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Published in:
American Journal of Respiratory and Critical Care Medicine

DOI:
10.1164/rccm.201910-1972OC

Publication date:
2020

Document Version
Peer reviewed version

The Relationship Between Symptoms, Exacerbations and Treatment Response in Bronchiectasis

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Running head: Symptom and exacerbation in bronchiectasis

Subject category: 10.16: Non-cystic fibrosis bronchiectasis

Word count of the manuscript: 3726

Supported by: This study was funded by the European Respiratory Society through the EMBARC2 consortium and an ERS long-term research Fellowship 2019 to YHG

(LTRF201901-00561). JDC is supported by the GSK/British Lung Foundation Chair of Respiratory Research.

Author contributions:

Conception and design: YHG, HAL, JDC

Patient recruitment and data collection: HAL, SF, TCF, GT, JDC

Analysis and interpretation: YHG, ML, SA, ADS, JDC

Drafting the manuscript: YHG, JDC

Revising the manuscript and final approval: all authors

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

At a Glance Commentary

Scientific knowledge on the subject:

Guidelines currently consider the prevention of exacerbations and reducing daily symptoms as separate objectives. The "threshold" concept of exacerbations suggests that patients report exacerbations when daily symptoms exceed normal day to day variation, and daily symptoms pass a threshold of severity above which patients feel the need to take antibiotics. Therefore, it is reasonable to hypothesize that patients with a higher daily symptom burden may experience more exacerbations. Accordingly, improving daily symptoms should reduce exacerbations, particularly in individuals with high symptom burden.

What this study added to the field:

This is the first study to demonstrate that a high daily respiratory symptom burden, measured using the St Georges Respiratory Questionnaire, is associated with increased exacerbation risk and shorter time to first exacerbation in bronchiectasis. In a post-hoc analysis of a randomized trial, patients with higher daily symptom burdens had increased time to first exacerbation, fewer exacerbations, symptom improvements and a trend for reduced exacerbation rates when treated with inhaled mannitol compared with control. This highlights the importance of therapies focused on symptom improvements in preventing exacerbation and the potential need for multimodality treatment in patients with the most severe disease.

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Abstract

Rationale: Bronchiectasis guidelines regard treatment to prevent exacerbation and treatment of daily symptoms as separate objectives.

Objective: We hypothesized that patients with greater symptoms would be at higher risk of exacerbations and therefore a treatment aimed at reducing daily symptoms would also reduce exacerbations in highly symptomatic patients.

Methods: An observational cohort of 333 patients from the East of Scotland (2012-2016). Symptoms were either modelled as a continuous variable or patients were classified as high, moderate and low symptom burden (>70, 40-70 and <40 using the SGRQ symptom score). The hypothesis that exacerbation reductions would only be evident in highly symptomatic patients was tested in a post-hoc analysis of a randomized trial of inhaled dry powder mannitol (N=461 patients)

Measurement and Main Results: In the observational cohort daily symptoms were a significant predictor of future exacerbations (rate ratio [RR] 1.10, 95% confidence interval [CI] 1.03-1.17, P=0.005). Patients with higher symptom scores had higher exacerbation rates (RR 1.74, 95% CI 1.12-2.72, P=0.01) over 12 months follow-up compared to those with lower symptoms. Inhaled mannitol treatment improved the time to first exacerbation (hazard ratio [HR] 0.56; 95% CI 0.40-0.77; P<0.001) and the proportion of patients remaining exacerbation free for 12 months treatment was higher in the mannitol group (32.7% vs. 14.6%; RR 2.84, 95% CI 1.40-5.76; P=0.003) but only in highly symptomatic patients. In

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contrast no benefit was evident in patients with lower symptom burden.

Conclusions: Highly symptomatic patients have increased risk of exacerbations, and exacerbation benefit with inhaled mannitol was only evident in patients with high symptom burden.

Introduction

Exacerbations of bronchiectasis are acute events characterized by a worsening of daily symptoms usually requiring antibiotic treatment (1, 2). Exacerbations are a major driver of disease progression and are associated with poor prognosis and high healthcare costs (3–5). Preventing exacerbations are one of key goals in international guidelines for bronchiectasis. Macrolides and inhaled antibiotics are recommended as the first-line treatment for patients with three or more exacerbations per year (after underlying causes have been treated and airway clearance has been optimized) (6, 7).

The published guidelines consider the prevention of exacerbations and reducing daily symptoms as separate objectives (6–8). This is consistent with recent evidence showing that prophylactic antibiotic treatments, in particular, reduce exacerbations without a major impact on daily symptoms (9, 10). A recent meta-analysis found that inhaled antibiotics reduce exacerbation frequency (11), but have no significant impact on daily symptoms. Even larger reductions in exacerbation rates were observed for macrolides, again without clinically meaningful improvements in symptoms (12). Notably macrolides appear to be effective at reducing exacerbations regardless of the severity of baseline symptoms (12).

The current definition of exacerbation in bronchiectasis is based on an increase in respiratory symptoms such as cough, sputum and breathlessness, requiring antibiotic treatment (2). It is reasonable to hypothesize that patients with more severe daily symptoms would require smaller incremental changes to pass a threshold prompting treatment and would therefore be more likely to report exacerbations. (13). Accordingly

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improving daily symptoms should reduce exacerbations. In chronic obstructive pulmonary disease (COPD), several studies have suggested that highly symptomatic patients are more likely to have exacerbations. Highly symptomatic COPD patients have clearer reductions in exacerbations from bronchodilators than those with low daily symptoms (14, 15). In contrast inhaled corticosteroids reduce exacerbations of COPD independent of daily symptoms (16). Such a paradigm is not established in bronchiectasis. No previous study has investigated the relationship between respiratory symptoms and exacerbations, or investigated whether a higher daily symptom burden could identify bronchiectasis patient population more likely to have exacerbation benefit with a symptom targeting therapy (6, 7).

The dominant symptoms of bronchiectasis are cough and sputum production. For this reason, bronchiectasis guidelines recommend airway clearance with or without mucoactive drugs as key strategies to reduce symptoms (6-8). The largest study to evaluate a mucoactive drug in bronchiectasis found that inhaled dry powder mannitol did not reduce exacerbation frequency despite achieving a statistically significant improvement in daily symptoms measured using the SGRQ (17). We have tested the relationship between baseline symptoms and exacerbations in an observational cohort study and re-analysed the prior randomized controlled trial of inhaled dry powder mannitol (17). We now show that highly symptomatic patients are at greater risk of exacerbations and that mannitol achieved a reduction in exacerbations in the subgroup of patients with a high symptom burden at baseline.

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Methods

Study Design

Observational cohort

This was a prospective observational study (TAYBRIDGE [Tayside Bronchiectasis Registry Integrating Datasets, Genomics, and Enrolment into Clinical Trials] registry) at two hospitals in the East of Scotland 2012–2016. The study was approved by the East of Scotland Research Ethics committee (12/ES/0059), and all patients gave written informed consent. Inclusion criteria were age >18 years, high-resolution computed tomography–confirmed bronchiectasis, and clinical symptoms consistent with bronchiectasis. Exclusion criteria were inability to give informed consent, active nontuberculous mycobacterial infection, active allergic bronchopulmonary aspergillosis, active tuberculosis, active malignancy, cystic fibrosis, or pulmonary fibrosis with secondary traction bronchiectasis.

Daily symptom burden was measured using SGRQ symptom score. The SGRQ is an instrument that is validated in bronchiectasis and has been extensively used in bronchiectasis trials (9, 18, 19). We divided patients with 3 groups: high symptom burden (>70), moderate symptom burden (40-70), and low symptom burden (<40). These cut-offs were determined a priori based on tertiles (tertiles were identified at cut-offs of 47 and 72 points. Therefore, for clinical ease, 40 and 70 were chosen as cut-offs). A sensitivity analysis was performed using the SGRQ total score.

Severity of disease was evaluated using the bronchiectasis severity index (BSI), as previously

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described (1). Exacerbations were recorded by patient self-report and further validated by reviewing prescription records for antibiotics which are available through electronic medical records for all participants. The primary outcome was the relationship between daily symptoms and exacerbations over 12 months after baseline. The Secondary outcome was time to first exacerbation.

Mannitol study

We conducted a post hoc analysis of a randomized double-blind controlled trial of inhaled dry powder mannitol treatment in bronchiectasis. Results of the original trial have been published (17). Patients were randomized (1:1) to 52 weeks treatment with inhaled mannitol 400 mg or low-dose mannitol control twice a day. Patients were included if they had HRCT confirmed bronchiectasis, baseline FEV1≥40% and ≤85% predicted and ≥1 L, a baseline SGRQ score ≥30 and at least 2 exacerbations in the previous year or 4 exacerbations in the previous 2 years.

The primary end point was exacerbation rates per patient per year, and the secondary end points included time to first exacerbation and quality of life (QoL) measured by change in the SGRQ questionnaire.

Individual participant data from the study was used to firstly confirm the relationship between daily symptoms and exacerbation observed in our prospective observational study and secondly to examine whether baseline SGRQ symptom score would predict treatment response. Treatment response was based on time to first exacerbation, frequency of exacerbations, number of subjects experiencing exacerbations and change in SGRQ total

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score from baseline to week 52. Daily symptom scores were analysed as a continuous variable and using the categories according to the cut-off points established in the observational cohort study.

Statistical Analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM) and R software version 3.6.1. Variables were presented by number (percentage), mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate. We used the Student's t test, ANOVA tests, or their corresponding non-parametrical tests for continuous variables, and chi-square test or Fisher exact test for categorized variables, for the comparisons of groups when required. Patients were stratified by SGRQ symptom score at baseline as high (>70), moderate (40-70), low (<40) symptom burden. The post hoc analyses of mannitol were conducted using the modified intent-to-treat population. Spearman correlation was used to examine the relationship between linear variables.

Unadjusted and adjusted analyses were performed using a negative binomial model to assess the relationship between baseline SGRQ symptom scores and the frequency of exacerbations and hospitalizations. Time to first exacerbation was modelled using Cox's proportional hazards models. The rate ratio (RR), hazard ratio (HR) and corresponding 95% confidence interval (CI) for exacerbations and time to first exacerbation for the uncategorized score represent 10 points increase in SGRQ symptom score when entered as a continuous variable. Relevant clinical factors that could affect the outcomes or baseline SGRQ symptom scores were included in the adjusted analyses: age, sex, body mass index

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

(BMI), smoking status, FEV_1 % of predicted at baseline, radiological score, bacterial isolation (*Pseudomonas aeruginosa, Haemophilus influenzae and Moraxella catarrhalis*), idiopathic and post-infective etiologies. To explore the relationship between baseline SGRQ and treatment response generalized additive models were fitted to the data from the study (using the mgcv library within R 3.6.1) with smooth (spline) terms for both control and treatment effects of baseline SGRQ symptom score. The model of exacerbation frequency again used a negative binomial error distribution, and a log link function, while that of time to first exacerbation used a Cox proportional hazard model. A two-tailed P value of less than 0.05 was regarded as statistically significant.

Results

Observational Study

Three hundred thirty-three clinically stable patients were recruited for the study. Table 1 shows the demographic characteristics of the study population. Median age (IQR) was 68 (60-74) years old, 63.1% were female and median FEV_1 was 72 (50-90) % of predicted. Most patients were classified as idiopathic (47.7%) and post-infective (18.6%). *P. aeruginosa* was present in the sputum of 13.9% patients at baseline, and median SGRQ symptom score at baseline was 59.8 (40.1-79.8) points. Eighty-two patients (24.6%) had low symptom burden, 127 patients (38.1%) had moderate symptom burden and 124 (37.2%) patients had high symptom burden. Patients with high symptom burden had higher BMI, lower FEV_1% of predicted, lower LCQ total score, a higher number of exacerbations in the previous year, a higher isolation of *P. aeruginosa*, *H. influenzae* and *M. catarrhalis*, and a lower proportion of post-infective etiology and stroke. No other differences among groups were found.

SGRQ symptom score was weakly associated with FEV_1 % of predicted (r=-0.37; P<0.001) and disease severity (r=0.39; *P*<0.001 with BSI score and r=0.25; *P*<0.001 with FACED score) (Figure S1 online). Compared to those with moderate and low symptom burden, patients with high symptom burden had more exacerbations in the previous year, median (3 [1-5] vs. 1.5 [0-2] vs. 1 [0-2], P<0.001), lower FEV_1 % of predicted (56.1 [42.2-81.9] vs. 74.0 [59.4-91.8] vs. 82.9 [68.0-96.9], P<0.001) and more severe disease using the BSI (10 [6-13] vs. 6 [4-8] vs. 5 [3-7.25], P<0.001) (Figure 1).

Symptoms at baseline predicted the risk of exacerbations during follow-up. The median (interquartile range, IQR) exacerbation rate per patient per year in the following year was 2 (0-4), 1 (0-2) and 1 (0-1) in the high, moderate and low symptom group (P<0.001), respectively.

The results of univariate and multivariate analyses evaluating the relationship between the SGRQ symptom score and risk of exacerbations, hospitalizations and time to first exacerbation are summarized in Table 2. SGRQ symptom score was a significant predictor of future exacerbations (RR 1.10, 95% CI 1.03-1.17, P=0.005 for a 10 point change in SGRQ symptom score) and hospitalizations (RR 1.19, 95% CI 1.02-1.35, P=0.03) when entered as a continuous variable in the negative binomial model and a trend for shorter time to first exacerbation (HR 1.04, 95% CI 0.997-1.10, P=0.27) after adjusting for the relevant confounders. Using the cut-offs, high SGRQ symptom score >70 was associated with significantly higher exacerbation risk (RR 2.33; 95% CI 1.61-3.37; p<0.001), higher

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hospitalization risk (RR 6.88, 95% CI 2.59-17.73, P<0.001) and shorter time to first exacerbation (HR 1.41; 95% CI 0.99-2.02; p=0.06) compared to patients with lower symptom scores. Compared to those with low symptom scores, a moderate SGRQ symptom score (40-70) was also associated with higher hospitalization risk (RR 3.53, 95% 1.31-9.54, P=0.01). Nevertheless, the difference was not statistically significant (RR 1.07; 0.73 to 1.58; P=0.72 for exacerbation rate and HR 0.96; 95% CI 0.66-1.38; P=0.30 for time to first exacerbation; respectively) in unadjusted analysis when comparing moderate and low symptom groups. The higher risk in the highly symptomatic group remained significant even after adjusting the effect of potential confounders for the risk of having bronchiectasis exacerbation (RR 1.74; 95% CI 1.12-2.72; p=0.01) and hospitalization (RR 3.28, 95% CI 1.09-9.88, P=0.04). However, high SGRQ score categories were not significantly associated with shorter time to first exacerbation compared with the low burden (HR 1.16; 95% CI 0.76-1.77; P=0.49) after adjusting the relevant confounders. Notably, the relationship between SGRQ symptom score and exacerbation risk were not influenced by disease severity regardless of whether this was assessed by BSI or FEV_1 % of predicted ($P_{interaction}$=0.25 and $P_{interaction}$=0.62, respectively) (Figure S2 online). Repeating these analyses using the SGRQ total score rather than the symptom score produced similar results (Table S1 online). Analysis using the Leicester cough questionnaire also found similar results (Table S2 online).

Mannitol Study

The main clinical characteristics of patients included in the study has been reported previously (Table S3 online). Median age (IQR) was 63 (53-69) years old, 62.7% were female

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and median FEV_1 was 61.9 (51.9-72.3) % of predicted. Most patients were classified as idiopathic (38.8%) and post-infective (33.0%). *P. aeruginosa* was present in the sputum of 17.1% patients, and median SGRQ symptom score at baseline was 66.1 (53.9-77.7) points.

SGRQ symptom score was weakly associated with 24 hour sputum weight (r=0.09; P=0.05) and disease severity (r=0.23; $P<0.001$ with Bronchiectasis Severity Index [BSI] score), but not FEV_1 % of predicted (r=-0.06, P=0.19), although this analysis is limited by the inclusion criteria which required FEV_1 between 40 and 85% predicted. Thirty-five patients (7.6%) had low symptom burden, 232 patients (50.3%) had moderate symptom burden and 194 (42.1%) patients had high symptom burden using the cut-offs established in the observational cohort. No statistically significant differences among clinical characteristics according to symptom burden were found.

A total of 380 patients with documented baseline SGRQ symptom score (82.4%) completed the double-blind treatment period.

The results of univariate and multivariate analyses evaluating the relationship between the SGRQ score and risk of exacerbations and time to first exacerbation are summarized in Table 3. SGRQ symptom score was a significant predictor of future exacerbations (RR 1.09, 95% CI 1.02-1.17, P=0.02 for each 10 point increment in the score) and higher symptoms were associated with shorter time to first exacerbation (HR 1.09, 95% CI 1.02-1.15, P=0.009) after adjusting the relevant confounders. In unadjusted analysis, higher SGRQ symptom score categories were associated with significantly higher exacerbation risk (RR 1.71; 95% CI 1.07-2.76; p=0.03), and shorter time to first exacerbation (HR 1.87; 95% CI 1.16-3.02; p=0.01)

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

compared with low symptom burden. These relationships remained significant even after adjusting the effect of potential confounders for the risk of having bronchiectasis exacerbation (RR 1.75; 95% CI 1.07-2.86; p=0.03), and shorter time to first exacerbation compared with the low burden (HR 1.78; 95% CI 1.09-2.90; p=0.02) after adjusting the relevant confounders. We further re-analyzed the data only in the control arm and found that higher symptom burden was still associated with higher exacerbation risk (Table S4 online). We found no modifying effect of disease severity, regardless of whether this was assessed by BSI or FEV_1 % of predicted on the relationship between symptoms and exacerbations ($P_{interaction}$=0.65 and $P_{interaction}$=0.54, respectively). Figure S3 (online) shows that patients with higher symptom scores experienced more exacerbations in mild, moderate and severe subgroups based on the BSI.

Primary endpoint. In the original trial, Mannitol treatment was not associated with reduced exacerbations compared to the low dose mannitol control with a rate ratio of 0.92 (95% CI 0.78 to 1.08), P=0.31. We observed a relationship between exacerbation benefit with mannitol compared to control with increasing SGRQ (Figure 2). Comparing inhaled mannitol with control, there was no benefit in exacerbation rate for patients with low symptom burden (RR 1.01; 95% CI 0.41-2.46; P=0.98) and moderate symptom burden (RR 1.07; 95% CI 0.78-1.47; P=0.69). However, there was a clear trend for exacerbation reduction in favor of inhaled mannitol treatment patients with baseline high symptom burden (RR 0.76; 95% CI 0.54-1.06; P=0.107) despite lack of statistical significance. We then determined the proportion of patients who had no exacerbation for 12 months after receiving inhaled mannitol or control. In patients with high symptom burden, we found that

32.7% in inhaled mannitol group had no exacerbation compared with 14.6% in control group (RR 2.84, 95% CI 1.40-5.76, P=0.003). However, there was no significant difference in the proportion of patients who had no exacerbations in patients with low or moderate symptom burden (Moderate 26.7% vs. 25.9%, RR 1.05, 95% CI 0.58-1.88, P=0.88; Low 52.6% vs. 37.5%; RR 1.85, 95% CI 0.49-7.18; P=0.37).

Secondary endpoint. For the secondary endpoints of time to first exacerbation, inhaled mannitol treatment prolonged the time to first exacerbation (193 days vs. 118 days; HR 0.56; 95% CI 0.40-0.77; P<0.001) compared with control in the high symptom burden group (Figure S4 online). The effect was not different in moderate and low symptom burden groups (HR 0.99; 95% CI 0.73-1.34; P=0.94 and HR 0.76; 95% CI 0.31-1.88; P=0.55; respectively) (Figure 3). The relationship between SGRQ and time to first exacerbation in the generalized additive model is shown in figure 2B. Patients with higher symptom burden had a significant improvement in SGRQ total scores above the minimal clinically important difference (MCID) in favor of inhaled mannitol treatment compared with control (mean difference -5.86; 95% CI -10.49 to -1.22; P=0.014). However, there was no improvement in SGRQ total score for patients with moderate (mean difference 1.06; 95% CI -3.22 to 5.33; P=0.63) and low symptom burden at baseline (mean difference -0.85; 95% CI -10.41 to 8.71; P=0.86) on mannitol compared with control. A decrease in SGRQ total score of greater or equal to four points is regard as clinically meaningful. There was no significant difference in the percentage of responders in patients with low or moderate symptom burden. In patients with high symptom burden, 75% achieved a SGRQ total score decrease above the MCID compared with 52.7% of patients in the control group (P=0.001). There were no overall improvements in the FEV_1 % of predicted among groups.

Discussion

Exacerbations and daily symptoms have the greatest impact on patient's survival and quality of life in bronchiectasis and therefore reducing exacerbations and relieving daily symptoms are the key objectives of therapy. We, for the first time, demonstrate that high respiratory symptom burden, regardless of whether these are measured by SGRQ symptom score, total score or LCQ total score, is associated with increased exacerbation risk and shorter time to first exacerbation in bronchiectasis. This led us to hypothesize that improving daily symptom could reduce exacerbations. We then conducted a post-hoc analysis of one previously published "negative" randomized controlled trial of inhaled mannitol, where we found that only patients with high baseline symptom burden had increased time to first exacerbation, fewer exacerbations, symptom improvements and a trend for reduced exacerbation rates when treated with inhaled mannitol compared with control. These findings suggest that control of daily symptoms can result in reduced exacerbations if targeted towards highly symptomatic patients

Guidelines primarily consider these outcomes separately, with a different algorithm for patients with 3 or more exacerbations per year where prophylactic antibiotic therapies are considered, compared to symptomatic patients with and without exacerbations where bronchitic symptoms are treated with airway clearance with or without mucoactive drugs and breathlessness treated with pulmonary rehabilitation and bronchodilators where appropriate (6, 7).

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

It is intuitive that, as in other chronic conditions like COPD (20–22), there would be a relationship between daily symptoms and exacerbations but ours is, to the authors knowledge, the first study to specifically address this question. The “threshold” concept of exacerbations suggests that patients report exacerbations when daily symptoms exceed normal day to day variation, and daily symptoms pass a threshold of severity above which patients feel the need to take antibiotics (2, 6, 7). This threshold may be different from patient to patient. Some exacerbation events may involve a very large increase in symptoms while others may represent only small changes from the patient’s usual baseline. If this concept is true, patients with a higher baseline level of symptoms would be closer to the threshold and would therefore require a lesser insult to report exacerbations, resulting in a higher frequency of events. This model also predicts that reducing daily symptoms would therefore result in reduced exacerbation frequency.

It is puzzling therefore that our recent meta-analysis of macrolides found no impact of baseline symptoms on the benefit of macrolides vs placebo for reducing exacerbations (12). Patients with an SGRQ score >50 points had a rate ratio of 0.5 (0.28-0.90) for exacerbation frequency which was the same as for the patients with SGRQ scores <30 (0.50 95% CI 0.29-0.84). The 50% reduction in exacerbations was accompanied by only a borderline improvement in symptoms. Likewise, in the ORBIT studies of inhaled liposomal ciprofloxacin there was a reduction in the frequency of exacerbations in the pooled analysis of both replicate trials (10), but no benefit in terms of symptoms and similar results were observed in the large RESPIRE programme (9, 23). It seems therefore that for antibiotics, the benefit in exacerbation reduction is disconnected from baseline symptoms or symptom responses.

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

Nevertheless, the finding in recent studies that pulmonary rehabilitation and airway clearance can reduce exacerbation frequency suggests that at least a subset of exacerbations are symptom driven and therefore preventable with treatment focused on symptoms (24–26). It is tempting therefore to speculate that antibiotics prevent a subset of exacerbations that are inflammation and infection driven (27, 28), while symptomatic therapies may prevent a different exacerbation subtype. This is analogous to the established concept in COPD that bronchodilators reduce exacerbations through reducing symptoms and are therefore indicated as first line treatment for patients with symptoms and exacerbations (GOLD D) while inhaled corticosteroids appear to reduce exacerbations independent of symptom reductions and are therefore indicated both in patients with exacerbations and low symptom burden (GOLD C) and GOLD D patients that continue to exacerbation despite symptomatic therapy (16). Confirming that this concept also applies in bronchiectasis will require further experimental work including testing the role of airway inflammation as a mediator in these relationships. This concept would predict that anti-inflammatory therapies such as neutrophil elastase inhibitors may reduce exacerbations without having a large effect on symptoms.

Our results nevertheless support the “treatable traits” concept in management of bronchiectasis. In patients with frequent exacerbations with a low symptom burden, it may be adequate to treat such patients with airway clearance and the addition of anti-infective or anti-inflammatory therapy with macrolides, inhaled antibiotics or inhaled corticosteroids if they continue to frequently exacerbate. In contrast, in patients with a high symptom burden, symptomatic treatment with airway clearance and mucoactive drugs may be

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

effective to prevent exacerbations, contributing to antibiotic stewardship. In patient with both a high symptom burden and a high frequency of exacerbations, there is likely to be requirement for therapy directed at both aspects of disease, using phenotyping/endotyping to identify the most appropriate therapies (29, 30).

Our analysis has limitations. The observational cohort and mannitol trials were conducted prior to the validation of the quality of life bronchiectasis questionnaire and bronchiectasis heath questionnaire which are specific for bronchiectasis (31–33), but we and others have demonstrated that the QOL-B and SGRQ are highly correlated and the SGRQ is the most widely used quality of life tool in bronchiectasis research and particularly in clinical trials (31, 33, 34). The analysis of the mannitol study is post-hoc and results should be considered as hypothesis generating.

In summary, we have demonstrated that patients with a high burden of symptoms are at higher risk of exacerbations even after adjustment for underlying severity of disease. This highlights the importance of therapies focused on symptom improvements and the potential need for multimodality treatment in patients with the most severe disease.

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

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Figure legends

Figure 1. Association of low (SGRQ symptom score<40 points), moderate (SGRQ symptom score 40-70 points) and high (SGRQ symptom score>70 points) symptom burden with the number of exacerbations in previous year (Panel A), Bronchiectasis Severity Index (BSI) (Panel B) and Forced expiratory volume in 1 second (Panel C). p value is from comparison of all groups (Kruskall-Wallis test for A-C)

Figure 2. Relationship between baseline SGRQ symptom score and exacerbation outcomes in the mannitol trial. The figure shows the estimated ratio between the treatment and control arms for different SGRQ scores, with 95% confidence intervals.

Figure 3. Hazard ratio for time to first exacerbation in patients with bronchiectasis divided into high, moderate and low symptom burden. The vertical dotted line represents a hazard ratio of 1.

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

Table 1. Patient Demographics of All Study Population and Divided according to SGRQ symptom score in Observational Study

	All (n=333)	Low Symptom Burden (n=82)	Moderate Symptom Burden (n=127)	High Symptom Burden (n=124)	P value
Age, yr, median (IQR)	68 (60-74)	67 (60.75-74.25)	68 (60-74)	68 (58-74)	0.76
Female sex	210 (63.1%)	54 (65.9%)	80 (63%)	76 (61.3%)	0.806
FEV1% predicted, median (IQR)	72 (50-90)	82.9 (68.0-96.9)	74.0 (59.4-91.8)	56.1 (42.2-81.9)	<0.001
BMI, kg/m^2, median (IQR)	25.3 (21.8-28.6)	24.7 (21.3-27.3)	24.9 (22.0-28.4)	26.7 (22.6-30.7)	0.01
Smoking status					
Never	203 (61%)	53 (64.6%)	79 (62.2%)	71 (57.3%)	0.11
Ex-smoker	116 (34.8%)	27 (32.9%)	46 (36.2%)	43 (34.7%)	
Current	14 (4.2%)	2 (2.4%)	2 (1.6%)	10 (8.1%)	
Exacerbation in the preceding year	1 (0-3)	1 (0-2)	1.5 (0-2)	3 (1-5)	<0.001
Radiologic score, median (IQR)	3 (2-6)	3 (2-5)	3.5 (2-6）	3 (2-7)	0.24
Pseudomonas aeruginosa	47 (13.9%)	2 (2.4%)	16 (12.6%)	29 (23.4%)	<0.001
Haemophilus influenzae	109 (32.2%)	25 (30.5%)	28 (22.0%)	54 (43.5%)	0.001
Moraxella catarrhalis	42 (12.4%)	7 (8.5%)	11 (8.7%)	23 (18.5%)	0.03
Staphylococcus aureus	30 (8.8%)	4 (4.9%)	14 (11.0%)	11 (8.9%)	0.28
Enterobacteriaceae	42 (12.4%)	6 (7.3%)	19 (15.0%)	17 (13.7%)	0.24
SGRQ symptom score, median (IQR)	59.8 (40.1-79.8)	27.5 (15.2-32.7)	55.5 (48.6-61.6)	85.8 (77.8-90.6)	<0.001
LCQ total score median (IQR)	14.3 (10.6-17.9)	18.9 (16.8-20.1)	14.9 (11.9-17.6)	10.2 (7.9-13.1)	<0.001
Etiology					
Idiopathic	159 (47.7%)	48 (58.5%)	51 (40.2%)	60 (48.4%)	0.03
Post-infection	62 (18.6%)	16 (19.5%)	32 (25.2%)	14 (11.3%)	0.02
Previous ABPA	29 (8.7%)	4 (4.9%)	12 (9.4%)	13 (10.5%)	0.31
Asthma	9 (2.7%)	2 (2.4%)	3 (2.4%)	4 (3.2%)	0.90
COPD	14 (4.2%)	4 (4.9%)	5 (3.9%)	5 (4%)	0.94
Rheumatoid arthritis	13 (3.9%)	2 (2.4%)	3 (2.4%)	8 (6.5%)	0.19
Immunodeficiency	16 (4.8%)	3 (3.7%)	6 (4.7%)	7 (5.6%)	0.80
Sarcoidosis	6 (1.8%)	1 (1.2%)	3 (2.4%)	2 (1.6%)	0.82
IBD	9 (2.7%)	0 (0)	5 (3.9%)	4 (3.2%)	0.07
Comorbidities					
Cardiac disease	66 (19.8%)	16 (19.5%)	29 (22.8%)	21 (16.9%)	0.50
Stoke	31 (9.3%)	11 (13.4%)	15 (11.8%)	5 (4.0%)	0.04

Diabetes	39 (11.7%)	15 (18.3%)	6 (4.7%)	18 (14.5%)	0.006
Osteoporosis	20 (6.0%)	5 (6.1%)	6 (4.7%)	9 (7.3%)	0.70

Data were presented as mean (standard deviation, SD), median (interquartile range, IQR), number (%) as appropriate.

Abbreviation: ABPA=allergic bronchopulmonary aspergillosis; BMI=body mass index kg/m^2; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 s; IBD=Inflammatory bowel disease; LCQ=Leicester Cough Questionnaire; SGRQ=St. George's Respiratory Questionnaire; yr=year;

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Table 2. Relationship Between Baseline SGRQ Symptom Score and Exacerbations in Observational Study

SGRQ symptom score	Exacerbations (any)		Hospitalizations		Time to first exacerbations	
	Rate ratio (95% CI)	P value	Rate ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Uncategorized score (unadjusted)	1.15 (1.09-1.21)	<0.001	1.27 (1.15-1.39)	<0.001	1.07 (1.01-1.13)	0.02
Uncategorized score (adjusted)	1.10 (1.03-1.17)	0.005	1.19 (1.02-1.35)	0.03	1.04 (0.997-1.10)	0.27
Categorized score (unadjusted)						
Low (<40)	1		1		1	
Moderate (40-70)	1.07 (0.73-1.58)	0.72	3.53 (1.31-9.54)	0.01	0.96 (0.66-1.38)	0.3
High (>70)	2.33 (1.61-3.37)	<0.001	6.88 (2.59-17.73)	<0.001	1.41 (0.99-2.02)	0.06
Categorized score (adjusted)						
Low (<40)	1					
Moderate (40-70)	1.01 (0.66-1.54)	0.96	2.29 (0.77-6.83)	0.14	0.96 (0.65-1.43)	0.84
High (>70)	1.74 (1.12-2.72)	0.01	3.28 (1.09-9.88)	0.04	1.16 (0.76-1.77)	0.49

*Adjusted for age, sex, BMI, smoking, FEV_1 % of predicted, Pseudomonas aeruginosa isolation, Haemophilus influenzae isolation, Moraxella catarrhalis isolation, idiopathic bronchiectasis, post-infective bronchiectasis, radiological score. CI=confidence interval.

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Table 3. Relationship Between Baseline SGRQ Symptom Score and Exacerbations in Mannitol Study

SGRQ symptom score	Exacerbations		Time to first exacerbations	
	Rate ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Uncategorized score (unadjusted)	1.09 (1.02-1.16)	0.011	1.10 (1.04-1.17)	0.001
Uncategorized score (adjusted)*	1.09 (1.02-1.17)	0.017	1.09 (1.02-1.15)	0.009
Categorized score (unadjusted)				
Low (<40)	1		1	
Moderate (40-70)	1.45 (0.91-2.33)	0.12	1.74 (1.08-2.79)	0.02
High (>70)	1.71 (1.07-2.76)	0.03	1.87 (1.16-3.02)	0.01
Categorized score (adjusted)*				
Low (<40)	1		1	
Moderate (40-70)	1.50 (0.92-2.45)	0.10	1.73 (1.07-2.80)	0.03
High (>70)	1.75 (1.07-2.86)	0.03	1.78 (1.09-2.90)	0.02

*Adjusted for age, sex, BMI, smoking, FEV_1 % of predicted, Pseudomonas aeruginosa isolation, Haemophilus influenzae isolation, Moraxella catarrhalis isolation, idiopathic bronchiectasis, post-infective bronchiectasis, radiological score. CI=confidence interval.

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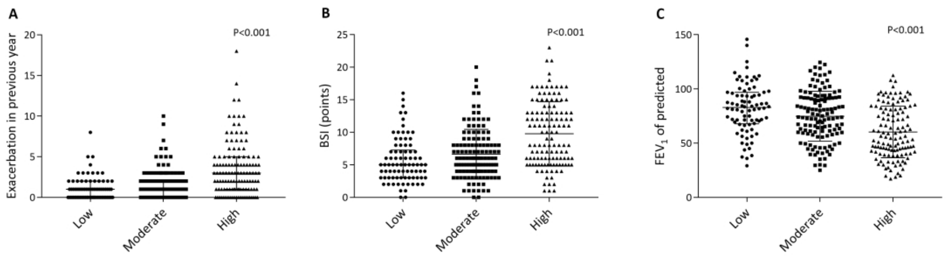

Figure 1. Association of low (SGRQ symptom score<40 points), moderate (SGRQ symptom score 40-70 points) and high (SGRQ symptom score>70 points) symptom burden with the number of exacerbations in previous year (Panel A), Bronchiectasis Severity Index (BSI) (Panel B) and Forced expiratory volume in 1 second (Panel C). p value is from comparison of all groups (Kruskall-Wallis test for A-C)

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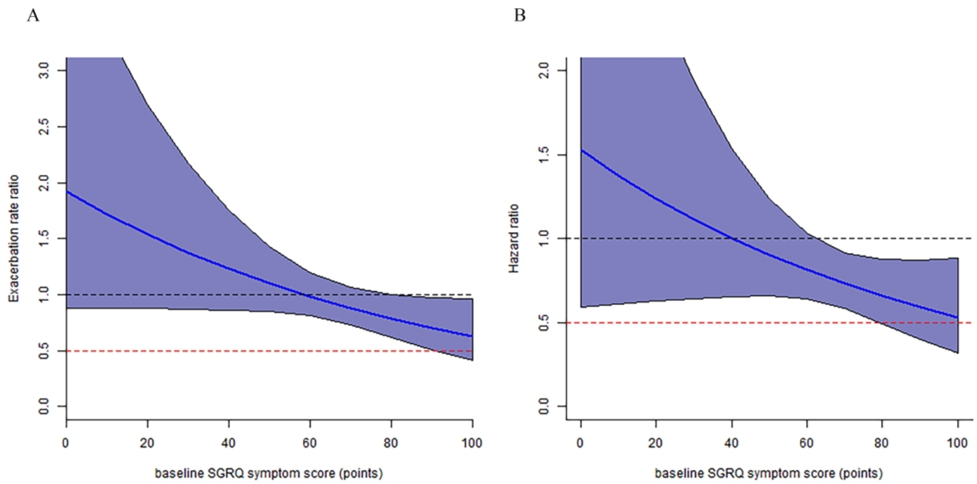

Figure 2. Relationship between baseline SGRQ symptom score and exacerbation outcomes in the mannitol trial. The figure shows the estimated ratio between the treatment and control arms for different SGRQ scores, with 95% confidence intervals.

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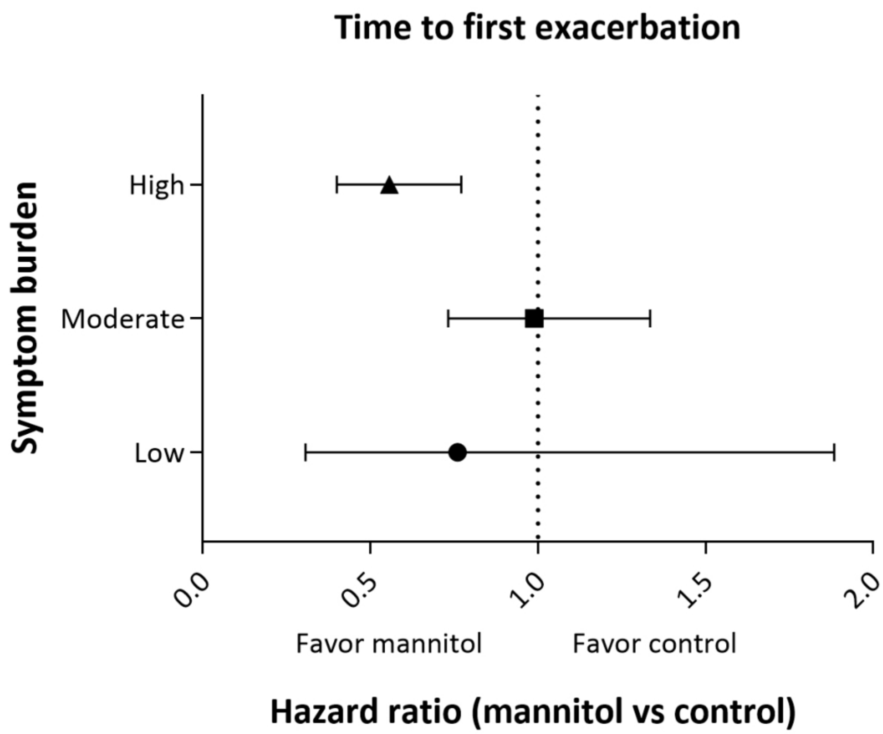

Figure 3. Hazard ratio for time to first exacerbation in patients with bronchiectasis divided into high, moderate and low symptom burden. The vertical dotted line represents a hazard ratio of 1.

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ONLINE SUPPLEMMENT FOR

The Relationship Between Symptoms, Exacerbations and Treatment Response in Bronchiectasis

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Running head: Symptom and exacerbation in bronchiectasis

Subject category: 10.16: Non-cystic fibrosis bronchiectasis

Word count of the manuscript: 3726

AJRCCM Articles in Press. Published February 25, 2020 as 10.1164/rccm.201910-1972OC

Supported by: This study was funded by the European Respiratory Society through the EMBARC2 consortium and an ERS long-term research Fellowship 2019 to YHG (LTRF201901-00561). JDC is supported by the GSK/British Lung Foundation Chair of Respiratory Research.

Supplementary methods

Leicester cough questionnaire (LCQ): daily symptom burden was also measured using LCQ total score, an instrument that is validated in bronchiectasis for assessing cough (1). We divided patients with 3 groups: high symptom burden (<11), moderate symptom burden (11-17), and low symptom burden (>17). These cut-offs were determined based on tertiles (tertiles were identified based on cut-offs of 11.68 and 16.86 points. Therefore, for clinical ease, 11 and 17 were chosen as cut-offs).

Supplementary results

Observational study

The results of univariate and multivariate analyses evaluating the relationship between the SGRQ total score and risk of exacerbations and time to first exacerbation are summarized in Table S1. SGRQ total score was still a significant predictor of future exacerbations (RR 1.15, 95% CI 1.07-1.23, P<0.0001) and higher SGRQ total score was associated with shorter time to first exacerbation (HR 1.11, 95% CI 1.01-1.19, P=0.004) after adjusting the relevant confounders.

The results of univariate and multivariate analyses evaluating the relationship between the LCQ total score and risk of exacerbations and time to first exacerbation are summarized in Table S2. LCQ total score was a significant predictor of future exacerbations when entered as a continuous variable in the negative binomial model (RR 0.95, 95% CI 0.91-0.98, P=0.005) and a trend for shorter time to first exacerbation (HR 0.97, 95% CI 0.94-1.01, P=0.14) after adjusting the relevant confounders. Using the cutoffs, high LCQ total score <11 was associated with significantly higher exacerbation risk (RR 2.18; 95% CI 1.51-3.15; p<0.001), and a shorter time to

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first exacerbation (HR 1.45; 95% CI 1.02-2.06; p=0.04) compared to patients with lower LCQ total score. Compared to those with low symptom scores, a moderate LCQ total score was also associated with higher exacerbation risk (RR 1.49; 95% CI 1.06-2.10; P=0.02). The difference for time to first exacerbation was not statistically significant (HR 0.99; 95% CI 0.71-1.37; P=0.93) in unadjusted analysis when comparing moderate and low LCQ total score categories. The higher risk in the highly symptomatic group remained significant even after adjusting the effect of potential confounders for the risk of having bronchiectasis exacerbation (RR 1.70; 95% CI 1.09-2.64; p=0.02), but these associations were lost for time to first exacerbation (HR 1.33; 95% CI 0.89-1.99; P=0.17).

In addition, the relationship between symptoms and exacerbation risk classified by bronchiectasis severity index (BSI) and FEV1 % of predicted as measures of disease severity, respectively, were shown in Figure S2. The RR and 95% CI for exacerbation rate was 1.10 (1.00-1.20, P=0.05) in patients with severe bronchiectasis (BSI≥9 points), as compared with 1.07 (0.998-1.16, P=0.15) in patients with moderate bronchiectasis (BSI=5-8 points), and 1.07 (0.994-1.02, P=0.30) in patients with mild bronchiectasis (BSI=0-4 points). And the RR and 95% CI for exacerbation rate was 1.19 (1.05-1.34, P=0.009) in patients with FEV1 % of predicted<50%, as compared with 1.15 (1.05-1.26, P=0.003) in patients with FEV1 % of predicted≥50%, ≤80%, and 1.13 (1.04-1.22, P=0.005) in patients with FEV1 % of predicted >80%.

Mannitol study

The relationship between symptoms and exacerbation risk classified by bronchiectasis severity index (BSI) and FEV1 % of predicted as measures of disease severity, respectively, were shown

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in Figure S3. The RR and 95% CI for exacerbation rate was 1.09 (0.994-1.24, P=0.26) in patients with severe bronchiectasis (BSI≥9 points), as compared with 1.06 (0.996-1.15, P=0.26) in patients with moderate bronchiectasis (BSI=5-8 points), and 1.12 (0.996-1.29, P=0.13) in patients with mild bronchiectasis (BSI=0-4 points). And the RR and 95% CI for exacerbation rate was 1.15 (0.997-1.33, P=0.10) in patients with FEV1 % of predicted<50%, as compared with 1.07 (0.999-1.16, P=0.09) in patients with FEV1 % of predicted≥50%, ≤80%, and 1.13 (0.991-1.37, P=0.25) in patients with FEV1 % of predicted >80%.

The results of univariate and multivariate analyses evaluating the relationship between the SGRQ symptom score in control arm and risk of exacerbations and time to first exacerbation in control arm are summarized in Table S4. SGRQ symptom score was a significant predictor of future exacerbations (RR 1.14, 95% CI 1.03-1.25, P=0.01) and higher symptoms were associated with shorter time to first exacerbation (HR 1.14, 95% CI 1.05-1.24, P=0.002) after adjusting the relevant confounders. In unadjusted analysis, higher SGRQ symptom score categories were associated with a trend of higher exacerbation risk (RR 1.97; 95% CI 0.98-3.96; p=0.06), and shorter time to first exacerbation (HR 2.21; 95% CI 1.14-4.28; p=0.02) compared with low symptom burden. These relationships remained significant even after adjusting the effect of potential confounders for the risk of shorter time to first exacerbation compared with the low burden (HR 2.09; 95% CI 1.06-4.12; p=0.033).

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Figure Legends

Figure S1. Correlation between SGRQ symptom score and the number of exacerbations in previous year (rho=0.39, P<0.0001) (Panel A), bronchiectasis severity index (rho=0.39, P<0.0001) (Panel B) and FEV1 % of predicted in Observational study (rho=-0.37, P<0.0001) Panel C).

Figure S2. Rate ratio for baseline SGRQ symptom score and future exacerbation risk in patients with different disease severity assessed by bronchiectasis severity index (Panel A) and FEV1 % of predicted (Panel B) in Observational study. Error bars represent 95% CI. The vertical dotted line represents a rate ratio of 1.

Figure S3. Rate ratio for baseline SGRQ symptom score and future exacerbation risk in patients with different disease severity assessed by bronchiectasis severity index (Panel A) and FEV1 % of predicted (Panel B) in Mannitol study. Error bars represent 95% CI. The vertical dotted line represents a rate ratio of 1.

Figure S4. Kaplan-Meier plot of the time to first exacerbation in high symptomatic patients.

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Table S1. Relationship Between Baseline SGRQ Total Score and Exacerbations in Observational Study

SGRQ total score	Exacerbations		Time to first exacerbations	
	Rate ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Uncategorized score (unadjusted)	1.16 (1.11-1.22)	<0.0001	1.13 (1.06-1.19)	<0.0001
Uncategorized score (adjusted)*	1.15 (1.07-1.22)	<0.0001	1.11 (1.04-1.19)	0.004

*Adjust for age, gender, BMI, FEV_1 % of predicted, smoking status, Pseudomonas aeruginosa isolation, Haemophilus influenzae isolation, Moraxella catarrhalis isolation, radiological score, idiopathic bronchiectasis, post-infective bronchiectasis

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Table S2. Relationship Between Baseline LCQ Total Score and Exacerbations in Observational Study

LCQ total score	Exacerbations		Time to first exacerbations	
	Rate ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Uncategorized score (unadjusted)	0.93 (0.90-0.95)	<0.001	0.97 (0.94-1.00)	0.02
Uncategorized score (adjusted)*	0.95 (0.91-0.98)	0.005	0.97 (0.94-1.01)	0.14
Categorized score (unadjusted)				
Low (>17)	1			
Moderate (11-17)	1.49 (1.06-2.10)	0.02	0.99 (0.71-1.37)	0.93
High (<11)	2.18 (1.51-3.15)	<0.001	1.45 (1.02-2.06)	0.04
Categorized score (adjusted)*				
Low (>17)	1			
Moderate (11-17)	1.48 (1.02-2.16)	0.04	1.03 (0.72-1.47)	0.88
High (<11)	1.70 (1.09-2.64)	0.02	1.33 (0.89-1.99)	0.17

*Adjust for age, gender, BMI, FEV_1 % of predicted, smoking status, *Pseudomonas aeruginosa* isolation, *Haemophilus influenzae* isolation, *Moraxella catarrhalis* isolation, radiological score, idiopathic bronchiectasis, post-infective bronchiectasis

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Table S3. Patient Demographics of All Study Population and Divided according to SGRQ Symptom Score in Mannitol Study

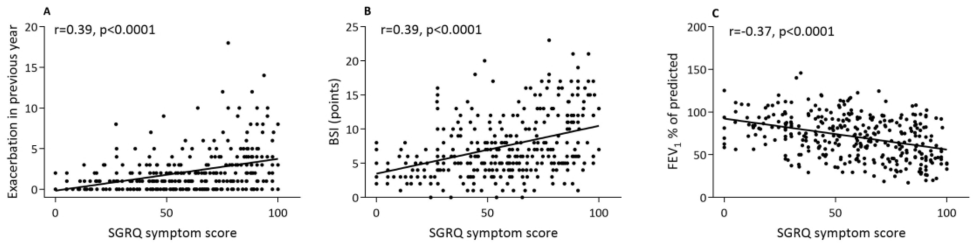
	All (n=461)	Low Symptom Burden (n=35)	Moderate Symptom Burden (n=232)	High Symptom Burden (n=194)	P value
Age, yr, median (IQR)	63 (53-69)	68 (57-70)	62 (50.3-69)	63 (55.8-69)	0.24
Female sex	289 (62.7%)	23 (65.7%)	149 (64.2%)	117 (60.3%)	0.66
FEV_1% predicted, median (IQR)	61.9 (51.9-72.3)	67.3 (59.0-76.0)	61.1 (50.3-71.5)	61.6 (51.8-72.5)	0.12
BMI, kg/m^2, median (IQR)	25.6 (22.4-29.1)	26.2 (21.6-28.7)	25.1 (21.8-28.3)	26.4 (22.8-29.7)	0.04
Ex-smoker	181 (39.3%)	12 (34.3%)	82 (35.3%)	87 (44.8%)	0.11
Exacerbation in the preceding year	3 (2-4)	2 (2-4)	3 (2-4)	3 (2-4)	0.14
Pseudomonas aeruginosa	79 (17.1%)	2 (5.7%)	41 (17.7%)	36 (18.6%)	0.11
Haemophilus influenzae	67 (14.5%)	7 (20%)	30 (12.9%)	30 (15.5%)	0.48
Moraxella catarrhalis	16 (3.5%)	3 (8.6%)	6 (2.6%)	7 (3.6%)	0.28
Staphylococcus aureus	13 (2.8%)	2 (5.7%)	6 (2.6%)	5 (2.6%)	0.63
Streptococcus pneumoniae	20 (4.3%)	2 (5.7%)	10 (4.3%)	8 (4.1%)	0.92
SGRQ symptom score, median (IQR)	66.1 (53.9-77.7)	32.4 (27.2-37.8)	57.7 (50.7-64.5)	79.4 (75.2-85.0)	<0.001
Etiology					
Idiopathic	179 (38.8%)	14 (40.0%)	99 (42.7%)	66 (34.0%)	0.19
Post-infection	152 (33.0%)	15 (42.9%)	81 (34.9%)	56 (28.9%)	0.18

Data were presented as mean (standard deviation, SD), median (interquartile range, IQR), number (%) as appropriate. Abbreviation: BMI=body mass index kg/m^2; FEV_1=forced expiratory volume in 1 s; SGRQ=St. George's Respiratory Questionnaire; yr=year;

Table S4. Relationship between baseline SGRQ symptom score and exacerbations in control arm in Mannitol study

SGRQ symptom score	Exacerbations		Time to first exacerbations	
	Rate ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Uncategorized score (unadjusted)	1.15 (1.05-1.26)	0.004	1.17 (1.08-1.26)	<0.001
Uncategorized score (adjusted)*	1.14 (1.03-1.25)	0.01	1.14 (1.05-1.24)	0.002
Categorized score (unadjusted)				
Low (<40)	1			
Moderate (40-70)	1.41 (0.71-2.84)	0.33	1.54 (0.80-2.97)	0.20
High (>70)	1.97 (0.98-3.96)	0.06	2.21 (1.14-4.28)	0.02
Categorized score (adjusted)*				
Low (<40)	1		1	
Moderate (40-70)	1.41 (0.69-2.90)	0.34	1.54 (0.79-3.02)	0.21
High (>70)	1.91 (0.93-3.95)	0.08	2.09 (1.06-4.12)	0.03

*Adjust for age, gender, BMI, FEV_1 % of predicted, smoking status, Pseudomonas aeruginosa isolation, Haemophilus influenzae isolation, Moraxella catarrhalis isolation, radiological score, idiopathic bronchiectasis, post-infective bronchiectasis



Supplementary Figure 1

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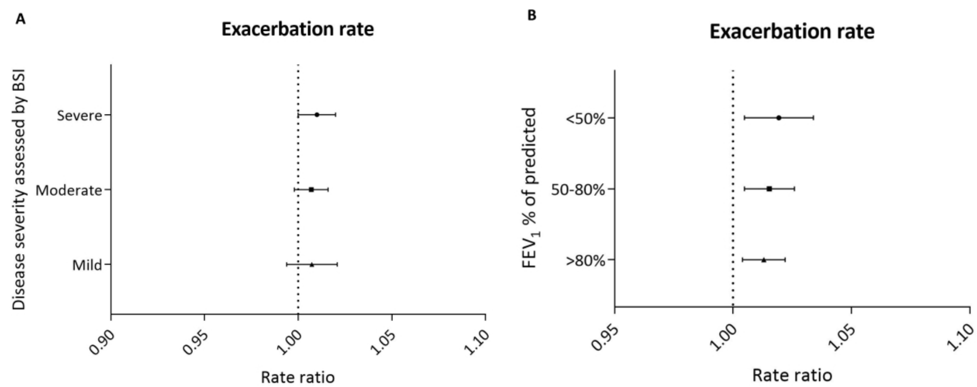

Supplementary Figure 2

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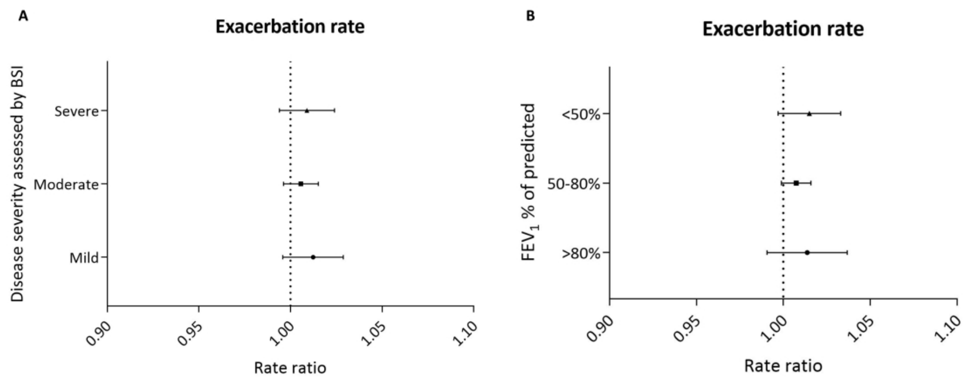

Supplementary Figure 3

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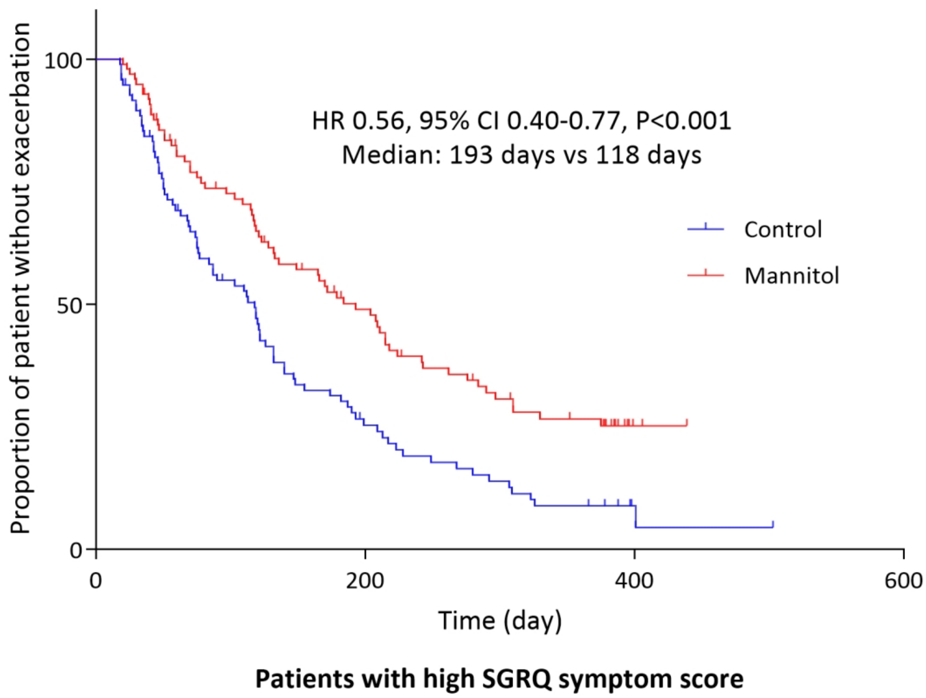

Supplementary Figure 4

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