org/10.1378/chest.119.3.737

43. Parr D, Dirksen A, Piitulainen E, et al. Exploring the optimum approach to the use of CT densitometry in a randomized placebo-controlled study of augmentation therapy in alpha-1 antitrypsin deficiency. ***Respir Res.*** 2009;10:75. doi: https://doi.org/10.1186/1465-9921-10-75