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Title: Characterisation of the "frequent exacerbator phenotype" in bronchiectasis

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At a glance commentary

Scientific knowledge on the subject

Exacerbations are thought to be key events in the natural history of bronchiectasis. No previous studies have identified the predictors of future bronchiectasis exacerbations. In contrast to other respiratory disorders such as COPD, a "frequent exacerbator phenotype" has not been described in bronchiectasis. A clinically relevant phenotype should be stable over time, and be associated with clinically relevant outcomes. This study of more than 2000 bronchiectasis patients from 10 clinical centres across Europe and Israel examined the temporal stability and clinical outcomes of frequently exacerbating patients with bronchiectasis.

What this study adds to the field

We demonstrate that a prior history of exacerbations is the strongest predictor of future exacerbations over 3 years follow-up. The "frequent exacerbator phenotype" was relatively stable over time and was consistently identified in all 10 centres. Patients with frequent exacerbations, particularly those experiencing 3 or more exacerbations per year, had worse

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quality of life, more frequent hospitalizations and increased mortality over 5 years after adjustment for relevant confounders. These data demonstrate the critical importance of exacerbations the natural history of bronchiectasis and emphasise the importance of exacerbation prevention in clinical management.

Abstract:

Rationale: Exacerbations are key events in the natural history of bronchiectasis, but clinical predictors and outcomes of frequently exacerbating patients are not well described.

Objectives: To establish if there is a "frequent exacerbator phenotype" in bronchiectasis and the impact of exacerbations on long-term clinical outcomes.

Methods:

We studied bronchiectasis patients enrolled from 10 clinical centres in Europe and Israel, with up to 5-years follow-up. Patients were categorized by baseline exacerbation frequency (0, 1, 2 or ≥3 per year). The repeatability of exacerbation status was assessed as well as the independent impact of exacerbation history on hospitalizations, quality of life and mortality.

Measurements and Main Results:

2572 patients were included. Frequent exacerbations were the strongest predictor of future exacerbation frequency suggesting a consistent "phenotype". The incident rate ratios for future exacerbations were 1.73 (95%CI 1.47-2.02, p<0.0001) for 1 exacerbation per year, 3.14 (95%CI 2.70-3.66, p<0.0001) for 2 exacerbations and 5.97 (95%CI 5.27-6.78, p<0.0001) for patients with ≥3 exacerbations per year at baseline.

Additional independent predictors of future exacerbation frequency were *Haemophilus influenzae and Pseudomonas aeruginosa* infection, forced expiratory volume in 1 second, radiological severity of disease and co-existing COPD. Frequently exacerbating patients had worse quality of life and were more likely to be hospitalized during follow-up. Mortality over up to 5 years follow-up increased with increasing exacerbation frequency.

Conclusions: The frequent exacerbator phenotype in bronchiectasis is consistent over time and shows high disease severity, poor quality of life and increased mortality during follow-up.

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Keywords: exacerbations, bronchiectasis, antibiotics, infection, mortality

Background:

Bronchiectasis is a clinical syndrome defined by abnormal, usually permanent dilatation of the bronchi associated with cough and sputum production.(1) In addition, for many patients the daily symptoms of the disease are accompanied by unpredictable worsening of symptoms greater than the normal day to day variation and referred to as exacerbations.(2,3)

Exacerbations are recognised as important events in the natural history of bronchiectasis. International guidelines for bronchiectasis recommend treatment with, for example, inhaled or oral prophylactic antibiotic therapy for patients with 3 or more exacerbations per year with the aim of preventing exacerbations.(4-6) Exacerbations form part of the Bronchiectasis Severity Index (BSI), a multidimensional severity assessment tool for bronchiectasis.(7) In addition, exacerbation frequency or the time to first exacerbation have been the primary end-point for the majority of phase 3 randomized clinical trials in bronchiectasis.(8-11)

It is surprising, therefore, that there have been few published studies describing the frequency of exacerbations over time and risk factors for exacerbations in bronchiectasis. Bronchiectasis is a highly heterogeneous disease in terms of aetiology, severity and clinical outcomes.(1-7) Exacerbation frequency is no different and patient characteristics vary, with reported frequency of exacerbations across different populations ranging from 0 to 9 events per patient per year.(1)

In clinical practice, it is important to identify patients who are at risk of future exacerbations in order to target preventative therapies appropriately. For research, it is important to identify patients likely to have future exacerbations in order to adequately power clinical trials.(7-11) In COPD, Hurst et al, identified a frequent exacerbator “phenotype” by demonstrating that over a 3 year period, exacerbation frequency showed a relative degree of stability.(12) An accepted definition of phenotypes for COPD originally proposed by Han et al requires “a single or combination of disease attributes that describe differences between individuals with COPD

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as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)".(13) This definition can also be applied to patients with bronchiectasis.(13,14) Thus to be a valid patient phenotype in bronchiectasis, the "frequent exacerbator" should show stability over time and should be linked to clinically meaningful outcomes such as quality of life (QoL), future exacerbations, disease progression and/or death.

In this study, we used a European patient cohort to determine whether frequent exacerbator status was stable over time and to determine its relationship with clinical outcomes. Some of the results of this study have previously been reported as an abstract.(15)

Methods:

We analysed data from bronchiectasis patients enrolled in 10 different bronchiectasis clinical centres across Europe (including Israel as an EU affiliated country) (Dundee, Edinburgh, Newcastle – United Kingdom; Haifa - Israel; Galway - Ireland; Leuven - Belgium; Athens - Greece; Monza - Italy; Barcelona - Spain; Vojvodina - Serbia) between 2007 and 2013. Details of this cohort has been described previously.(16,17) Inclusion criteria were : Consecutive patients aged ≥18 years; diagnosis of bronchiectasis made by a specialist physician; high-resolution computed tomographic scan (HRCT); a clinical history consistent with bronchiectasis. Exclusion criteria were: Cystic fibrosis, traction bronchiectasis due to pulmonary fibrosis and active non-tuberculous mycobacterial disease.

Local ethics committee or institutional review board, approved the data collection at each site. Diagnostic work-up and assessment was made following the 2010 British Thoracic Society (BTS) guidelines. (6)

Baseline data collection was performed when patients were clinically stable and free from antibiotic therapy for exacerbations for a minimum of 4 weeks. Chronic infection was defined by isolation of the same pathogen in two or more cultures, at least 3 months apart in a 12-month span, with the patient in stable state (18). A core dataset consisting of demographics, previous medical history, comorbidities, as well as radiological, laboratory and microbiological findings was recorded at each site. QoL was measured by the St Georges Respiratory Questionnaire (SGRQ) and severity of disease was evaluated by the Bronchiectasis Severity Index (BSI). (7) Prophylactic antibiotic therapy at baseline was defined as administration of antibiotics with prophylactic intention, rather than for treatment of an exacerbation, for at least 28 days prior to baseline.

For the purposes of analysis, 3 or more exacerbations per year were regarded as frequent exacerbations based on the ERS bronchiectasis guidelines (4) and patients were subdivided by a history of 0, 1, 2 or 3 or more exacerbations per year for analysis.

Outcomes

Outcomes were evaluated for up to 5 years of follow-up. Outcomes were: all cause mortality; exacerbations: defined as as the requirement for antibiotics in the presence of one or more symptoms of increasing cough, increasing sputum volume, worsening sputum purulence, worsening dyspnoea, increased fatigue/malaise, fever, and haemoptysis; and severe exacerbations: defined according to BTS guidelines as unscheduled hospitalisations or emergency department visits for exacerbations or complications as recorded from patient histories and verified using administrative databases.(6)

Exacerbations were recorded for 12 months after the first visit in all patients and for 3 years in a subset.

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Statistical analysis

Descriptive statistics of median with 25-75% interquartile range (IQR) were used for continuous data, and absolute frequencies and percentages for categorical data. Subgroup comparisons were performed using the Mann-Witney U-Test or Chi-squared test, depending on data type. A comparison-wise significance level of 5% was used.

To determine independent predictors of future exacerbation frequency we used a negative bionomial model with adjustment for length of follow-up time. Results are reported as incident rate ratios (IRR) with 95% confidence intervals (95% CI). For multivariable mortality analysis, a multivariable Cox regression analysis was used. The proportional hazards assumption was checked by inspection of log minus log plots. Variables included in the model were those determined to be clinically significant in impacting on mortality. Multivariable analysis of binary outcomes was performed using multivariable logistic regression. The accuracy of prior exacerbations to predict future exacerbations was reported using sensitivity and specificity and associated likelihood ratios. Discrimination was assessed by the area under the receiver operator characteristic curve (ROC). A multiple linear regression model was applied to determine the variables with independent impact on QoL. All analyses were performed using SPSS version 21 (SPSS, Chicago, IL, USA) for Windows and Graph Pad Prism Version 5 (Graph Pad Software, Inc. San Diego, CA, USA).

Results:

Patient characteristics:

The study population was composed of 2596 patients. The median age was 67 years (interquartile range (IQR) 57-74), 38.9% were male and 61.9% of patients were never smokers. Further patient characteristics are shown in table 1. The aetiologies of bronchiectasis were typical of European cohorts, with most patients classified as idiopathic (42%), with post-infective aetiology (17%), COPD (9%), asthma (6%), connective tissue diseases (6%) and allergic bronchopulmonary aspergillosis (5%) also being common underlying causes.

The patient disposition in the study is shown in figure 1. The median exacerbation frequency prior to the study baseline was 2 per year. Exacerbation history was not recorded in 24 subjects. In the remaining 2572 patients, 657 (25.3%) patients had 0 exacerbations, 452 (17.4%) had 1 exacerbation, 497 (19.1%) had 2 exacerbations and 966 (37.2%) patients had 3 or more exacerbations. 25.9% of patients had at least one hospital admission for a severe exacerbation prior to the study.

Table 1 shows the characteristics of patients according to their previous exacerbation history.

A number of characteristics were statistically significantly different between groups at baseline. Reported p-values in table 1 should be interpreted with caution in view of the multiple comparisons performed.

Consistency of the "frequent exacerbator phenotype" over time

In the full analysis set, we examined the association between prior exacerbations and future exacerbation events. Compared to patients with 0 exacerbations at baseline, the IRR for future exacerbations was 1.73 (95%CI 1.47-2.02, p<0.0001) for 1 exacerbation per year, 3.14 (95%CI 2.70-3.66, p<0.0001) for 2 exacerbations and 5.97 (95%CI 5.27-6.78, p<0.0001) for patients

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with ≥3 exacerbations per year, indicating that increasing exacerbations at baseline were associated with higher rates of exacerbation during follow-up.

We next examined the ability of prior exacerbations to predict exacerbations in the following year (year 1 of follow-up). A history of 3 or more exacerbations in the previous year predicted 3 or more exacerbations in the following year with a sensitivity 79.9% (95% CI 76.5-83.0%), specificity 75.8% (95% CI 73.9-77.7%), negative predictive value 92.3% (95% CI 90.8-93.5%), positive predictive value 51.1% (95% CI 47.9-54.3%), positive likelihood ratio 3.31 (95% CI 3.03-3.61) and negative likelihood ratio 0.26 (95% CI 0.23-0.31). The area under the ROC curve for prior exacerbations to predict 3 or more exacerbations in the following year was 0.83 (95% 0.81-0.85, p<0.0001).

Equivalent data for a history of ≥2 exacerbations per year to identify patients having ≥2 exacerbations in year 1 were the following: sensitivity 82.6% (95% CI 80.2-84.6%), specificity 68.1% (95% CI 65.5-70.6%), positive predictive value 70.3% (95% CI 67.9-72.7%), negative predictive value 81.0% (95% CI 78.5-83.2%), positive likelihood ratio 2.59 95% CI 2.38-2.81, negative likelihood ratio 0.26 95% CI 22.6-29.0). The area under the ROC curve was 0.76 (95% CI 0.74-0.78, p<0.0001). These data suggest a high degree of agreement between baseline and first year exacerbation frequency.

1236 patients had complete data for 4 years of exacerbation recording, including the frequency of exacerbations in the year prior to the study and for 3 years prospectively. Excluded patients were those who died during follow-up and any patient lost to follow-up. Patients with complete follow-up data therefore tended to be milder, with fewer co-morbidities (supplementary table E1 and supplementary table E2 shows the proportion of patients lost to follow-up in each group).

Using this cohort, figure 2 demonstrates the repeatability of exacerbation frequency over time. It demonstrates a clear relationship between prior exacerbation history and future risk even

up to year 3. The proportion of patients that had 3 or more exacerbations at baseline and had 3 or more exacerbations in each year of the study was 24.0% of those with 3 or more events at baseline and 6.7% overall. The proportion of patients that experienced no exacerbations through all 4 years of exacerbation recording was 23.1% of those with 0 events at baseline and 8.2% of patients overall.

To understand variation in exacerbation frequency, we used multivariable logistic regression to examine factors associated with a change in exacerbation status. Patients with <3 exacerbations a year at baseline were more likely to change to have 3 or more exacerbations at follow-up if they were younger (age per year as continuous variable) OR 0.98 (95% CI 0.97-0.99, p=0.002), had prior hospital admissions OR 2.45 (95% CI 1.40-4.26, p=0.002), *H. influenza*e infection OR 2.13, (95% CI 1.37-3.32, p=0.001), *Enterobacteriaceae* infection OR 2.97 (95% CI 1.59-5.54, p=0.001), *P. aeruginosa* infection OR 2.17 (95% CI 1.12-4.21, p=0.02), a history of asthma OR 2.51 (95% CI 1.40-4.50, p=0.002) and lower FEV_1 % predicted (as a continuous variable) OR 0.99 (95% CI 0.98-0.99, p=0.02). Predictors of a change from frequent to infrequent exacerbator status are shown in table E3 online.

Independent risk factors for future exacerbations

Based on the observation that prior exacerbations predict future events, we conducted a multivariable analysis to determine the independent contribution of different variables to future exacerbation risk. The strongest predictor of future exacerbations was a past history of exacerbations. The IRRs (95% CI) were 1.81 (1.54-2.12) for one exacerbation per year, 3.07 (2.62-3.60) for 2 per year and 5.18 (4.51-5.95) for $\geq$3 per year (all p<0.0001 compared to 0 exacerbations per year). The univariate and multivariate relationship between other risk factors and exacerbation frequency are listed in table 2. Sensitivity analyses adjusting for additional findings were consistent with this primary analysis and are shown in Table E4 online.

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The clear relationship between prior and future exacerbations remained significant in subgroups with mild, moderate and severe bronchiectasis. (table E4). Patients with a history of severe exacerbations were at higher risk of all exacerbations during follow-up, IRR 1.43 95% CI 1.26-1.63,p<0.0001. Considering a history of severe and non-severe exacerbations separately made no difference to the overall conclusions (table E4 online).

Impact of exacerbation history of morbidity and mortality

Patients with frequent exacerbations at baseline had worse health status as measured by the SGRQ (figure 3). Differences between all groups were greater than the 4 point minimum clinically important difference except for the difference between patients with 0 and 1 exacerbation per year at baseline. The scores were 32.5 (18.1-48.8) for patients with 0 exacerbations, and then 35.9 (22.9-55.3), 44.0 (29.8-87.4) and 59.0 (37.7-74.9) for those with 1, 2 and 3 or more exacerbations per year at baseline respectively, p<0.0001. Patient QoL was worse in frequent exacerbators across all domains of the SGRQ (p<0.0001) and this is shown in figure E1 online.

In a multivariable linear regression model, after adjustment for multiple confounders as listed in table 2, each additional exacerbation per year was associated with an independent 3.7-point increase in SGRQ total score (95% CI 2.58-4.87,p<0.0001). Separating hospitalized and non-hospitalized exacerbations, the equivalent data were a 1.4 point increase for each individual outpatient exacerbation (95% CI 0.57-2.07,p=0.001) and a 9.8 point increase in those with a history of hospitalized exacerbations (95% CI 6.28-13.3,p<0.0001).

The number of hospital admissions was also greater for those with $\geq$3 exacerbations in the previous year (40% of patients were hospitalized during follow-up) compared with those with 2 (20.3%), 1 (11.3%) or 0 (11.1%) exacerbations at baseline, (p<0.0001 across groups), figure 4.

Mortality was increased in patients with 3 or more exacerbations per year (figure 4).

In a Cox proportional hazard regression adjusting for relevant confounding variables, compared to patients with 0 exacerbations at baseline, the hazard ratios (HR) for mortality were 0.92 (95% CI 0.57-1.48),p=0.7 for patients with 1 exacerbation, 1.60 (95% CI 1.06-2.42,p=0.03) for patients with 2 exacerbations and HR 1.86 (95% CI 1.30-2.66, p=0.001) for patients with $\geq$3 exacerbations per year. Therefore patients with 2 or more exacerbations per year at baseline have an independent increase in mortality risk.

Examining hospitalized and non-hospitalized exacerbations separately, the unadjusted and adjusted Hazard ratios were 3.24 95% CI 2.56-4.09,p<0.0001 and 1.97 95% CI 1.51-2.57,p<0.0001 respectively for hospitalized exacerbations. For outpatient exacerbations only, the hazard ratios were consistent with the primary analysis with HR 0.83 95% CI 0.53-1.31,p=0.4 for 1 exacerbation, 1.45 95% CI 0.98-2.16,p=0.06 for 2 exacerbations and HR 1.53 95% CI 1.04-2.25,p=0.03 for 3 or more exacerbations.

Sensitivity analysis- consistency of exacerbation frequency by centre and the impact of long-term antibiotic treatment

We finally investigated whether the consistency of the frequent exacerbator phenotype was a universal finding across European centres, and whether it was impacted by prior or newly initiated prophylactic antibiotic therapy. The results are shown in table 3. The precision of estimates varied across centres due to sample size, but the models indicated increasing future risk of exacerbations with increasing prior exacerbations in all countries. The AUC values ranged from 0.73-0.93 but all showed good to excellent discrimination of prior exacerbations for future exacerbations.

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Patients receiving prior antibiotic therapy had a higher frequency of exacerbations at baseline and during follow-up (mean 3.5 (standard deviation (SD) 2.5) per year at baseline, and 2.3 (SD 1.9) during follow-up) as reflected in the higher rate ratio's for future exacerbations in table 2, compared to patients not receiving prophylactic antibiotics at baseline 1.9 (SD 2.2) and follow-up, 1.6 (SD 1.6). These data also show the trend for exacerbation frequency to reduce over time.

We conducted a further sensitivity analysis examining the exacerbation frequency in 203 patients who newly commenced prophylactic antibiotic therapy during follow-up, which are known to impact on future risk of exacerbation in clinical trials.(1,8) Data on patients newly commencing prophylactic antibiotic treatment was only available in 5 cohorts (Dundee, Newcastle, Edinburgh, Haifa and Leuven). These patients had a mean exacerbation rate of 4.1 (SD 3.1) prior to therapy, reducing to 2.0 (SD 1.9) following therapy. Table 3 shows that despite this apparent response in terms of reduction in exacerbations, patients with a higher exacerbation frequency at baseline still had a higher rate of exacerbations during follow-up. Finally, since the frequent exacerbator phenotype has already been described in COPD, we conducted a sensitivity analysis excluding patients with co-existing COPD. These results are shown in table 3, and identified very similar estimates to the overall analysis.

Discussion

The objective of this study was to establish if the "frequent exacerbator" was a valid and clinically important phenotype in bronchiectasis.(19) Recognition of a frequent exacerbator phenotype in COPD linked to poorer health status, lung function decline and mortality has had a major impact on clinical care and clinical trial design.(20-24)

In order to qualify as a phenotype, the characteristic or group of characteristics being studies should be measurable, consistent over time and be linked to clinically relevant outcomes.(13)

Our results suggest that the frequent exacerbator phenotype meets these criteria, as exacerbation frequency showed relative stability over time, particularly in those with 3 or more exacerbations per year at baseline. Exacerbations were associated with an increased risk of death, an independent increase in the SGRQ, suggesting an independent contribution to impaired health status and were also linked to hospital admissions during follow-up.

Our findings are clinically important because exacerbation reduction is one of the key goals of bronchiectasis management.(4-6) Our data suggests that without intervention, patients with frequent exacerbations are likely to continue to exacerbate frequently and that this will have negative consequences for QoL, healthcare utilization and mortality. This strengthens the arguments in favour of the use of therapies that have been shown to reduce exacerbations including macrolides, inhaled antibiotics, mucoactive therapies and pulmonary rehabilitation.(25-27) Data from the European and United States bronchiectasis registries suggest that despite a high burden of exacerbations, use of such therapies is low.(28-30) In the present cohort, 37% of patients had $\geq$3 exacerbations per year but only 1/3 were receiving prophylactic antibiotic therapies. It is acknowledged that the evidence base for most of these interventions remains weak. Our data also indicates the need for high quality randomized trials to prove conclusively that such therapies can reduce exacerbations.(25-27).

Existing published data support the importance of exacerbations as an end-point in bronchiectasis. They are a major contributor to healthcare costs, and severe exacerbations have been linked to accelerated lung function decline.(31) Exacerbations form part of the multidimensional BSI which has been validated internationally as a predictor of outcome in bronchiectasis patients.(7) Several recent comparisons between the BSI and the similar FACED score found that FACED did not accurately predict future risk of exacerbations suggesting that it was not a valid predictor of severity of disease.(16,32) The major difference between the scores is that BSI incorporates history of exacerbations which are not included in

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FACED.(16,32) Modification of the FACED to include a past history of exacerbations has been shown to improve its prediction of exacerbations.(33) Our analysis explains why, since overwhelmingly the strongest predictor of future exacerbations is a prior history of exacerbations. Our data suggests that exacerbation history alone, without incorporating other variables, is sensitive and specific for predicting future events and so clinicians can use prior history for clinical decision making with a high degree of confidence.

Our study was not designed to demonstrate why patients exacerbate and so our study does not imply that all patients with $\geq$3 exacerbations per year are the same. Most exacerbations of bronchiectasis are thought to be caused by bacterial infection, but there is also evidence that exacerbations are associated with viral infections(34), while other identified risk factors for exacerbations include elevated sputum neutrophil elastase activity(35), genetic polymorphisms such as FUT2(36) and mannose binding lectin(37), and multiple co-morbidities.(17) Within the frequent exacerbator "phenotype" there may be multiple endotypes, biological subgroups with different patterns of bacteriological, inflammatory or genetic susceptibility to exacerbation.(38,39) Future studies should aim to examine and better defined these endotypes now that the clinical phenotype has been clearly established.(39)

Our study has limitations. Exacerbations are poorly defined clinical entities in bronchiectasis and our study was conducted prior to the standardization of the definition of exacerbations by an EMBARC/Bronchiectasis research registry task force.(2) Hence, variations in antibiotic use in different countries may impact on the frequency of reported events. Our definition of severe exacerbations requires admission to hospital and may be affected by the availability of home intravenous antibiotic treatments in some countries.(40) Mild exacerbations not receiving antibiotic therapy but requiring an increase in the use of interventions like chest physiotherapy or inhaled therapies are not yet a widely accepted concept in bronchiectasis but have been

shown to be important to clinical outcomes in COPD.(41,42) Future studies should attempt to address whether such events are important in bronchiectasis.

For clinical trials, our data suggest that a history of exacerbations can be used to reliably identify a cohort of patients with future exacerbations to power trials where the primary outcome is the frequency of exacerbations. Recent trials recruiting patients with a history of ≥2 exacerbations per year have observed a relatively low rate of exacerbations during follow-up. There are many possible reasons for this, including the tendency for milder patients to agree to enrolment in clinical trials and differences in the methods used to collect prior exacerbation history and follow-up exacerbation frequency.(43) Our data suggested that a history of ≥3 exacerbations had an optimal sensitivity and specificity for predicting future events and future trials may wish to consider using this as their inclusion criteria.

In conclusion, frequently exacerbating patients with bronchiectasis represent a distinct clinical phenotype with different patient characteristics, a high risk of hospital admissions, poor QoL and a higher risk of death during follow-up. This study emphasizes the importance of prioritizing exacerbation reduction in the management of bronchiectasis.

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References:

1. Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. *Eur. Respir. J.* 2015; 45: 1446–1462.
2. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, Chalmers JD, De Soyza A, Dimakou K, Elborn JS, Feldman C, Flume P, Goeminne PC, Loebinger MR, Menendez R, Morgan L, Murris M, Polverino E, Quittner A, Ringshausen FC, Tino G, Torres A, Vendrell M, Welte T, Wilson R, Wong C, O'Donnell A, Aksamit T. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J.* 2017;49(6). pii: 1700051. doi: 10.1183/13993003.00051-2017. Print 2017 Jun
3. Brill SE, Patel AR, Singh R, Mackay AJ, Brown JS, Hurst JR. Lung function, symptoms, and inflammation during exacerbations of non-cystic fibrosis bronchiectasis: a prospective observational cohort study. *Respir Res* 2015; 16:16 doi: 10.1186/s12931-015-0167-9.
4. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50(3). pii: 1700629. doi: 10.1183/13993003.00629-2017.
5. Vendrell M, de Gracia J, Olveira C, Martínez MA, Girón R, Máiz L, Cantón R, Coll R, Escribano A, Solé A. Normativa SEPAR: diagnóstico y tratamiento de las bronquiectasias. Arch. Bronconeumol; 2008; 44: 629–640
6. Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65 Suppl 1: i1-58
7. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, Poppelwell L, Salih W, Pesci A, Dupont LJ, Fardon TC, De Soyza A, Hill AT.The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*. 2014;189(5):576-85

8. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. *Am. J. Respir. Crit. Care Med.* 2014; 189: 975–982
9. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA.* 2013;309(12):1260-7.
10. Bilton D, Tino G, Barker AF, Chambers DC, De Soyza A, Dupont LJ, O'Dochartaigh C, van Haren EH, Vidal LO, Welte T, Fox HG, Wu J, Charlton B Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. *Thorax.* 2014;69(12):1073-9.
11. Aksamit T, Bandel TJ, Criollo M, De Soyza A, Elborn JS, Operschall E, Polverino E, Roth K, Winthrop KL, Wilson R. The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. *Contemp Clin Trials.* 2017;58:78-85. doi: 10.1016/j.cct.2017.05.007. Epub 2017 May 8.
12. Hurst JR, Vestbo J, Anzueto A et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363(12):1128-38.
13. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, Fabbri LM, Goldin JG, Jones PW, Macnee W, Make BJ, Rabe KF, Rennard SI, Sciurba FC, Silverman EK, Vestbo J, Washko GR, Wouters EF, Martinez FJ. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010;182(5):598-604.
14. Vestbo J, Agusti A, Wouters EF, Bakke P, Calverley PM, Celli B, Coxson H, Crim C, Edwards LD, Locantore N, Lomas DA, MacNee W, Miller B, Rennard SI, Silverman EK, Yates JC, Tal-Singer R. Should we view chronic obstructive pulmonary diseasedifferently after ECLIPSE? A clinical perspective from the study team. *Am J Respir Crit Care Med*. 2014;189(9):1022-30. doi: 10.1164/rccm.201311-2006PP.
15. Chalmers JD, Filonenko A, Shteinberg M, Goeminne PC, McDonnell M, Aliberti S, Fardon TC, Obradovic D, Operschall E, Gerlinger C, Sotgiu G, Dimakou K, Polverino E, De Soyza A, Hill AT. Characterisation of the frequent exacerbator

AJRCCM Articles in Press. Published on 22-January-2018 as 10.1164/rccm.201711-2202OC

phenotype in bronchiectasis: data from the FRIENDS cohort. *Am J Respir Crit Care Med* 2017; 195:A7305.

16. McDonnell MJ, Aliberti S, Goeminne PC, Dimakou K, Zucchetti SC, Davidson J, Ward C, Laffey JG, Finch S, Pesci A, Dupont LJ, Fardon TC, Skrbic D, Obradovic D, Cowman S, Loebinger MR, Rutherford RM, De Soyza A, Chalmers JD. Multidimensional severity assessment in bronchiectasis- analysis of 7 European Cohorts. *Thorax* 2017; 71(12):1110-1118. doi: 10.1136/thoraxjnl-2016-208481.
17. McDonnell MJ, Aliberti S, Goeminne PC, Restrepo MI, Finch S, Pesci A, Dupont LJ, Fardon TC, Wilson R, Loebinger MR, Skrbic D, Obradovic D, De Soyza A, Ward C, Laffey JG, Rutherford RM, Chalmers JD. Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study. *Lancet Respir. Med*. 2016; 4: 969–979.
18. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis. *Ann Am Thorac Soc*. 2015;12(11):1602-11
19. Aliberti S, Lonni S, Dore S, McDonnell MJ, Goeminne PC, Dimakou K, Fardon TC, Rutherford R, Pesci A, Restrepo MI, Sotgiu G, Chalmers JD. Clinical phenotypes in adult patients with bronchiectasis. *Eur Respir J* 2016;47(4):1113-22.
20. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;157(5 Pt 1):1418-2
21. Wedzicha JA, Wilkinson T. Impact of chronic obstructive pulmonary diseaseexacerbations on patients and payers. *Proc Am Thorac Soc*. 2006;3(3):218-21.
22. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax.* 2005;60(11):925-31. Epub 2005 Jul 29.
23. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, Criner GJ, Curtis JL, Hanania NA, Nath H, Putcha N, Roark SE, Wan ES, Washko GR, Wells JM, Wendt CH, Make BJ; COPDGene Investigators. Acute Exacerbations and Lung Function Loss in Smokers with and

without Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2017;195(3):324-330. doi: 10.1164/rccm.201605-1014OC.

24. Wedzicha JA, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Hurst JR, Miravitlles M, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;50(3). pii: 1602265. doi: 10.1183/13993003.02265-2016. Print 2017 Sep.
25. Altenburg J. Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non – Cystic Fibrosis Bronchiectasis. JAMA; 2013; 309: 1251–1259
26. Brodt AM, Stovold E, Zhang L. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. *Eur Respir J*; 2014;44(2):382-93.
27. Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, Rautela L, Stirling RG, Thompson PJ, Holland AE. The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis- a randomised controlled trial. *Respir Res* 2014;15:44.
28. Aliberti S, Hill AT, Mantero M, Battaglia S, Centanni S, Lo Cicero S, Lacedonia D, Saetta M, Chalmers JD, Blasi F. Quality standards for the management of bronchiectasis in Italy: a national audit. *Eur Respir J* 2016;48(1):244-8.
29. Aksamit TR, O'Donnell AE, Barker A, Olivier KN, Winthrop KL, Daniels MLA, Johnson M, Eden E, Griffith D, Knowles M, Metersky M, Salathe M, Thomashow B, Tino G, Turino G, Carretta B, Daley CL. Adult patients with bronchiectasis: a first look at the US bronchiectasis research registry. *Chest* 2017;151(5):982-992.
30. Haworth CS, Johnson C, Aliberti S et al. Management of bronchiectasis in Europe: Data from the European bronchiectasis registry (EMBARC). *Eur Respir J* 2016;48:OA273;
31. Martínez-Garcia MA, Soler-Cataluña JJ, Perpiña-Tordera M, Roman Sanchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007;132:1565–1572
32. Rosales-Mayor E, Polverino E, Raguer L, Alcaraz V, Gabarrus A, Ranzani O, Menendez R, Torres A. Comparison of two prognostic scores (BSI and FACED) in a Spanish cohort of adult patients with bronchiectasis and improvement of

AJRCCM Articles in Press. Published on 22-January-2018 as 10.1164/rccm.201711-2202OC

the FACED predictive capacity for exacerbations. Plos One 2017;12(4):e0175171.

33. Martínez-García MA, de Gracia J, Vendrell Relat M, Girón RM, Máiz Carro L, de la Rosa Carrillo D, Olveira C. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur Respir J* 2014;43:1357–1367.
34. Gao YH, Guan WJ, Xu G, Lin ZY, Tang Y, Lin ZM, Gao Y, Li HM, Zhong NS, Zhang GJ, Chen RC.. The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: a prospective study. *Chest.* 2015;147(6):1635-43.
35. Chalmers JD, Moffitt KL, Suarez-Cuartin G, Sibila O, Finch S, Furrie E, et al. Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis. *Am J Respir Crit Care Med* 2017;195(10):1384-93.
36. Taylor SL, Woodman RJ, Chen AC et al. FUT2 genotype influences lung function, exacerbation frequency and airway microbiota in non-CF bronchiectasis. Thorax 2017;72(4):304-310.
37. Chalmers JD, McHugh BJ, Doherty CJ, Govan JRW, Kilpatrick DC, Hill AT. Mannose binding lectin deficiency and disease severity in non-CF bronchiectasis: a prospective study. *Lancet Resp Med* 2013; 1(3):175-274.
38. Chalmers JD, Chotirmall SH. New Therapies and new perspectives. *Lancet Resp Med* 2018; in press.
39. Aliberti S, Masefield S, Polverino E, De Soyza A, Loebinger MR, Menendez R, Ringshausen FC, Vendrell M, Powell P, Chalmers JD. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J.* 2016 ;48(3):632-47. doi: 10.1183/13993003.01888-2015. Epub 2016 Jun 10.
40. Bedi P, Sidhu MK, Donaldson LS, Chalmers JD, Smith MP, Turnbull K, Pentland JL, Scott J, Hill AT. A prospective cohort study of the use of domiciliary intravenousantibiotics in bronchiectasis. NPJ Prim Care Respir Med. 2014;24:14090. doi: 10.1038/npjpcrm.2014.90.
41. MacKay AJ, Donaldson GC, Patel ARC et al. Detection and severity grading of COPD exacerbations using the Exacerbations of chronic pulmonary disease tool (EXACT). *Eur Respir J* 2014; 43(3):735-44.

42. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agustí A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med.* 2017;195(5):557-582. doi: 10.1164/rccm.201701-0218PP.
43. Chalmers JD, McDonnell MJ, Rutherford R, Davidson J, Finch S, Crichton M, Dupont L, Hill AT, Fardon TC, De Soyza A, Aliberti S, Goeminne P. The generalizability of bronchiectasis randomized controlled trials: a multicentre cohort study. *Respir Med* 2016;112:51-8.

Figure Legends

Figure 1. Patient groups and endpoints used in the analysis

Figure 2. Exacerbation frequency during follow-up and the association with exacerbations in the previous year.

Figure 3. St Georges Respiratory Questionnaire scores (SGRQ) according to baseline exacerbation frequency. ($p<0.0001$ by Kruskal-Wallis test).

Figure 4. Follow-up hospitalization rates and Annual survival in groups based on baseline exacerbations.

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Variables	Full cohort		0 exacerbations per year	1 exacerbation per year	2 exacerbation per year	≥3 exacerbation per year	P-value (comparison across all groups)
n.	2596		657	452	497	966	n/a
Demographics							
Median (IQR) age, years	67 (57-74)		68 (58-75)	67 (58-75)	66 (55-75)	66 (57-74)	0.3
Age >65 years, n (%)	1395 (53.7%)		368 (56.0%)	251 (55.5%)	258 (51.9%)	505 (52.3%)	0.3
Age >75 years, n (%)	572 (22.0%)		164 (25.0%)	110 (24.3%)	107 (21.5%)	187 (19.4%)	0.03
Male, n (%)	1010 (38.9%)		244 (37.1%)	178 (39.4%)	181 (36.4%)	399 (41.3%)	0.2
Median (IQR) BMI	24.8 (21.8-28.1)		25 (22.0-27.9)	25 (21.9-28.1)	24.5 (21.5-27.5)	25 (21.5-28.6)	0.7
Either smokers or former smokers, n (%)	990 (38.1%)		219 (33.3%)	167 (37.0%)	188 (37.8%)	402 (41.6%)	0.009
Comorbidity							
Ischaemic heart disease, n (%)	453 (17.5%)		141 (21.5%)	80 (17.7%)	74 (14.9%)	155 (16.1%)	0.01
Stroke, n (%)	152 (5.9%)		57 (8.7%)	22 (4.9%)	20 (4.0%)	51 (5.3%)	0.003
Diabetes, n (%)	260 (10.0%)		85 (12.9%)	36 (8.0%)	35 (7.0%)	100 (10.4%)	0.004
Liver disease, n (%)	41 (1.6%)		7 (1.1%)	5 (1.1%)	6 (1.2%)	21 (2.2%)	0.2
Chronic renal failure, n (%)	154 (5.9%)		36 (5.5%)	24 (5.3%)	23 (4.6%)	70 (7.2%)	0.2
COPD, n (%)	431 (16.6%)		60 (9.1%)	63 (13.9%)	84 (16.9%)	215 (22.2%)	<0.0001
Asthma, n (%)	226 (8.7%)		37 (5.6%)	36 (8.0%)	53 (10.7%)	96 (9.9%)	0.006
Connective tissue disease, n (%)	210 (8.1%)		48 (7.3%)	29 (6.4%)	44 (8.9%)	89 (9.2%)	0.2
Neurological disease, n (%)	68 (2.6%)		19 (2.9%)	7 (1.5%)	12 (2.4%)	30 (3.1%)	0.4
Osteoporosis, n (%)	192 (7.4%)		64 (9.7%)	29 (6.4%)	40 (8.0%)	57 (5.9%)	0.02
GERD, n (%)	394 (15.2%)		84 (12.8%)	58 (12.8%)	86 (17.3%)	162 (16.8%)	0.04
Haematological malignancy, n (%)	33 (1.3%)		5 (0.8%)	2 (0.4%)	10 (2.0%)	16 (1.7%)	0.07
Solid tumor, n (%)	164 (6.3%)		24 (3.7%)	22 (4.9%)	32 (6.4%)	68 (7.0%)	0.02
Disease severity							
Median (IQR) BSI score,	6 (4-10)		5 (3-7)	5 (3-7)	5 (3-8)	11 (7-14)	<0.0001
BSI score Risk Class, n (%)	Mild	753 (29.0%)	277 (42.2%)	190 (42.0%)	186 (37.4%)	91 (9.4%)	
	Moderate	926 (35.7%)	290 (44.1%)	180 (39.8%)	196 (39.4%)	250 (25.9%)	
	Severe	917 (35.3%)	90 (13.7%)	82 (18.1%)	115 (23.1%)	625 (64.7%)	<0.0001
Radiological status							
Median (IQR) Reiff score	4 (2-6)		3 (2-6)	3 (2-5)	3 (2-5)	4 (2-6)	<0.0001

Clinical status						
MRC dyspnoea scale, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	3 (2-4)	<0.0001
Median (IQR) exacerbations in the previous year	2 (0-3)	0 (0-0)	1 (1-1)	2 (2-2)	4 (3-5)	<0.0001
a t least one hospitalization in the previous year, n (%)	672 (25.9%)	0 (0%)	27 (6.0%)	95 (19.1%)	550 (56.9%)	<0.0001
Functional Status						
Median (IQR) FEV_1 % predicted	73.8% (54.0-92.1)	80.8% (62.0-95.0)	79.2% (61.0-95.3)	75.7% (56.3-93.9)	65.0% (46-85)	<0.0001
FEV_1 <35% predicted, n (%)	181 (7.0%)	20 (3.0%)	20 (4.4%)	22 (4.4%)	118 (12.2%)	<0.0001
FEV_1 <50% predicted, n (%)	517 (19.9%)	79 (12.0%)	75 (16.7%)	86 (17.3%)	274 (28.4%)	<0.0001
Microbiology						
Chronic infection with at least one pathogen, n (%)	1300 (50.7%)	244 (37.1%)	192 (42.5%)	244 (49.1%)	618 (64.0%)	<0.0001
P. aeruginosa, n (%)	389 (15.0%)	36 (5.5%)	26 (5.8%)	49 (9.9%)	277 (28.7%)	<0.0001
H. influenzae, n (%)	569 (21.9%)	131 (19.9%)	93 (20.6%)	107 (21.5%)	237 (24.5%)	0.1
S. aureus, n (%)	156 (6.0%)	30 (4.6%)	21 (4.6%)	35 (7.0%)	70 (7.2%)	0.06
M. catarrhalis, n (%)	154 (5.9%)	31 (4.7%)	32 (7.1%)	31 (6.2%)	59 (6.1%)	0.4
Enterobacteriaceae, n (%)	158 (6.1%)	23 (3.5%)	23 (5.1%)	37 (7.4%)	75 (7.8%)	0.002
long-term antibiotic Treatment						
Oral antibiotic treatment (incl. macrolides), n (%)	503 (19.4%)	51 (7.8%)	50 (11.1%)	79 (15.9%)	320 (33.1%)	<0.0001
Inhaled antibiotic treatment, n (%)	166 (6.4%)	9 (1.4%)	7 (1.5%)	17 (3.4%)	132 (13.7%)	<0.0001

Table 1. Patient characteristics according to previous exacerbation history. Abbreviations: BMI= body mass index, BSI= bronchiectasis severity index, COPD= chronic obstructive pulmonary disease, FEV1= forced expiratory volume in 1 second, GERD= gastrooesophageal reflux disease, IQR= interquartile range, MRC= medical research council, n/a= not applicable.

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	Unadjusted			Adjusted		
	IRR	95% CI	p-value	IRR	95% CI	p-value
0 Exacerbations	1.0 (reference)			1.0 (reference)		
1 Exacerbation	1.73	1.47-2.02	<0.0001	1.81	1.54-2.12	<0.0001
2 Exacerbation	3.14	2.70-3.66	<0.0001	3.07	2.62-3.60	<0.0001
3 Exacerbations	5.97	5.27-6.78	<0.0001	5.18	4.51-5.95	<0.0001
Age (per 10 years)	1.00	0.96-1.03	0.8	0.96	0.95-1.03	0.6
Gender (Male)	1.11	1.00-1.23	0.04	0.95	0.86-1.06	0.4
MRC dyspnoea score	1.24	1.19-1.29	<0.0001	1.02	0.97-1.07	0.4
FEV1 % predicted (per 10%)	0.88	0.87-0.90	<0.0001	0.96	0.94-0.98	0.001
Reiff Score	1.04	1.03-1.06	<0.0001	1.02	1.00-1.03	0.05
Smoking history	1.22	1.10-1.35	<0.0001	0.95	0.85-1.06	0.3
Haemophilus influenzae	1.07	0.96-1.20	0.2	1.13	1.01-1.28	0.04
Moraxella catarrhalis	0.94	0.78-1.14	0.5	0.94	0.77-1.15	0.5
Staphylococcus aureus	1.19	0.97-1.45	0.1	1.08	0.88-1.32	0.5
Enterobacteriaceae	1.30	1.08-1.57	0.006	0.99	0.82-1.20	0.9
Pseudomonas aeruginosa	1.94	1.69-2.23	<0.0001	1.20	1.04-1.40	0.01
Asthma	1.22	1.03-1.44	0.02	1.16	0.98-1.38	0.09
COPD	1.89	1.66-2.16	<0.0001	1.43	1.22-1.67	<0.0001
Idiopathic	0.72	0.65-0.79	<0.0001	0.92	0.83-1.02	0.1

Table 2. Adjusted and unadjusted incident rate ratios for exacerbation frequency during follow-up. Abbreviations: COPD= chronic obstructive pulmonary disease, FEV1= forced expiratory volume in 1 second, MRC= medical research council.

Subgroup	**Incident rate ratio's from the Poisson model**			**Area under the curve**	
	1 exacerbations	**2 exacerbations**	**3 or more exacerbations**	**2 or more exacerbations**	**3 or more exacerbations**
Country					
Belgium	**2.92 (1.47-5.82)**	**4.72 (2.36-9.44)**	**6.24 (3.32-11.7)**	**0.78 (0.71-0.84)**	**0.83 (0.76-0.89)**
Greece	**0.71 (0.09-5.86)**	**1.52 (0.20-11.5)**	**3.57 (0.50-25.6)**	**0.77 (0.68-0.87)**	**0.85 (0.76-0.94)**
Ireland	**0.94 (0.07-12.0)**	**2.15 (0.19-24.9)**	**4.16 (0.37-46.2)**	**0.83 (0.78-0.88)**	**0.84 (0.78-0.90)**
Israel	**5.63 (0.62-51.4)**	**9.47 (1.09-82.1)**	**13.1 (1.60-106)**	**0.73 (0.62-0.83)**	**0.79 (0.70-0.89)**
Italy	**1.58 (1.08-2.33)**	**2.26 (1.56-3.29)**	**3.66 (2.65-5.07)**	**0.80 (0.76-0.85)**	**0.81 (0.76-0.87)**
Serbia	**6.00 (2.17-16.4)**	**11.0 (4.40-27.5)**	**20.9 (8.15-53.5)**	**0.91 (0.83-0.99)**	**0.93 (0.80-1.00)**
Spain	**2.72 (1.78-4.15)**	**5.67 (3.68-8.73)**	**31.6 (22.3-45.0)**	**0.89 (0.87-0.91)**	**0.88 (0.86-0.90)**
UK	**1.39 (1.14-1.69)**	**2.60 (2.12-3.19)**	**5.49 (4.66-6.47)**	**0.80 (0.78-0.83)**	**0.85 (0.83-0.88)**
Prophylactic antibiotic use at baseline	**3.27 (1.67-6.41)**	**5.81 (3.1-10.7)**	**8.90 (4.9-16.2)**	**0.78 (0.74-0.82)**	**0.78 (0.74-0.82)**
No prophylactic antibiotic use at baseline	**2.00 (1.64-2.45)**	**2.93 (2.44-3.52)**	**5.66 (4.81-6.67)**	**0.80 (0.78-0.82)**	**0.84 (0.82-0.87)**
Commenced prophylactic antibiotics during the study	**4.57 (1.35-15.5)**	**6.83 (2.12-22.1)**	**13.3 (4.26-41.4)**	**0.76 (0.70-0.83)**	**0.77 (0.70-0.83)**
Excluding COPD patients	**2.14 (1.74-2.62)**	**3.12 (2.59-3.76)**	**5.98 (5.07-7.05)**	**0.79 (0.77-0.81)**	**0.83 (0.81-0.85)**

Table 3. Sensitivity analysis of different countries and patient subgroups demonstrating the consistency of the frequent exacerbator phenotype over time.

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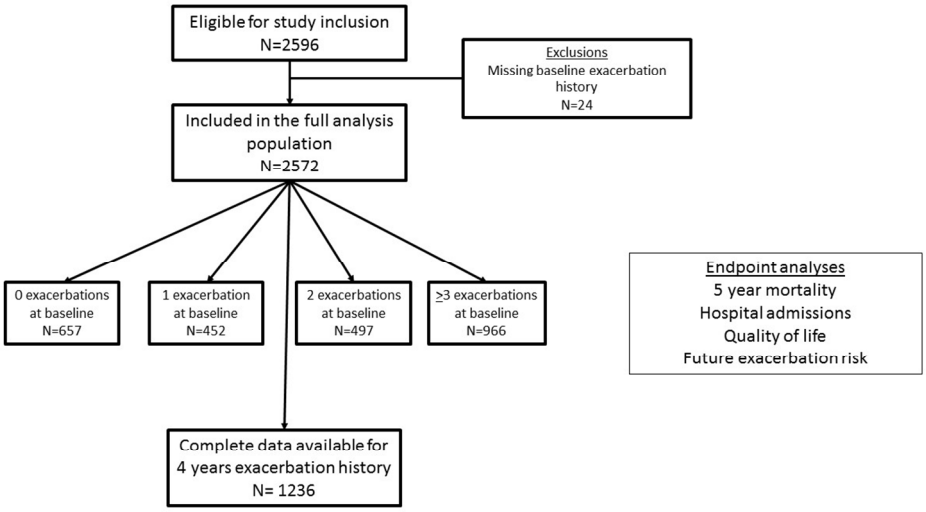

Figure 1. Patient groups and endpoints used in the analysis

338x190mm (96 x 96 DPI)

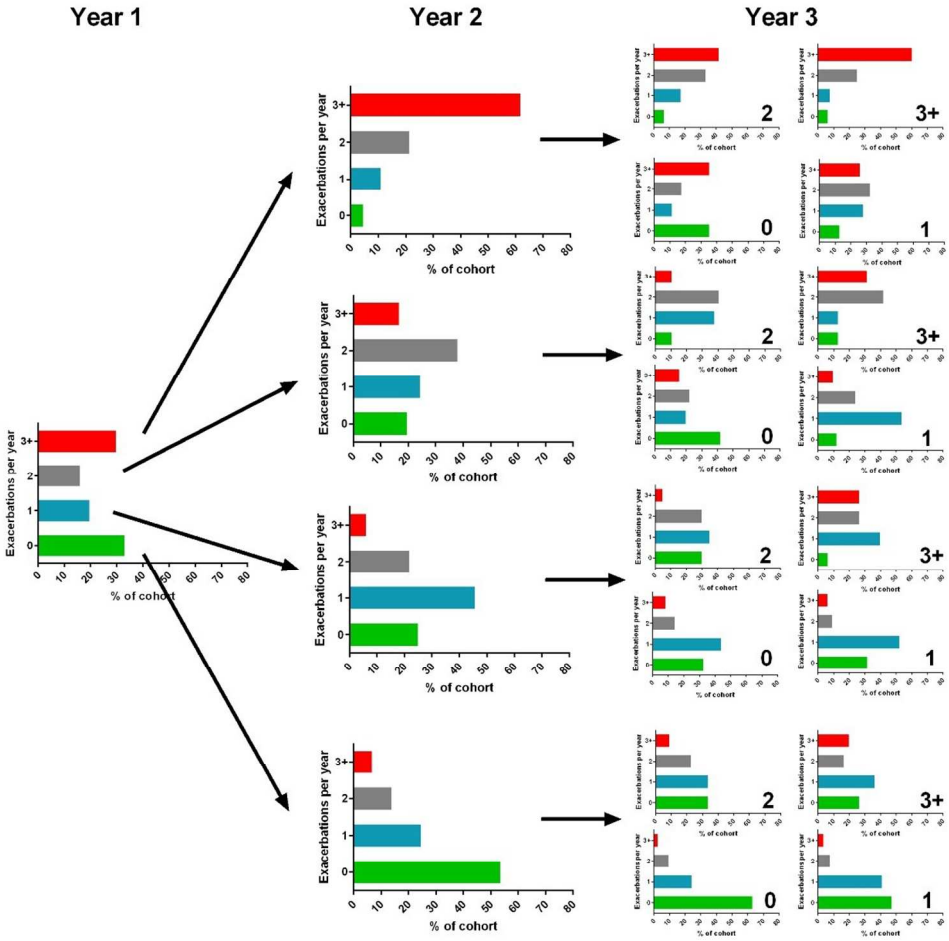

Figure 2. Exacerbation frequency during follow-up and the association with exacerbations in the previous year.

149x145mm (220 x 220 DPI)

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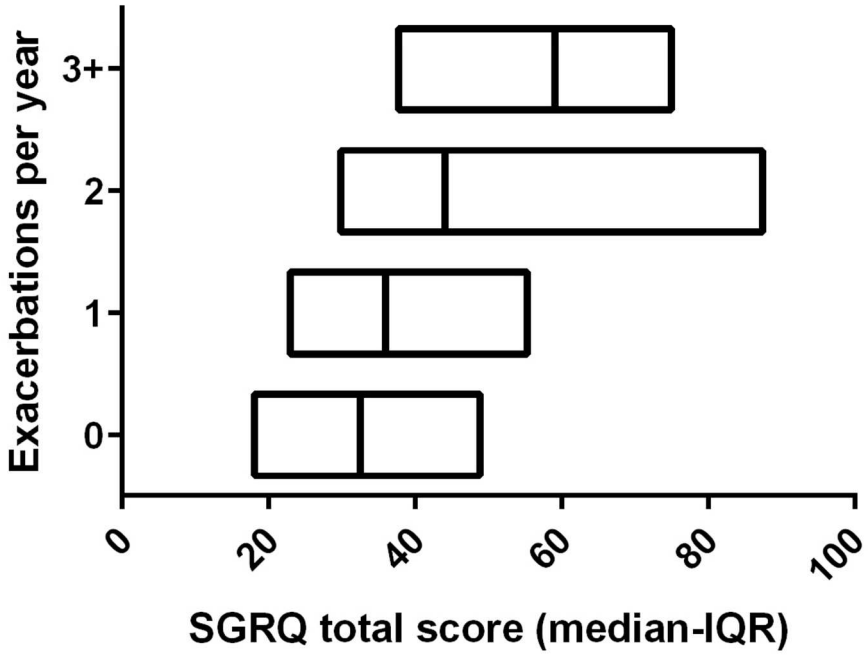

Figure 3. St Georges Respiratory Questionnaire scores (SGRQ) according to baseline exacerbation frequency. (p<0.0001 by Kruskal-Wallis test).

104x77mm (300 x 300 DPI)

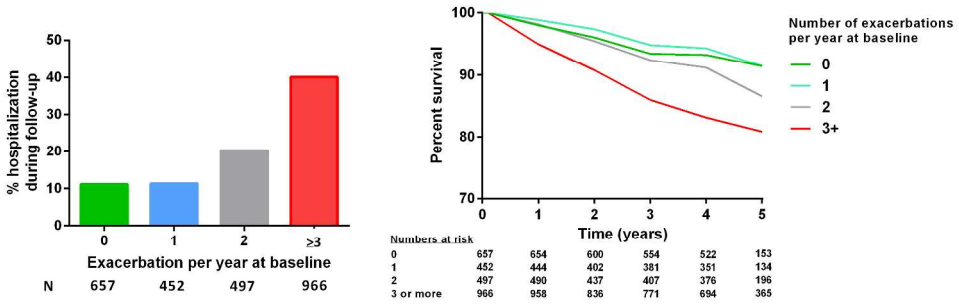

Figure 4. Follow-up hospitalization rates and Annual survival in groups based on baseline exacerbations.

278x98mm (300 x 300 DPI)

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ONLINE SUPPLEMENT

LOSS TO FOLLOW-UP AND LONGITUDINAL EXACERBATIONS

1 year exacerbation follow-up data was mandatory for all cohorts but the frequency of missing data increases progressively because not all cohorts had follow-up data available for exacerbations beyond year 1. For the purposes of analysis these patients are considered “lost to follow-up” although the patients may be under follow-up with data recorded for mortality, but missing for exacerbation frequency. The below analysis shows a comparison between patients with complete data and those lost to follow-up.

Variables	Complete data for 4 years	Lost to follow-up	
n.	1236	1360	
Demographics			
Median (IQR) age, years	67 (58-73)	66 (56-75)	0.01
Age >65 years, n (%)	691 (55.9%)	704 (51.8%)	0.03
Age >75 years, n (%)	245 (19.8%)	327 (24.0%)	0.01
Male, n (%)	470 (38.0%)	539 (39.6%)	0.4
Median (IQR) BMI	25.0 (21.9-28.4)	24.6 (21.6-27.8)	0.6
Either smokers or former smokers, n (%)	385 (31.2%)	605 (44.5%)	<0.0001
Comorbidity			
Ischaemic heart disease, n (%)	290 (23.5%)	163 (12.0%)	<0.0001
Stroke, n (%)	92 (7.4%)	60 (4.4%)	0.001
Diabetes, n (%)	124 (10.0%)	136 (10.0%)	0.9
Liver disease, n (%)	16 (1.3%)	25 (1.8%)	0.3
Chronic renal failure, n (%)	52 (4.2%)	102 (7.5%)	0.0004
COPD, n (%)	82 (6.6%)	349 (25.7%)	<0.0001
Asthma, n (%)	110 (8.9%)	116 (8.5%)	0.7
Connective tissue disease, n (%)	52 (4.2%)	158 (11.6%)	<0.0001
Neurological disease, n (%)	39 (3.2%)	29 (2.1%)	0.1
Osteoporosis, n (%)	95 (7.7%)	97 (7.1%)	0.6
GERD, n (%)	104 (8.4%)	290 (21.3%)	<0.0001
Haematological malignancy, n (%)	11 (0.9%)	22 (1.6%)	0.1
Solid tumor, n (%)	41 (3.3%)	120 (8.8%)	<0.0001
Disease severity			
Median (IQR) BSI score,	6 (4-9)	7 (4-12)	<0.0001
BSI score Risk Class, n (%)	391 (31.6%)	362 (26.6%)	<0.0001
	501 (40.5%)	425 (31.3%)	
	344 (27.8%)	573 (42.1%)	
Radiological status			
Median (IQR) Reiff score	3 (2-6)	4 (2-6)	<0.0001
Clinical status			

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MRC dyspnoea scale, median (IQR)	2 (1-3)	2 (1-3)	0.3
Median (IQR) exacerbations in the previous year	1 (0-2)	2 (1-4)	<0.0001
a t least one hospitalization in the previous year, n (%)	234 (18.9%)	438 (32.2%)	<0.0001
Functional Status			
Median (IQR) FEV_1 % predicted	76.1% (57.1-93.9%)	71.0% (52-90.0%)	0.1
FEV_1 <35% predicted, n (%)	61 (4.9%)	120 (8.8%)	0.0001
FEV_1 <50% predicted, n (%)	232 (18.8%)	285 (21.0%)	0.2
Microbiology			
Chronic infection with at least one pathogen, n (%)	666 (53.9%)	486 (39.4%)	<0.0001
P. aeruginosa, n (%)	151 (12.2%)	238 (17.5%)	0.0002
H. influenzae, n (%)	372 (30.1%)	197 (14.5%)	<0.0001
S. aureus, n (%)	76 (6.5%)	80 (5.9%)	0.8
M. catarrhalis, n (%)	125 (10.1%)	29 (2.1%)	<0.0001
Enterobacteriaceae, n (%)	118 (9.5%)	40 (2.9%)	<0.0001
long-term antibiotic Treatment			
Oral antibiotic treatment (incl. macrolides), n (%)	144 (11.7%)	359 (26.4%)	<0.0001
Inhaled antibiotic treatment, n (%)	50 (4.0%)	116 (8.5%)	<0.0001

Table E1. Comparison of patients lost to follow-up (including patients dying during follow-up) and those with complete exacerbation data for 4 years.

Timing of loss to follow-up across the cohort.

Baseline		Year 1					Year 2					Year 3				
	N	0	1	2	3+	Lost to f/u	0	1	2	3+	Lost to f/u	0	1	2	3+	Lost to f/u
0	657	407	140	70	35	5	241	139	52	23	202	220	130	55	31	221
1	452	127	212	81	22	10	83	123	44	21	181	69	127	43	14	199
2	497	94	143	171	67	22	38	73	73	32	281	41	77	44	33	302
3+	966	58	120	252	494	42	33	46	103	187	597	28	80	82	146	630
Missing	24	12	3	0	3	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table E2- number of exacerbation events over time stratified by baseline exacerbation frequency for all patients included in the study. Patients that died during the study contributed exacerbation data for the year of death if such data was recorded. 76 patients died in year 1 (and are therefore coded as lost to f/u in year 2) 67 patients died in year 2 (and are therefore coded as lost to follow-up in year 3) and 79 patients died in year 3. NR= not relevant as patient baseline data could not be missing after year 1.

Determinants of switch from Frequent to non-frequent exacerbator status.

A logistic regression analysis was used to identify variables associated with an improvement in exacerbation status during follow-up.

Independent predictors of a switch from frequent (2 or more exacerbations per year) to infrequent (<2 per year) were *Moraxella catarrhalis* infection, *P. aeruginosa* infection, COPD, asthma, lower FEV1 (as a continuous variable), worse radiological bronchiectasis and the presence of connective tissue disease. All of these factors were "protective" against a switch to infrequent exacerbations (odds ratio <1), indicating that these are poor prognostic features that identify cohorts of patients that continue to frequently exacerbate despite standard treatment.

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Independent variables	Odds ratio with 95% CI and p-value
Gender	**1.11 (0.84-1.45),p=0.5**
Age	**1.00 (0.99-1.01),p=0.6**
MRC dyspnoea score	**0.91 (0.80-1.03),p=0.1**
Idiopathic BE	**0.77 (0.59-1.01),p=0.06**
Prior hospitalization (1 yr)	**0.77 (0.57-1.04),p=0.06**
Smoking status (non-smokr)	**0.82 (0.61-1.10),p=0.2**
Hamophilus Influenzae infection	**0.74 (0.54-1.02),p=0.06**
Moraxella catarrhalis infection	**0.44 (0.23-0.83),p=0.01**
Enterobactericeae infection	**0.62 (0.37-1.05),p=0.08**
Pseudomonas aeruginosa infection	**0.58 (0.38-0.88),p=0.01**
Oral long term antibiotics	**0.99 (0.73-1.34),p=0.9**
Inhaled long term antibiotics	**0.77 (0.41-1.42),p=0.4**
COPD	**0.60 (0.40-0.89),p=0.01**
Asthma	**0.49 (0.31-0.75),p=0.001**
FEV1 % predicted	**1.01 (1.00-1.02),p=0.001**
Reiff score	**0.96 (0.92-0.99),p=0.04**
Connective tissue disease	**0.49 (0.30-0.78),p=0.003**

Table E3. Logistic regression model with endpoint of "Switch 3" from frequent (2 or more per year) to infrequent (<2 per year) exacerbations

Model	0 exacerbations	1 exacerbation	2 exacerbations	3 or more exacerbations
Unadjusted	1.00 (reference)	1.73 (1.47-2.02)	3.14 (2.70-3.66)	5.97 (5.27-6.78)
Primary model	1.00 (reference)	1.81 (1.54-2.12)	3.07 (2.62-3.60)	5.18 (4.51-5.95)
BSI only	1.00 (reference)	1.77 (1.51-2.08)	3.14 (2.68-3.68)	4.82 (4.17-5.56)
All aetiologies included	1.00 (reference)	1.80 (1.53-2.12)	2.99 (2.55-3.51)	5.04 (4.38-5.80)
Co-morbidities included	1.00 (reference)	1.81 (1.54-2.13)	3.07 (2.61-3.60)	5.19 (4.52-5.97)
Adjusted for oral and inhaled antibiotics at baseline	1.00 (reference)	1.72 (1.52-2.11)	3.01 (2.57-3.53)	4.95 (4.30-5.70)
Excluding severe exacerbations	1.00 (reference)	1.74 (1.49-2.04)	3.03 (2.60-3.54)	4.65 (4.03-5.36)
Mild subgroup using the BSI	1.00 (reference)	1.92 (1.92-2.48)	3.49 (2.71-4.50)	5.29 (3.91-7.16)
Moderate subgroup using the BSI	1.00 (reference)	1.56 (1.22-2.00)	2.81 (2.22-3.55)	4.52 (3.66-5.59)
Severe subgroup using the BSI	1.00 (reference)	1.60 (1.09-2.33)	2.70 (1.90-3.82)	4.20 (3.18-5.55)

Table E4. Sensitivity analysis adjusting for additional confounders and in severity subgroups.

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Figure E1 shows the individual domains of the SGRQ score and how these relate to the past history of exacerbations

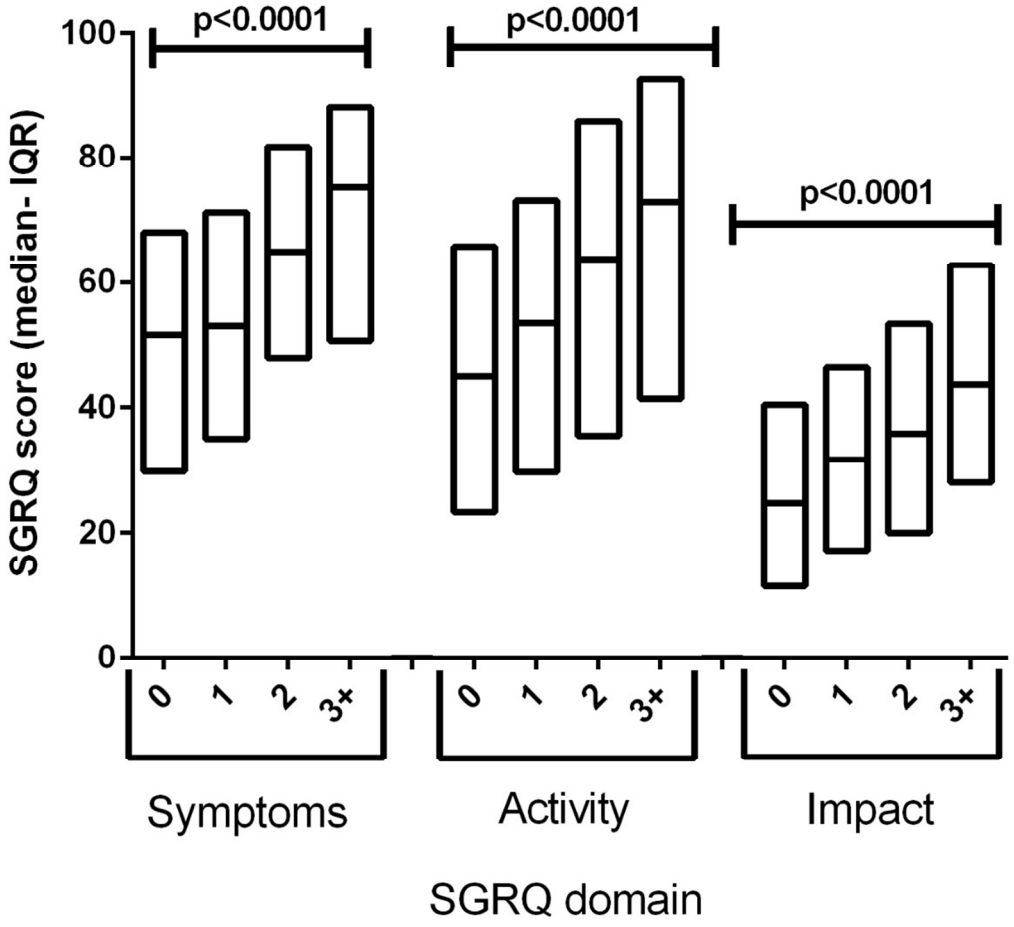

Figure E1. SGRQ domains and history of exacerbations at baseline. Data are presented as median with interquartile range (IQR).

Aetiology	**Incident rate ratio's (95% CI) and p-values.**
Idiopathic	0.70 (0.63-0.78),p<0.0001
Post-infective	0.84 (0.75-0.95),p=0.005
ABPA	0.88 (0.72-1.09),p=0.2
Asthma	1.24 (1.05-1.46),p=0.01
COPD	1.88 (1.66-2.14),p<0.0001
Connective tissue diseases	1.48 (1.24-1.77),p<0.0001
Inflammatory bowel disease	0.75 (0.53-1.05),p=0.1
Immunodeficiency	1.24 (0.97-1.55),p=0.09
NTM	0.70 (0.49-0.99),p=0.046
Post-TB bronchiectasis	0.66 (0,52-0.84),p=0.001
PCD	1.74 (1.11-2.71),p=0.02
Alpha-1 antitrypsin deficiency	1.10 (0.56-2.16),p=0.8

Table E5. Univariate association between aetiology and frequency of exacerbations.