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# Exacerbations in subjects with alpha-1 antitrypsin deficiency receiving augmentation therapy

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**Summary**
*Background:* The frequency, characteristics and impact of acute exacerbations in patients with alpha-1 antitrypsin deficiency (AATD) and COPD who are on intravenous alpha-1 antitryp-sin augmentation therapy have not been described.

*Methods:* 922 subjects with AATD and COPD on augmentation therapy (mean age 54.5 years) were followed with monthly telephone surveys to record exacerbation characteristics, as well as healthcare resource utilization and health-related quality of life (HRQoL). Exacerbations were defined by symptom-based and healthcare resource utilization (HRU) criteria. *Results:* During the 1-year follow-up, 91.5% of participants experienced at least one exacerba-tion (mean 2.4 exacerbations per subject, median 2, and mean duration 17 days per episode, regardless of the definition used). Most exacerbations were categorized as severe by symptoms and moderate by HRU criteria. Subjects who had 3 or more exacerbations (48.6%) were younger, had higher medication use and had higher tobacco consumption compared with subjects with less exacerbations. Subjects with frequent exacerbations had the worst baseline HRQoL scores, as well as more physician visits, emergency room visits, and hospitalizations. Although most subjects received augmentation therapy on a weekly basis, other infusion schedules were more commonly observed in subjects with fewer exacerbations.

*Conclusion:* COPD exacerbations occur frequently and are associated with significant disease burden in subjects with AATD receiving augmentation therapy.

*Abbreviations:* AATD, alpha-1 antitrypsin deficiency; COPD, chronic Obstructive Pulmonary Disease; $FEV_1$, forced expiratory volume in 1 s; GOLD, global Initiative for COPD; HRU, healthcare resource utilization; HRQoL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire; SF-36, Short-Form-36.

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## Introduction

It is widely recognized that acute exacerbations of chronic obstructive pulmonary disease (COPD) play a central role in COPD-related morbidity and mortality.[1] Exacerbations are associated with marked physiologic deterioration that may affect disease progression by accelerating reductions in forced expiratory volume in 1 s ($FEV_1$)[2,3] and have a significant negative effect on the individual's health-related quality of life (HRQoL).[4,5] The profound impact that COPD exacerbations have on individuals, along with the high healthcare costs associated with them,[6] has led to a need for early recognition of patients at risk of frequent exacerbations.

Subjects with severe alpha-1 antitrypsin deficiency (AATD) have decreased lung protection against the effects of neutrophil elastase and susceptible subjects are at risk for early-onset COPD, with most affected individuals being diagnosed around the age 44–45 years.[7,8] During acute exacerbations, the excess neutrophil burden is significantly higher in AATD than in non-AATD COPD subjects.[9] Whether this translates into more frequent and/or more severe exacerbations is not known, as only a few studies have addressed exacerbations in this specific population. In the National Heart, Lung, and Blood Institute (NHLBI) AATD Registry Study, ''chest illness'' that kept patients off work, indoors at home, or in bed in the prior 3 years was self-reported by 68% of the 1129 patients followed.[10] In a more recent study of 265 subjects with AATD, 54% of subjects recalled having at least one COPD exacerbation during the prior year.[11]

Therapy for subjects with lung disease from AATD includes the usual treatments for COPD with the addition of specific intravenous augmentation therapy with purified alpha-1 antitrypsin.[12] Augmentation therapy has been shown to decrease bronchial inflammatory markers in these individuals[13] and a report based on subjective data suggested that this therapy may decrease the frequency of exacerbations.[14] Since the incidence and impact of acute exacerbation episodes in individuals with AATD who receive augmentation therapy have not previously described, we report here the characteristics of acute exacerbations in a large cohort of individuals with AATD and COPD who receive augmentation therapy and characterize the subgroup of subjects who suffer the most exacerbations.

## Methods

The exacerbation data analyzed here belongs to a 12-month non-interventional baseline follow-up of 922 subjects with AATD, who participated in a project to assess the impact of a disease management program. From the 1062 participants who started the baseline survey, 140 were excluded for the reasons shown in Fig. 1. All subjects were receiving augmentation therapy for AATD (Prolastin®, Talecris Biotherapeutics, Research Triangle Park, NC) and were members of AlphaNet, a not-for-profit health management company that coordinates services for patients with AATD, including the distribution of augmentation therapy.

### Study design

The study design and informed consent process were approved by the University of Miami's Institutional Review Board and have been described previously.[7,15] In brief, since participants resided throughout the United States data were collected via phone interviews. Experienced surveyors (Qessential Medical Market Research LLC, Exeter, NH) collected initial baseline clinical and demographic data and obtained HRQoL information with the St. George's Respiratory Questionnaire (SGRQ)[16] at 0 and 12 months and the Short-Form-36 (SF-36) at baseline.[17] Twelve additional standardized monthly phone surveys were undertaken by regionally based AlphaNet coordinators to collect data on COPD exacerbations and healthcare resource utilization (HRU). All survey results were entered directly into a secure database via an encrypted Web-based system at the time they were obtained.

### Definition of exacerbations

The surveys included questions that directly assessed exacerbations according to 2 different criteria: symptom-based and HRU-based. The symptom-based criteria, proposed by Anthonisen et al.,[18] use a combination of three cardinal exacerbation symptoms (increased dyspnea, sputum volume and sputum purulence) and categorize exacerbations as severe if the patient has all the 3 symptoms, moderate if only two are present, and mild if the patient has only one of the above symptoms, combined

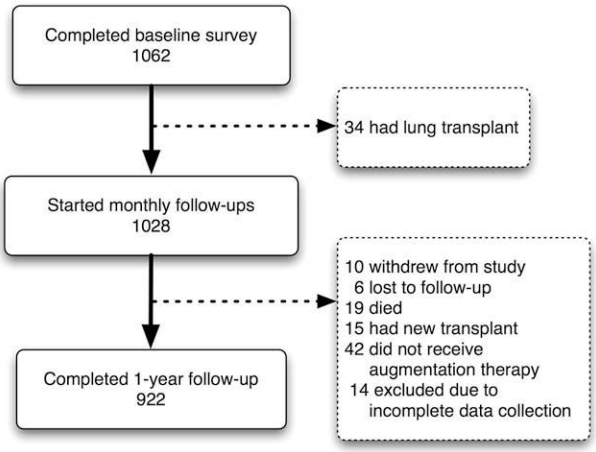


**Figure 1** Diagram showing study enrollment process.

with cough, wheeze, or symptoms of an upper respiratory tract infection. The HRU-based criteria are a consensus definition by an expert panel and define an exacerbation as ''a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variation, that is acute in onset and necessitates a change in regular medication''.[19] By this criteria, an exacerbation is categorized as mild if it can be managed in the normal environment with an increase in the usual medication, moderate if it needs additional medical assistance (physician contact or emergency room visits), and severe if it requires hospitalization. Duration of exacerbations was recorded by asking the number of days with symptoms during the prior month. To avoid overestimation of exacerbation frequency, subjects reporting exacerbation symptoms on the prior 30 days were asked if they were experiencing symptoms at the time of the phone interview. If their answer was positive, and they reported exacerbation symptoms in the following survey (month), both were clustered together as one exacerbation (and duration was recorded from the second survey).

### Study subjects

All study participants were diagnosed with AATD by their own physicians and were placed on augmentation therapy because of symptomatic obstructive lung disease. The mean age of participants was $54.5 \pm 9.6$ years and their mean age at diagnosis of AATD was $45.5 \pm 9.5$ years. The cohort was 52% male and 98% Caucasian. Most were ex-smokers (82%). There were 7 subjects that reported active smoking (0.07%) when entering the study, but all quit during the study year after intensive counseling and encouragement by the study coordinators. Participants were asked to send a copy of their genotype/phenotype at diagnosis (94% were genotype ZZ) and spirometry results if performed during the study year while in a stable clinical state. We had to rely on spirometry tests performed by each individual's healthcare provider since they were geographically spread throughout the country.

The spirometry data were used only for COPD staging purposes using the Global Initiative for COPD (GOLD) criteria.[1] The mean $FEV_1$ of the 658 subjects (67% of the total) with available spirometry results was $1.2 \pm 0.6$ L and their mean % predicted post-bronchodilator $FEV_1$ was $39.5 \pm 19.3$. The clinical characteristics of individuals with unavailable spirometry results did not differ clinically from the whole group (Table 1).

### Analysis

Data were analyzed using SAS version 9.1.3 for Windows (SAS Institute, Inc., Cary, NC). Descriptive statistics are displayed as the mean and standard deviation, or percentage. Chi-square test was used to compare proportions, and Student's *t* test and analysis of variance (ANOVA) with Bonferroni test to compare means between groups defined by sociodemographic or clinical characteristics. Variables that did not have a normal distribution were compared with the Mann–Whitney *U* test. All tests were performed two-sided with a significance level of 5%.

## Results

### Characteristics of exacerbations

During the 1-year follow-up, 844 subjects (91.5%) reported at least one acute disease exacerbation. Most exacerbations were categorized as severe by the symptom-based criteria and moderate by the HRU-based criteria (Table 2). With either criterion, the median number of exacerbations was two per patient. Most exacerbations lasted approximately 2 weeks (mean 17 days, median 15 days) and in the majority of cases ($>$ 85%) lasted less than 29 days (Fig. 2A). Exacerbations were reported throughout the year, with at least 28–30% of the subjects reporting an exacerbation in any given calendar month, but mostly during the winter months (Fig. 2B).

Subjects with COPD stage I and II ($n = 128$) had statistically significantly fewer total exacerbations using either criteria when compared with subjects with COPD stage III ($n = 164$) or stage IV ($n = 366$) (Fig. 2C) and statistically significantly shorter duration of exacerbations (mean $14.2 \pm 8.6$, median 12 days) than subjects in GOLD stage III (mean $17.8 \pm 12.3$, median 15 days) and GOLD IV (mean $17.5 \pm 12.9$, median 15 days).

### Characteristics of subjects with frequent exacerbations

We defined subjects with frequent exacerbations those who reported more exacerbations than the median for the cohort ($\geq$3 exacerbations per year). The clinical and demographic characteristics of these subjects ($n = 448$, 48.6%) were compared with those of subjects who had 1–2 ($n = 391$; 42.4%) or no ($n = 83$, 9.0%) exacerbations during the 12-month follow-up (Table 3). Subjects with frequent exacerbations were more likely to be women, younger, unemployed, ex-smokers and with symptoms of chronic bronchitis. These subjects also had higher medication utilization and were more likely to be on long-term oxygen therapy. Although no differences were observed among the 3 groups regarding duration or weekly dose of augmentation therapy (not shown), subjects with frequent exacerbations were more likely to be receiving weekly doses. Baseline HRQoL scores were also significantly worse for subjects with frequent exacerbations throughout all the domains of both the SGRQ and SF-36 surveys (Table 3). Over the year, the total SGRQ scores decreased (improved) in all three groups, but not by a clinically significant extent (more than four points). Although there was a trend for less improvement in SGRQ total scores in the frequent exacerbation group, the difference was not statistically significant (not shown).

During the 12-month follow-up, 357 subjects (38.7%) had at least one unscheduled physician visit (median 2), 171 subjects (18.5%) visited an emergency room (ER) at least once (median 1) and 105 subjects (11.3%) were hospitalized at least once (median 1). Subjects with frequent exacerbations experienced significantly more of these adverse COPD outcomes compared with subjects in the other 2 groups (Table 4).

**Table 1** Baseline patient characteristics.[a]

| | All subjects | Subjects with available pulmonary function tests | Subjects without available pulmonary function tests | *p*-Value[b] |
|---|---|---|---|---|
| Number of subjects | 922 | 658 | 264 | |
| Male sex | 52.6% | 51.8% | 53.6% | NS |
| Age (years) | 54.5 ± 9.6 | 55.1 ± 9.6 | 52.7 ± 9.6 | <0.05 |
| Marital status (has partner) | 73.5% | 74.1% | 72.2% | NS |
| Live with children at home | 19.7% | 19.6% | 19.9% | NS |
| Employed | 34.4% | 34.2% | 35.6% | NS |
| Tobacco history | | | | |
| Ever smoked (>10 pack-years) | 82.1% | 81.2% | 82.9% | NS |
| Total pack-years | 23.5 ± 14.8 | 23.4 ± 14.9 | 23.6 ± 14.5 | NS |
| Passive smoking exposure | 80.8% | 80.0% | 82.4% | NS |
| Age AATD was diagnosed (years) | 45.5 ± 9.5 | 46.5 ± 9.4 | 43.5 ± 9.9 | <0.05 |
| Years symptomatic before AATD diagnosis | 15.1 ± 9.2 | 14.4 ± 9.5 | 15.4 ± 9.4 | NS |
| Years on augmentation therapy | 6.6 ± 4.3 | 6.7 ± 4.1 | 6.4 ± 4.3 | NS |
| Dose of augmentation therapy (mg/kg/week) | 62.2 ± 9.7 | 62.4 ± 9.5 | 61.9 ± 9.1 | NS |
| SGRQ Total Score | 48.1 ± 18.4 | 47.6 ± 18.7 | 50.1 ± 18.2 | <0.05 |
| SF-36 Physical Composite Score | 35.3 ± 9.7 | 35.6 ± 9.2 | 35.1 ± 9.9 | NS |
| SF-36 Mental Composite Score | 52.1 ± 11.7 | 51.8 ± 12.1 | 52.5 ± 11.3 | NS |

[a] Values represent percentages or mean ± SD.
[b] Differences between subjects with available and unavailable spirometry results.

## Exacerbations and frequency of augmentation therapy

All participants received augmentation therapy during the study period, but with variable infusion schedules: 553 (60%) received weekly infusions, 299 (32.4%) received infusions every 2 weeks, and 70 (7.6%) received monthly infusions. Regardless of the infusion schedule, there were no significant differences in dose (mean 62.2 ± 9.7 mg/kg/week) or length of augmentation therapy (mean 6.51 ± 4.4 years). Although most subjects received the recommended weekly infusion schedule, alternate schedules were more likely observed among subjects with less frequent exacerbations during follow-up (Fig. 3).

**Table 2** Reported exacerbations over 1-year.

| | Symptom-based criteria | HRU-based criteria |
|---|---|---|
| *Exacerbations per subject per year* | | |
| Median, range | 2 (0—6) | 2 (0—6) |
| All exacerbations, mean ± SD | 2.44 ± 1.3 | 2.45 ± 1.3 |
| Mild exacerbations, mean ± SD | 0.55 ± 0.8 | 0.42 ± 0.7 |
| Moderate exacerbations, mean ± SD | 0.68 ± 0.8 | 1.78 ± 1.2 |
| Severe exacerbations, mean ± SD | 1.22 ± 1.2 | 0.25 ± 0.4 |
| *Duration of exacerbations (days per episode)* | | |
| All exacerbations, mean ± SD | 17.4 ± 11.4 | 17.8 ± 12.0 |
| Mild exacerbations, mean ± SD | 14.4 ± 11.8 | 13.4 ± 10.4 |
| Moderate exacerbations, mean ± SD | 15.5 ± 13.7 | 17.9 ± 14.1 |
| Severe exacerbations, mean ± SD | 17.5 ± 14.0 | 20.9 ± 18.9 |
| *Number of subjects with at least one exacerbation per year* | | |
| At least one mild exacerbation, *n* (%) | 391 (40.1) | 268 (27.5) |
| At least one moderate exacerbation, *n* (%) | 467 (47.9) | 820 (84.1) |
| At least one severe exacerbation, *n* (%) | 624 (64.0) | 229 (23.5) |

## Discussion

Although based mostly on observational data, augmentation therapy with purified alpha-1 antitrypsin preparations is generally recommended for all symptomatic subjects with AATD and documented lung disease.[12] The effect in slowing lung function decline appears to be more effective in subjects with moderate impairment of lung function ($FEV_1$ between 30% and 65% predicted).[20,21] Although it is believed that it may affect exacerbation frequency,[14] the true effect of augmentation therapy on the natural history of acute exacerbations is unknown. We report here the frequency and impact of acute exacerbations of COPD in a large cohort of subjects with AATD on augmentation therapy.

Probably the most striking finding of our study is the documentation of a very high prevalence of exacerbations in this population (>85% of subjects, mean 2.4 episodes per

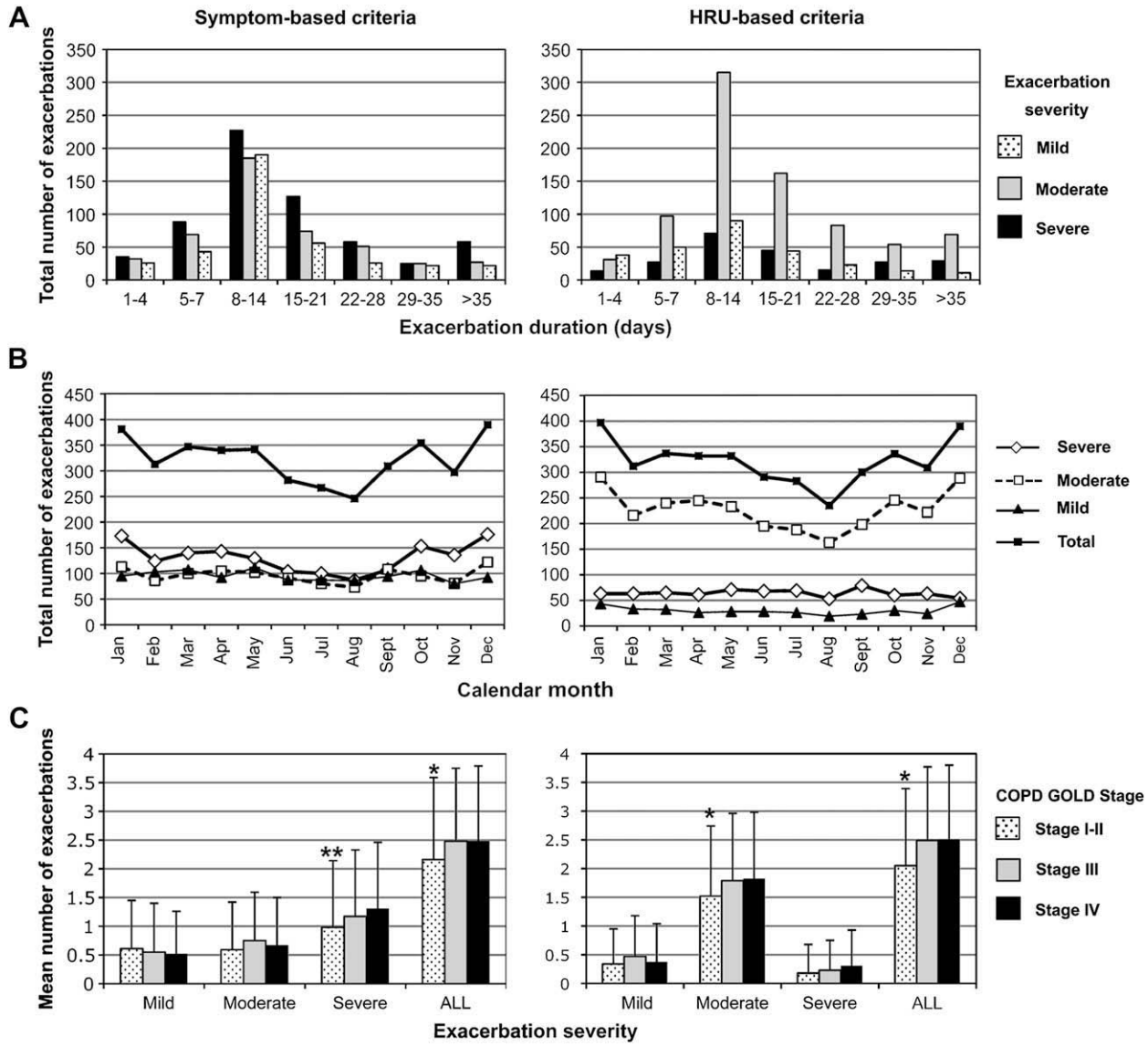


**Figure 2** Chronic obstructive pulmonary disease exacerbations in subjects with alpha-1 antitrypsin (AAT) deficiency, using both symptom-based and HRU-based criteria. A) Duration of exacerbation in days according to exacerbation severity. B) Monthly variation of exacerbation frequency plotted by calendar year. C) Severity of exacerbations according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage ($N = 658$ subjects). Bars represent standard deviation. *$p < 0.05$ for GOLD stage I—II vs. stage III and IV. **$p < 0.05$ for GOLD stage I—II vs. stage IV.

year). The reported frequency of exacerbations in a U.K. cohort of subjects with AATD not receiving augmentation therapy was less,[11] in which 54% of 265 subjects reported at least one exacerbation over 1 year (mean rate 1.2 episodes per subject per year). This difference with our report is likely due to different methodology of data collection, in particular recall interval (monthly vs. yearly), since a follow study using dairy cards in the same U.K. cohort, exacerbation rates increased to 5 episodes per subject per year (3 treated and 1.5 untreated).[22] More frequent querying about exacerbation symptoms in our study may have allowed us to detect many (milder) exacerbations that will be otherwise unrecognized. Indeed, 17% of the exacerbations evaluated by the HRU-based criteria were categorized as mild, in other words, exacerbations that did not require evaluation or consultation by a healthcare provider. The annual exacerbation frequency observed in our cohort is similar to that observed in 38 AATD subjects receiving augmentation therapy in the recently reported EXACTLE study ($2.55 \pm 2.1$ episodes per subject).[23] These highlights that exacerbations in subjects with AATD are frequent despite the administration of augmentation therapy, and represent a more significant burden than what is usually recognized.

Exacerbations in our cohort lasted approximately 15 days per episode. Although no direct comparisons can be made, the length is importantly different (7 days) from that reported in other non-AATD subjects with similar lung function and mean exacerbation rates.[3] Similar longer exacerbation duration was also reported in the U.K. AATD cohort not receiving augmentation therapy (14—16 days).[11,22] In this study, the authors suggested that the lack of alpha-1 antitrypsin had no effect in modulating exacerbation frequency but affected its

**Table 3** Patient characteristics at baseline.[a]

| | Subjects with No exacerbations over 1 year | Subjects with 1-2 exacerbations over 1 year | Subjects With ≥3 exacerbations over 1 year | ANOVA *p*-value |
|---|---|---|---|---|
| Number of subjects | 83 | 391 | 448 | |
| Male sex | 53.0% | 59.3% | 47.2% | 0.01[d] |
| Age (mean ± SD) | 56.2 ± 9.5 | 54.8 ± 9.4 | 53.8 ± 9.7 | <0.05[b] |
| Marital status (has partner) | 73.7% | 77.4% | 70.8% | 0.07 |
| Currently employed | 49.4% | 35.2% | 29.6% | <0.01[b,c] |
| Live with children at home | 16.9% | 18.8% | 22.2% | 0.44 |
| Ever smoked (>10 pack-years) | 76.3% | 78.5% | 86.4% | <0.01[d] |
| Chronic bronchitis | 16.9% | 24.0% | 30.0% | <0.01[b,d] |
| Medication use | | | | |
| Short-acting beta agonists | 61.0% | 77.3% | 87.5% | <0.01[b,c,d] |
| Long-acting beta agonists | 45.5% | 59.4% | 65.6% | <0.01[b,c,d] |
| Short-acting anticholinergics | 50.7% | 57.7% | 69.4% | <0.01[b,d] |
| Theophylline | 14.3% | 14.5% | 20.2% | 0.08 |
| Inhaled corticosteroids | 55.8% | 64.8% | 70.9% | <0.01[b] |
| Systemic corticosteroids | 3.9% | 3.8% | 7.9% | 0.03[d] |
| Long-term oxygen therapy | 34.2% | 45.5% | 52.2% | <0.01[b] |
| SGRQ, mean ± SD | | | | |
| Total | 37.3 ± 17.3 | 44.5 ± 16.6 | 52.4 ± 16.5 | <0.01[b,d] |
| Activity | 57.5 ± 23.4 | 64.1 ± 21.2 | 71.0 ± 20.5 | <0.01[b,d] |
| Symptoms | 33.1 ± 43.5 | 43.0 ± 22.1 | 54.0 ± 21.4 | <0.01[b,d] |
| Impacts | 27.0 ± 16.5 | 33.6 ± 16.5 | 41.2 ± 17.6 | <0.01[b,d] |
| SF-36, mean ± SD | | | | |
| Physical composite score | 40.3 ± 10.0 | 36.5 ± 9.7 | 33.4 ± 8.9 | <0.01[b,c,d] |
| Mental composite score | 56.8 ± 7.8 | 54.2 ± 10.1 | 49.4 ± 13.0 | <0.01[b,d] |
| Physical functioning | 35.3 ± 11.4 | 32.9 ± 10.2 | 29.4 ± 9.3 | <0.01[b,c,d] |
| Role-physical | 46.2 ± 10.6 | 40.9 ± 10.8 | 36.7 ± 10.7 | <0.01[b,c,d] |
| Bodily pain | 56.3 ± 9.5 | 52.8 ± 10.8 | 50.2 ± 11.4 | <0.01[b,c,d] |
| General health | 39.1 ± 12.1 | 35.3 ± 11.9 | 30.5 ± 10.7 | <0.01[b,c,d] |
| Vitality | 51.0 ± 12.0 | 47.3 ± 11.6 | 43.8 ± 11.1 | <0.01[b,c,d] |
| Social functioning | 49.1 ± 10.3 | 47.3 ± 11.6 | 42.4 ± 12.9 | <0.01[b,d] |
| Role-emotional | 52.5 ± 6.7 | 48.7 ± 10.3 | 43.9 ± 13.3 | <0.01[b,c,d] |
| Mental health | 54.4 ± 8.1 | 52.0 ± 9.8 | 47.7 ± 12.1 | <0.01[b,d] |

Definition of abbreviations: ANOVA = analysis of variance; GOLD = Global Initiative for Chronic Obstructive Lung Disease; MCS = mental component score; PCS = physical component score; SF-36 = Short-Form-36; SGRQ = St. George's Respiratory Questionnaire.

[a] Values represent percentages within each exacerbation group.

[b] Differences between subjects with no exacerbations vs. subjects with ≥3 exacerbations over 1 year.

[c] Differences between subjects with no exacerbations vs. subjects with 1–2 exacerbations over 1 year.

[d] Differences between subjects with 1–2 and ≥3 exacerbations over 1 year.

resolution time. From our findings, it appears that AATD subjects continue to experience long exacerbation times while receiving augmentation therapy. Duration of exacerbations should probably be considered as a marker of exacerbation severity, as it adds significantly to the burden of exacerbations.

In an Internet-based survey, 63% of 89 patients who received augmentation therapy for more than a year

**Table 4** Healthcare resource utilization in the study cohort.[a]

| | All (%) | No exacerbations in 1 year (%) | 1–2 Exacerbations in 1 year (%) | ≥3 Exacerbations in 1 year (%) |
|---|---|---|---|---|
| Unscheduled visits | 38.7 | 18.0 | 33.3 | 51.0 |
| Emergency room visits | 18.5 | 9.0 | 14.9 | 23.3 |
| Hospitalizations | 10.4 | 1.2 | 7.3 | 15.9 |

[a] Percent of subjects in each group who experienced at least one event in 1 year, using symptom-based criteria.

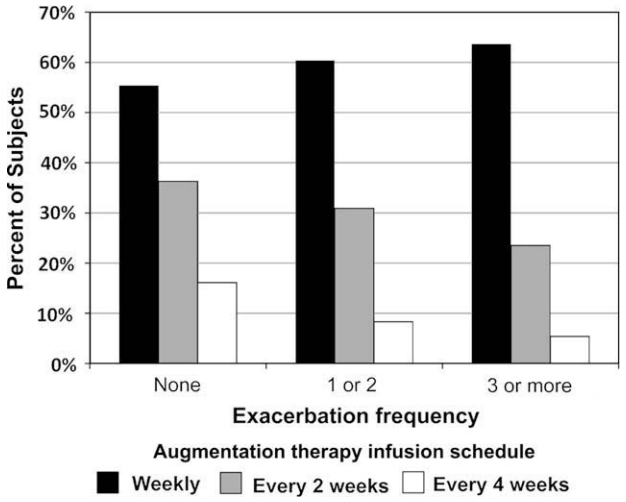


**Figure 3** Augmentation therapy infusion schedules according to frequency of exacerbations. The proportion of subjects receiving each infusion regimen was significantly different between subjects with no and 3 or more exacerbations by $\chi^2$ analysis.

subjectively believed they had a reduction in the number of lung infections since starting therapy, a subjective reduction from 3 to 5 infections per year, to 0 to 1.[14] From the currently three different purified alpha-1 antitrypsin formulations commercially available in the United States, there are (indirect) suggestions that some may have different effects on exacerbation frequency.[24] In the placebo-controlled EXACTLE study,[23] augmentation therapy did not reduce total exacerbation rates compared with placebo, but appeared to ameliorate disease severity in a post hoc analysis. Augmentation therapy decreases the inflammatory milieu in airway secretions, as reflected by significant reduction of elastase activity and levels of the chemoattractant leukotriene B4 in sputum within 1 month of treatment.[13] Whether this translates modulation of the natural history of exacerbations in AATD still unknown and further studies are needed to understand the effect of augmentation therapy on exacerbations.

We were able to define some characteristics of the subgroup of subjects who suffered the most exacerbations. Consistent with other reports, these subjects were more likely to have chronic bronchitis and worse baseline HRQoL scores. Radiologic information to determine if chronic bronchitis was associated with the presence of bronchiectasis was unavailable to us. We also found that these individuals are more likely to have been exposed to tobacco, which highlights the importance of tobacco exposure in modulating the pulmonary manifestations of AATD. The observation that younger subjects had more frequent exacerbations may reflect an association of exacerbations with more rapid disease progression, in which subjects with rapid disease progression are symptomatic at an earlier age. These younger subjects may have their disease course modulated by the higher tobacco exposure and/or by the effect of other modifier genes, subsequently worsened by exacerbations. In addition, younger individuals are more likely to be in close contact with children that may put them at higher risk of exposure to respiratory viruses.

It has been shown that weekly infusions of augmentation therapy result in adequate ''protective'' AAT trough levels,[25] while the more ''patient convenient'' biweekly and monthly regimens result in protective AAT levels throughout most (85%), but not all, the interval between infusions due to pharmacokinetic variability between individuals.[26,27] No controlled studies evaluating exacerbation rates and different infusion schedules exist. Our observation that subjects with frequent exacerbations were more likely receiving the recommended weekly infusion schedules,[12] likely reflects physician and patient preferences of more aggressive care for the most symptomatic subjects (and vice versa).

It must be considered that the subjects in our study received frequent follow-ups and advice as part of a network, which may have affected exacerbation outcomes by leading to the institution of earlier and/or more aggressive interventions. If this was the case, the true impact of acute exacerbations may have been underestimated. Further studies in this population can be improved with the use of objective measurements such as diary cards, measurements of acute changes in expiratory flow and biomarkers. Also, randomized studies comparing different augmentation dosages and infusion schedules may help assess the impact of this form of therapy on exacerbation outcomes. Finally, objective measures of lung function changes can provide a broader assessment of the impact of exacerbations on the natural history of the disease.

This study provides evidence that despite augmentation therapy, subjects with AATD still experience high annual exacerbation rates with profound impact on HRQoL and HRU, and calls for improved therapies for this population. We hope that our data will be useful for planning future therapeutic strategies and developing preventive interventions.

## Conflict of interest statement

None of the authors have any personal or financial support or author involvement with organization(s) with financial interest in the subject matter.

## Role of the funding source

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