Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Review

Exacerbations of Lung Disease in Alpha-1 Antitrypsin Deficiency

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is an important risk factor for development of chronic obstructive pulmonary disease (COPD). Patients with AATD classically develop a different pattern of lung disease from those with usual COPD, decline faster and exhibit a range of differences in pathogenesis, all of which may be relevant to phenotype and/or impact of exacerbations. There are a number of definitions of exacerbation, with the main features being worsening of symptoms over at least 2 days, which may be associated with a change in treatment. In this article we review the literature surrounding exacerbations in AATD, focusing, in particular, on ways in which they may differ from such events in usual COPD, and the potential impact on clinical management.

Abbreviations: alpha-1 antitrypsin, **AATD**; chronic obstructive pulmonary disease, **COPD**; alpha-1 antitrypsin, **AAT**; neutrophil elastase, **NE**; acute exacerbation of chronic obstructive pulmonary disease, **AECOPD**; tumour necrosis factor alpha, **TNF-α**; C-reactive protein, **CRP**; interleukin-1 beta, **IL-1ß**; interleukin-8, **IL-8**; potentially pathogenic microorganisms, **PPM**; cystic fibrosis, **CF**; interleukin-6, **IL-6**; leukotriene B-4, **LTB4**; mydoperoxidase, **MPO**; Z-protein, **Z-AAT**; TNF-α converting enzyme, **TACE**; reactive oxygen species, **ROS**; *Human rhinovirus*, **HRV**; interquartile range, **IQR**; oral corticosteroids, **OCSs**; odds ratio, **OR**; confidence interval, **CI**; EXAcerbation and Computed Tomography Scan in Lung Endpoints trial, **EXACTLE**; inhaled corticosteroids, **ICSs**; pulmonary rehabilitation, **PR**

Funding Support: DJS is supported by a grant from the British Lung Foundation; PRE is supported by grants from the Alpha-1 Foundation and the American Thoracic Society (ATS) Foundation; AMT has current grant funding from NIHR, Health Foundation, the Alpha-1 Foundation, the ATS Foundation, AstraZeneca, CSL Behring and Chiesi.

Date of Acceptance: September 18, 2020 | **Published Online Date:** November 19, 2020

Citation: Smith DJ, Ellis PR, Turner AM. Exacerbations of lung disease in alpha-1 antitrypsin deficiency. *Chronic Obstr Pulm Dis.* 2021;8(1):162-176. doi: https://doi.org/10.15326/jcopdf.2020.0173

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Keywords:

chronic obstructive pulmonary disease; COPD; alpha-1 antitrypsin deficiency; exacerbation; emphysema; neutrophil

Introduction

Alpha-1 antitrypsin deficiency (AATD) is an inherited disorder characterized by reduced levels of serum alpha-1 antitrypsin (AAT), a protease inhibitor. The imbalance between proteases and anti-proteases, respectively neutrophil elastase (NE) and AAT, together with the effect of polymerized AAT, predisposes affected patients to a spectrum of lung and liver diseases.[1] Respiratory manifestations of AATD classically involve basal panacinar emphysema, though chronic bronchitis and bronchiectasis are also recognized.[2-4] AATD is well-documented as a predisposing factor to the development of chronic obstructive pulmonary disease (COPD).[2] In contrast to non-AAT-deficient (usual) COPD, AATD COPD patients typically present at a younger age with a severity of lung dysfunction that is out of proportion to the relatively mild smoking burden, albeit with the same features of breathlessness, chronic cough and regular sputum production.

Patients with AATD COPD are known to experience acute exacerbations of COPD (AECOPD), defined

as an acute worsening of respiratory symptoms that results in additional therapy.[5] These events are common and typically manifest as a deviation from usual sputum volume, sputum purulence and breathlessness, lasting approximately 2 weeks on average.[6,7] Exacerbations in AATD are demonstrated to have a detrimental impact on disease progression and quality of life.[8-10] Despite this, evidence surrounding exacerbation in AATD is very limited, especially relating to the acute management and prevention of exacerbations in AATD. The only AATD-specific treatment, AAT augmentation therapy, is capable of reducing lung function decline, but in meta-analysis of randomized controlled trial data has been controversially demonstrated to associate with an increase in exacerbation rates.[11] Current management of exacerbations is based on limited evidence, alongside the assumption of transferable mechanisms in usual COPD. However, exacerbations of AATD are both biochemically and clinically dissimilar to usual COPD and it is possible that AATD may benefit from distinct management and prevention strategies.[7,12,13]

Controlling the frequency and severity of exacerbations in AATD, and the management thereof, could have a positive impact on the quality of life, disease progression and prognosis of affected patients. This article reviews the evidence base for decision making about acute exacerbation management and exacerbation risk reduction specific to AATD patients.

Causes of Exacerbations

The etiology of COPD exacerbations can be broadly classified into infective and non-infective. In usual COPD, viral, bacterial and viral-bacterial co-infections cause 23%, 29% and 25% of infective hospitalized exacerbations respectively.[14] Non-infective exacerbations are estimated to comprise 28% of exacerbations and result from a variety of stimuli, including atmospheric pollution, seasonal variation, pulmonary embolus and congestive cardiac failure.[14-18] Many exacerbations are also of unknown origin. Surprisingly, in AATD COPD, exacerbation etiology has rarely been reported, permitting only limited inferences to be made about differences from usual COPD.

Infective Exacerbations

Bacterial Events and Bacterial Colonization

Mechanisms for bacterial exacerbation in COPD include acquisition of new bacterial strains and expansion of stable bacterial colonies within the tracheobronchial tree. Bacteria implicated in infective exacerbations of AATD include *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae*.[12] It is not clear if this relates to new acquisition or expansion of stable bacterial colonies; however, isolation of new strains of these bacteria in usual COPD are associated with a significantly increased risk of an exacerbation.[19] Isolation of newly acquired H influenzae at exacerbation is reported to associate with greater forced expiratory volume in 1 second (FEV_1) decline than H influenzae-associated exacerbations in patients with pre-existing colonization.[20] This may relate to significantly greater increases in sputum concentrations of NE, tumor necrosis factor alpha (TNF-α) and serum C-reactive protein (CRP) in exacerbations attributed to new bacterial acquisition compared to infective exacerbations of an alternate nature.[21] Purified human AAT has been shown in vitro to significantly inhibit bacterial endotoxin-induced TNF-α and interleukin-1 beta (IL-1β) release by monocytes and interleukin-8 (IL-8) release by neutrophils in a concentration-dependent manner, suggesting a role for AAT in prohibiting excess bacterial-driven inflammation.[22] Since NE and TNF-α are elevated in stable AATD, acquisition of new bacterial strains in the absence of sufficient AAT may lead to excessive cumulative increases in inflammation which may be contributary to exacerbation pathogenesis.[13]

Approximately two-thirds of patients with AATD are reported to exhibit lower airway bacterial colonization by potentially pathogenic microorganisms (PPM), compared to 29%–52% in usual COPD.[23-26] Lower airway bacterial colonization is demonstrated to relate to increased exacerbation frequency (p=0.023), which may relate to the positive correlation between airway bacterial load and concentration of pulmonary inflammatory mediators (p<0.05).[23,27] Conversely, individuals with AATD have been observed to exhibit significantly lower total bacterial loads (as measured by 16S sequencing) in stable state sputum samples compared to usual COPD (p=0.008), including significantly decreased levels of *Moraxella catarrhalis* and *Streptococcus pneumoniae* (p=0.012 and p=0.001,

respectively).[28] After adjustment for lung function, Rosell et al observed that only positive cultures with a high PPM load are associated in a dose-dependent manner with exacerbation occurrence (p=0.005), supporting the concept of a theoretical threshold for minimum bacterial load beyond which inflammation may manifest in clinical features of exacerbation.[24,29] This may suggest a lesser contribution of PPM expansion in the etiology of AECOPD in AATD. One large scale study is currently underway which may provide insight in this area.[30]

Radiological bronchiectasic changes have been observed in up to 94% of individuals with AATD, although these changes were determined to be clinically significant in only 27% of patients.[3] Co-existence of bronchiectasis in COPD is associated with an increased prevalence of colonization and higher rates of *Pseudomonas aeruginosa* isolation.[31] Due to the relatively high NE burden shared by cystic fibrosis (CF)and AATD, it is conceivable that the conditions may have a synergistic effect on airway disease and colonization.[32] However, studies investigating this have reported contradicting outcomes in mild AAT phenotypes; it has not been tested in PiZZ phenotype individuals.[33-35] Accordingly, it is not clear if other CF-typical microbes may play a causative role in exacerbations of AATD.

Viral Events

As in usual COPD, viral and viral-bacterial co-infections may account for a significant proportion of exacerbations in AATD. However, there is not enough evidence reported at this stage to be able to make useful inferences regarding viral etiology in AATD, though there is much data in usual COPD.[36]

Non-infective Exacerbations

Non-infective exacerbations have not been reported on in AATD. Air pollutants are implicated in disease progression in AATD and it is plausible that they may comprise a further role in pathogenesis of non-infective exacerbations, as in usual COPD, due to the increase in pulmonary chemokines including IL-8 and interleukin-6 (IL-6).[37-39] In usual COPD populations, depression and cardiovascular disease are related to exacerbation frequency.[40] Analysis of a large population-based database revealed significantly lower prevalence of ischemic heart disease and depression in AATD compared to usual COPD, which could suggest a lower incidence of comorbidity-related exacerbations in AATD.[41]

Inflammatory Effects

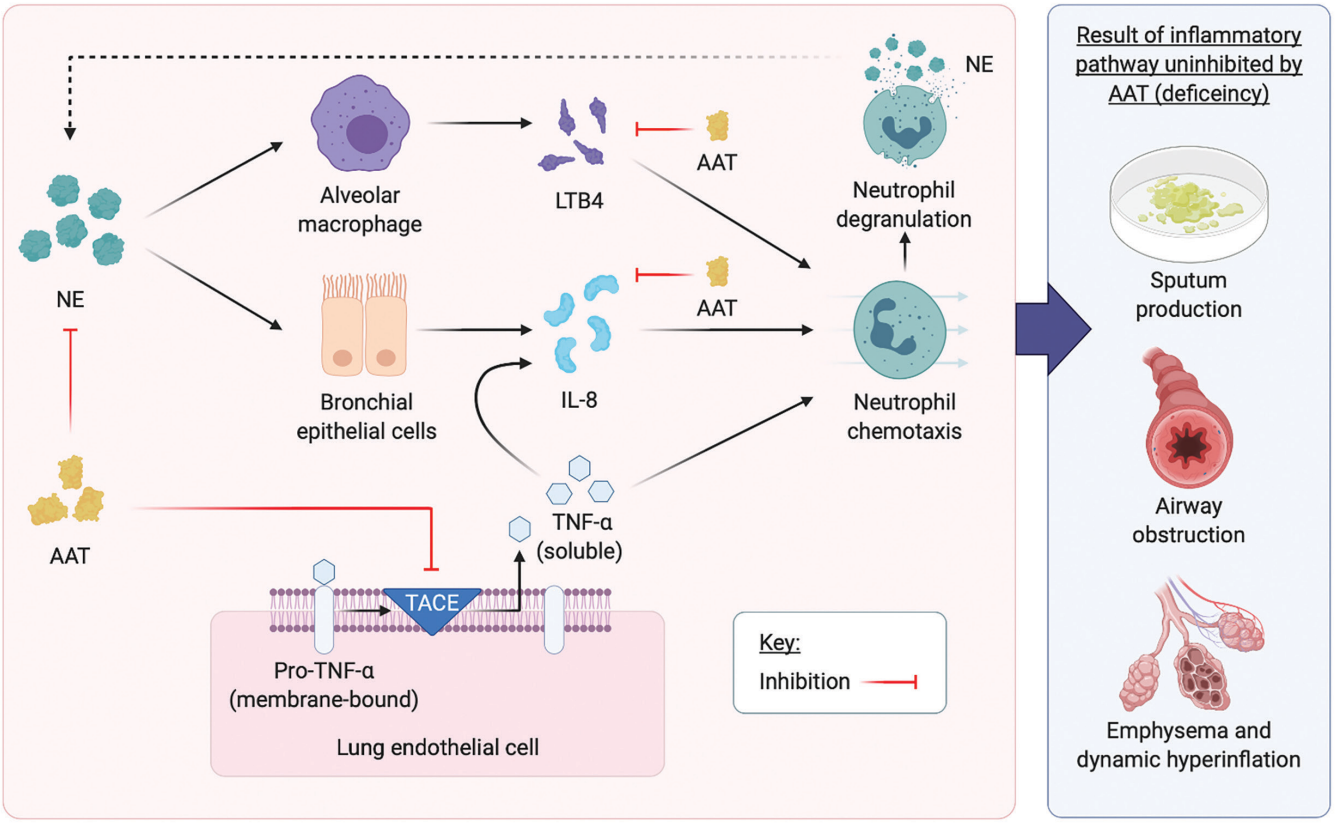
A major change between stable COPD and exacerbated COPD is the difference in airway inflammation. In particular, COPD exacerbations are associated with elevated neutrophils, which are considered a key driver of airway inflammation in exacerbations and related to exacerbation severity.[14,42,43] Mechanisms mediating concentrations and/or activity of neutrophils and other inflammatory mediators may be critical for understanding the differences in pathogenesis between usual and deficient exacerbations.

Leukotriene B-4 and Interleukin-8

In the setting of AATD COPD, elevated NE contributes to a pro-inflammatory milieu within the airways (Figure 1). NE acts on alveolar macrophages and bronchial epithelial cells to induce release of potent neutrophil chemoattractants leukotriene B4 (LTB4) and interleukin-8 (IL-8, CXCL8) respectively.[44-46] AAT also abrogates IL-8 and LTB4-mediated neutrophil chemotaxis by up to 40%, independently of anti-protease activity, potentially via direct binding and inhibition.[47-49] Consequently in AATD COPD, both the concentration and contribution to sputum chemotactic activity of LTB4 and IL-8 are significantly greater than in usual COPD.[12,50-52] IL-8 concentration is observed to be significantly higher in frequent, compared to infrequent, exacerbators (p=0.001) and may be causative in this respect.[27]

Increases in LTB4 and IL-8 at exacerbation are significantly higher in AATD than usual COPD (p=0.02 and p=0.01, respectively), although parallel rises in myeloperoxidase (MPO) at exacerbation are often not reported to be significantly different between the 2 groups, which is unexpected.[12,53] It is plausible that there are additional mechanisms of pro-inflammatory neutrophilic modulation in usual COPD, including aberrant neutrophil migration, which has been demonstrated to increase inflammation in non-deficient individuals.[54] Additionally, Z protein (Z-AAT) formation, polymerization and accumulation within neutrophils can enhance neutrophil apoptosis, and could, theoretically, contribute to a relatively supressed chemotactic response in AATD individuals during exacerbation.[55]

Figure 1. Effects of Alpha-1 Antitrypsin on Key Pulmonary Inflammatory Pathways



NE=neutrophil elastase; AAT=alpha-1 antitrypsin; LTB4=leukotriene-B4; IL-8=interleukin-8; TNF-α= tumour necrosis factor-α; TACE=TNF-α converting enzyme

Tumor Necrosis Factor-Alpha

AAT modulates the release and activity of pro-inflammatory cytokine TNF-α (Figure 1). Active TNF-α is a principal driver of inflammation in AECOPD with sputum concentrations observed to elevate more than fourfold during exacerbations of usual COPD.[56] TNF-α facilitates leucocyte and neutrophil migration to the bronchial mucosa, stimulates neutrophil degranulation and superoxide production and upregulates IL-8 release.[57-59] Sputum concentrations of TNF-α are observed to elevate more than fourfold during exacerbations of usual COPD compared to stable state (p=0.01), correlating with the percentage of neutrophils present within induced sputum samples. Application of AAT to neutrophils, airway macrophages and endothelial cells results in decreased TNF-α secretion.[13,52,60] Inhibition of TNF-α secretion occurs by AAT-induced inhibition of the TNF-α converting enzyme (TACE) on the membrane surface, which is responsible for cleavage of pro-TNF-α to the soluble active form.[13,49] Deficient AAT during exacerbation may permit dysregulated action and release of TNF-α within the pulmonary microenvironment, capable of promoting clinical features of exacerbation.[12] Future investigations of TNF-α concentrations during exacerbations of AATD may inform the provision of TNF-α targeted therapies, which to date, have only been investigated in usual COPD.[61]

AAT has other anti-inflammatory effects (Table 1),[62-76] however, these have not been investigated in the context of exacerbation, or even stable COPD in some cases.

Intrinsic Neutrophil Properties

Recent data suggests neutrophils isolated from patients in AATD may also differ intrinsically from those in usual COPD.[77] Murphy et al report that neutrophils isolated from AATD individuals have an increased quantity and activity of neutrophil primary granule proteins in the membrane proteome when compared to usual COPD. In response to stimulation,

Table 1. Table Describing Additional Inflammatory Modulating Effects of Alpha-1 Antitrypsin and Implication in Alpha-1 Antitrypsin Deficiency

Molecule	Action of Molecule	Action of AAT on Molecule	Possible Result of AAT Deficiency on This Interaction
Calpain I	Promote directional neutrophil migration toward chemotactic stimuli[62]	Inhibition of Calpain I[63]	Promote efficient neutrophil migration, capable of promoting acute and chronic inflammation[64]
Free Haem	Neutrophil activation. Amplification of inflammatory response and oxidative stress[65]	AAT acts as a free haem scavenger[66]	Increased neutrophilic activation and inflammation including IL-8 release and ROS production[66]
Gelatinase B	Mediates neutrophil migration into airway[67]	Inhibition of Gelatinase B[55]	Increased neutrophil infiltration into airways
High-density Lipoprotein	Reduces neutrophilic inflammation[68]	AAT forms a complex with HDL which provides a greater reduction in neutrophilic and cytokine-driven (TNF-α, MCP-1, IL-1β) inflammation when compared to HDL or AAT alone[68]	Reduced protective effect of HDL against neutrophilic and cytokine-driven inflammation [68]
IL-1β	Pro-inflammatory cytokine. Potent activator of alveolar macrophages[69] Stimulates production of neutrophil chemoattractants[70]	Inhibition of IL-1β[22]	Increased neutrophilic inflammation
Oxidized Methionine Residues on AAT	Act as anti-oxidant, controlling levels of neutrophil released ROS and reducing oxidant-driven amplification of lung inflammation[71-73]	n/a	Increased neutrophil ROS[71] Increased oxidant driven lung inflammation
Polymeric Z-AAT	Potent neutrophil chemoattractant[74]	n/a	Increased neutrophil chemoattraction[74]
Proteinase-3	Induces mucous secretion and reduce mucous clearance. Cytokine activation and release, including TNF-α and IL-8 Degradation of progranulin (anti-inflammatory mediator)[75]	Inhibition of PR3[76]	Increased neutrophil chemotaxis and activation. Increased net mucous production[75]

AAT=alpha-1 antitrypsin; ROS=reactive oxygen species; PR3=proteinase-3; IL-1β=interleukin-1β; TNF-α=tumour necrosis factor-α; HDL=high-density lipoprotein; MCP-1=monocyte chemoattractant protein-1

neutrophils isolated from AATD individuals mounted a significantly greater reactive oxygen species (ROS) and NE response compared to FEV_1-matched COPD controls.[77] These findings may be relevant in exacerbation pathogenesis. However, the sample size of the study was small (n=6 patients per cohort), so results should be viewed with caution.[77]

Clinical Features

Presentation of Exacerbations

The classical study by Anthonisen et al recognized 3 major symptoms in AECOPD; deviation in sputum purulence, sputum volume and dyspnea and categorized exacerbations as type 1 when all

3 major symptoms deteriorated, type 2 if only 2 major symptoms deteriorated and type 3 when 1 of 3 major symptoms deteriorated in combination with symptoms of an upper respiratory tract infection including wheeze and cough.[6] Vijayasaratha and Stockley demonstrated through diary card analysis that type 1, 2 and 3 exacerbations account for 34%, 32% and 14% of total exacerbations in a cohort of patients with AATD COPD, with the remaining 20% of exacerbations defined by 1 major symptom with no minor symptoms.[7] However, a previous investigation in AATD suggested that the proportion of severe exacerbations may be much greater (63%), although this study was less focused on identifying unreported exacerbations, which may account for the difference.[78] Anthonisen criteria has also been demonstrated to relate to exacerbation duration in AATD, with type 1 exacerbations lasting longer than type 2 exacerbations, which were longer than type 3 (p=0.001).[79]

Untreated exacerbations in AATD are estimated to contribute to 48% of total exacerbations, similar to rates seen in usual COPD.[7,80] Patients' perception of unwellness and breathlessness was significantly shorter in untreated versus treated AATD exacerbations, by approximately 80% and 50% respectively, implicating their role in patients' decisions to seek additional treatment.[7] Cold-like symptoms were reported in approximately one-third of AATD COPD exacerbations and coryzal illness was reported as the best independent predictive factor of AATD patients seeking treatment (p=0.001) according to regression analysis.[7,79] This may relate to the observation that cold-like symptoms during exacerbations of usual COPD relate to significantly greater falls in FEV_1 (p=0.043), compared to exacerbations without such features.[20] Upper-respiratory tract symptoms at exacerbation are considered to be associated with viral infections, with higher *Human rhinovirus* (HRV) loads detected in patients with cold-like symptoms or sore throats than those without (p=0.046 and p=0.006, respectively).[81] Colds in the absence of viral infection still predict a worse exacerbation symptom score and are more measurable in clinical terms.[82]

Rate of Exacerbations

Evaluation of daily diary cards to identify Anthonisen symptoms indicates a median (interquartile range [IQR]) annualized exacerbation rate of 5.0 episodes (4.0 to 7.0) per patient per year in AATD and 2.5 (1.3 to 3.9) in usual COPD.[7,80] Median (IQR) exacerbation duration in AATD is reported to be 14 days (7–21), which is approximately double that observed in usual COPD, using studies of similar methodology.[78,83] Additionally, a higher rate of hospitalized exacerbations can be observed in AATD COPD compared to usual COPD.[80,84] The difference in severity and slower resolution of exacerbations may relate to inflammatory differences. This is supported by the observation that sputum purulence, which associates with MPO, remained elevated for up to 6 weeks following exacerbation in deficient individuals.[7,85] Chronic bronchitis is associated with a higher frequency of exacerbations in AATD, which may relate to higher concentrations of IL-8 and NE in induced sputum of AATD patients who chronically expectorate.[4,78,86]

In a cohort of 87 AATD COPD participants, the proportion of patients experiencing exacerbations each year was consistent across a 3-year period, although, whether individual exacerbation rates remained consistent was not reported.[79] Patients experiencing exacerbations in year 1 were more likely to continue having exacerbations in the second and third year (p=0.04 and p<0.001, respectively).[79] The demographics and clinical characteristics of frequent exacerbators in AATD, and the influence of specific COPD phenotypes (e.g., small airways disease) upon rate of exacerbations are not currently known.

Clinical Consequences

Exacerbations in AATD are implicated in disease progression.[8,9] Decline in FEV_1 is significantly associated with an elevated annual exacerbation rate in AATD individuals.[8,84,87,88] AATD exacerbations are reported to be of greater impact in patients with more severe lung impairment, which might relate to an observed inverse relationship between baseline FEV_1 (percentage of predicted) and change in concentrations of sputum IL-8 and IL-6 at exacerbation.[20,79] This may be particularly detrimental in AATD, given the higher annual decline in FEV_1 observed in AATD patients when compared to usual COPD.[8,87-89] There is a significant relationship between increased self-reported exacerbation rate and longitudinal deterioration of the St George's Respiratory Questionnaire score, in

terms of both total score and sub-scales (p<0.001 for all).[10] In a cohort of AATD patients receiving AAT augmentation therapy, increased exacerbation frequency was demonstrated to relate to significantly lower Short Form-36 Health questionnaire mental composite scores, indicating poorer mental health in frequent exacerbators.[90] In this case, it is unclear whether pulmonary exacerbations contribute to the development of anxiety and depression or if the reverse is true.

Managing and Preventing Exacerbations

Acute Management

Antibiotic Therapy

The aim of acute management for AECOPD is to minimize the negative impact of the current exacerbation and reduce the occurrence of future events.[5] Antibiotic therapy is used frequently in usual COPD and treatment guidance often relates to sputum purulence.[6] Limited evidence suggests that antibiotic therapy in AATD is effective at reducing bacterial load and detectability of pathogens.[12] Investigations in AATD have shown that exacerbation duration is related to a delay in starting antibiotic treatment, although the period from treatment commencement to exacerbation resolution is unaltered, highlighting the importance of early intervention, potentially via patient rescue packs.[79]

Systemic Corticosteroids

Oral corticosteroids (OCSs) are recommended for acute management of AECOPD.[5] There is no published data on OCSs with regards to AATD. In a meta-analysis of usual COPD individuals, OCSs are demonstrated to reduce the risk of treatment failure (odds ratio[OR] 0.48; 95% confidence interval [CI] 0.35 to 0.67) and associate with a lower level of relapse, compared to controls.[91] These effects are attributed to the multiple actions of (systemic) corticosteroids, including decreased pulmonary inflammation, evidenced by significantly decreased MPO concentrations.[92,93] However, OCSs significantly increase the likelihood of adverse events (OR 2.33; 95% CI 1.59 to 3.43), most notably, hyperglycemia.[91] This may be particularly relevant for AATD individuals , who appear to exacerbate more frequently, as adverse effects of OCSs may follow a cumulative dose-response relationship.[7,94,95] Therefore, OCS therapy should be targeted to individuals who are most likely to benefit, which has effectively been predicted by eosinophilia (peripheral blood eosinophil count >2%) in usual COPD.[96,97] AATD and usual COPD have a similar prevalence of eosinophilia (approximately 40%).[98,99] However, the efficacy of OCS use in acute management of exacerbations should be tested in an AATD cohort, as pathogenesis between the 2 conditions differ which may impact clinical outcomes.

Reducing Risk of Future Events

Augmentation Therapy

Augmentation therapy is effective in reducing the rate of computed tomography-measured lung density decline, though its role in exacerbation is less clear.[11] In a recent meta-analysis, intravenous infusions of AAT were found to associate with a significantly increased annual exacerbation rate (0.29/year; CI 0.02–0.54; p=0.02), although the primary studies included in this analysis were not appropriately powered to detect differences in exacerbation rate.[11,100,101] The EXAcerbations and Computed Tomography Scan as Lung Endpoints (EXACTLE) study (included in the meta-analysis) reported no change in exacerbation frequency with augmentation therapy, although it did report a reduction in exacerbation severity.[100] Conversely, an observational study by Barros-Tizón et al reported a reduction in the mean number of exacerbations per patient and reduced incidence of severe exacerbations during the intravenous augmentation treatment period.[102] Such observations may relate to decreased LTB4 levels, which can be observed in deficient patients following AAT augmentation, probably as a direct response to decreased NE.[46] The effect of augmentation therapy on exacerbations would be a useful target of future research.

Inhaled Corticosteroids and Bronchodilators

Although no specific data in AATD exists, inhaled corticosteroids (ICSs) and bronchodilators are used in the management of AATD COPD.[5] The role of ICSs in reducing exacerbation rate in usual COPD is clearly demonstrated, both alone and in combination with long-acting beta agonists.[7,12,103,104] ICS use in usual COPD has been shown to cause a significant reduction in concentration of key inflammatory drivers of AECOPD, including IL-8, TNF-α and mean

percentages of neutrophils (p< 0.01 for all) although changes in LTB4 are repeatedly not observed.[105-107] ICSs may be particularly beneficial in AATD, where exacerbation rate and inflammation are known to be greater than usual COPD.[7,12]

Evidence of adverse effects of ICSs are also well-documented, particularly severe pneumonia, which is frequently associated with *Pseudomonas aeruginosa* infection and results in excess death.[108-110] It is conceivable that this may be of greater consequence to AATD individuals. This follows observations in transgenic mice that human AAT is protective against mortality due to *Pseudomonas aeruginosa* pneumonia.[111] Effectiveness of ICS therapy, as with OCS, may be informed by eosinophilia in usual COPD.[99,112] Blood eosinophilia has also been suggested in AATD as an indication for ICS use in order to reduce FEV_1 decline, which may in turn reduce exacerbation burden.[81,113] In instances where eosinophilia is absent, or ICS therapy is not successful, long-acting bronchodilators may be effective at reducing exacerbation rate and severity.[114]

Vaccination

Influenza and pneumococcal vaccinations, PCV13 and PPSV23, are recommended for patients with COPD and are demonstrated to reduce exacerbation rate in usual COPD.[5,115,116] Köhnlein et al observed significantly fewer exacerbations in 267 AATD patients vaccinated against pneumococci, influenza or both (p=0.01), according to a self-reported questionnaire, with a loose definition of exacerbation.[117] In a larger study of influenza vaccinations, adopting stricter definitions of exacerbations and recorded via telephone interviews, Campos et al reported no significant differences in exacerbation rate or severity in vaccinated AATD patients versus controls.[118] In fact, where exacerbations were defined according to the definition proposed by Rodriguez-Roisin, Campos et al found that vaccinated patients over 60 years of age experienced significantly more exacerbations compared to controls (p=0.05), although this difference was not observed according to the Anthonisen definition of exacerbation.[118,119] While discrepancy remains over the efficacy of vaccination in moderating exacerbation occurrence and severity in AATD, recommendations for vaccination in this population are justified based on the efficacy of reducing influenza and invasive pneumococcal disease.

Smoking

Smoking cessation is associated with a reduced risk of COPD exacerbations, which is related to the duration of abstinence.[120] In AATD, significantly lower frequencies of exacerbation were observed in PiSZ phenotype individuals compared to PiZZ phenotype individuals in a group of moderate smokers, but these inter-genotypic differences were observed to diminish in the group of intensive smokers, supporting evidence for a role of smoking cessation in controlling exacerbation frequency.[84,121]

Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) is demonstrated to have favorable effects on re-exacerbation frequency/severity following AECOPD in usual COPD patients and is also demonstrated to significantly reduce FEV_1 decline.[122,123] In individuals with AATD, PR has shown comparable effectiveness in improving 6-minute walking distance compared to usual COPD individuals.[124] However, skeletal muscle biopsy showed that muscle adaptation patterns in AATD are suggestive of smaller improvements versus controls, suggesting that the exacerbation benefit of PR in usual COPD may not be entirely transferable to AATD.[125]

Prophylactic Macrolide Therapy

Macrolide antibiotics have not been investigated in AATD but have been found to be effective in reducing exacerbation rate in usual COPD compared to placebo (RR 0.58, 95% CI 0.42-0.79; p=0.001).[126] The immunomodulatory effects of macrolides appear to directly oppose the pro-inflammatory milieu which results from deficient AAT, providing a conceivable biochemical mechanism in which macrolides may be of greater efficacy in reducing exacerbation burden in AATD.[127] Long-term macrolide therapy has been reported to decrease exacerbation frequency in *Pseudomonas Aeruginosa* colonized CF patients, who have a comparable pulmonary inflammatory environment to AATD individuals.[32,128,129] Erythromycin has also been demonstrated to prevent rhinovirus infection in cultured human tracheal epithelial cells, potentially via ICAM-1 modulation, suggesting potential in preventing viral

exacerbations.[130]

Conclusion

Exacerbations of AATD COPD are known to differ from usual COPD, but the extent and consequence of this is are not entirely known (Table 2). In AATD, exacerbations are demonstrated to be of greater frequency and duration than those in usual COPD, which is likely related to differences in inflammation. Further understanding of the mechanisms by which exacerbations of AATD COPD arise may assist with informing the biochemical rationale for future preventative and acute management strategies for exacerbations. Exacerbations of AATD COPD have a significant negative impact on lung function decline and quality of life. Despite this, there is a lack of targeted research investigating exacerbations in AATD, with particularly limited evidence on the management and prevention of exacerbations. Accordingly, conventional COPD treatments are used in AATD, despite any substantial evidence indicating their efficacy. Furthermore, the only currently available AATD specific therapy is yet to be proven effective at reducing exacerbation rate. In order to see improvements in patients' quality of life and prognosis, primary research targeted to investigate exacerbations in AATD would be highly beneficial in order to inform more effective management and preventative strategies.

Acknowledgements

DJS drafted the article, PRE contributed to the draft of the article, AMT conceived and reviewed the article.

Declaration of Interest

DJS and PRE have no conflicts of interest. AMT has received grants from AstraZeneca, Chiesi Farmaceutici and CSL Behring.

Table 2. Summary of the Known Features of Acute Exacerbation of COPD in Alpha-1 Antitrypsin Deficiency COPD and non-Alpha-1 Antitrypsin Deficiency COPD

Feature of AECOPD	Non-AATD COPD	AATD COPD
Presentation	Clinical features and severity markers well known	Clinical features and severity of exacerbations only moderately reported
Frequency	Exacerbation frequency is well reported. Characteristics and demographics of frequent exacerbators have been identified	Exacerbation frequency less well known Characteristics and demographics of frequent exacerbators are not well reported
Clinical Consequences	Effect of exacerbation on disease progression and QoL outcomes have been extensively reported	Poorly reported relative to non-AATD COPD
Preventative Management	The effectiveness of ICS, bronchodilators, macrolide therapy, smoking cessation, vaccination, and pulmonary rehabilitation on exacerbation outcomes have been extensively reported	Vaccination and pulmonary rehabilitation have been moderately investigated Smoking cessation effects reported briefly Effects of other treatments are unknown
Bacterial Etiology	Causative microorganisms have been identified	Currently unknown
Viral Etiology	Causative viruses have been identified	Currently unknown
Non-infective Etiology	The effect of comorbidity, air pollution and seasonal variation on exacerbation outcomes have been reported	Currently unknown
Acute Management	Effectiveness of antibiotics and OCS have been extensively reported	Currently unknown

COPD=chronic obstructive pulmonary disease; AATD=alpha-1 antitrypsin deficiency; AECOPD=acute exacerbation of COPD; QoL=quality of life; ICS=inhaled corticosteroids; OCS=oral corticosteroids

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