Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC)

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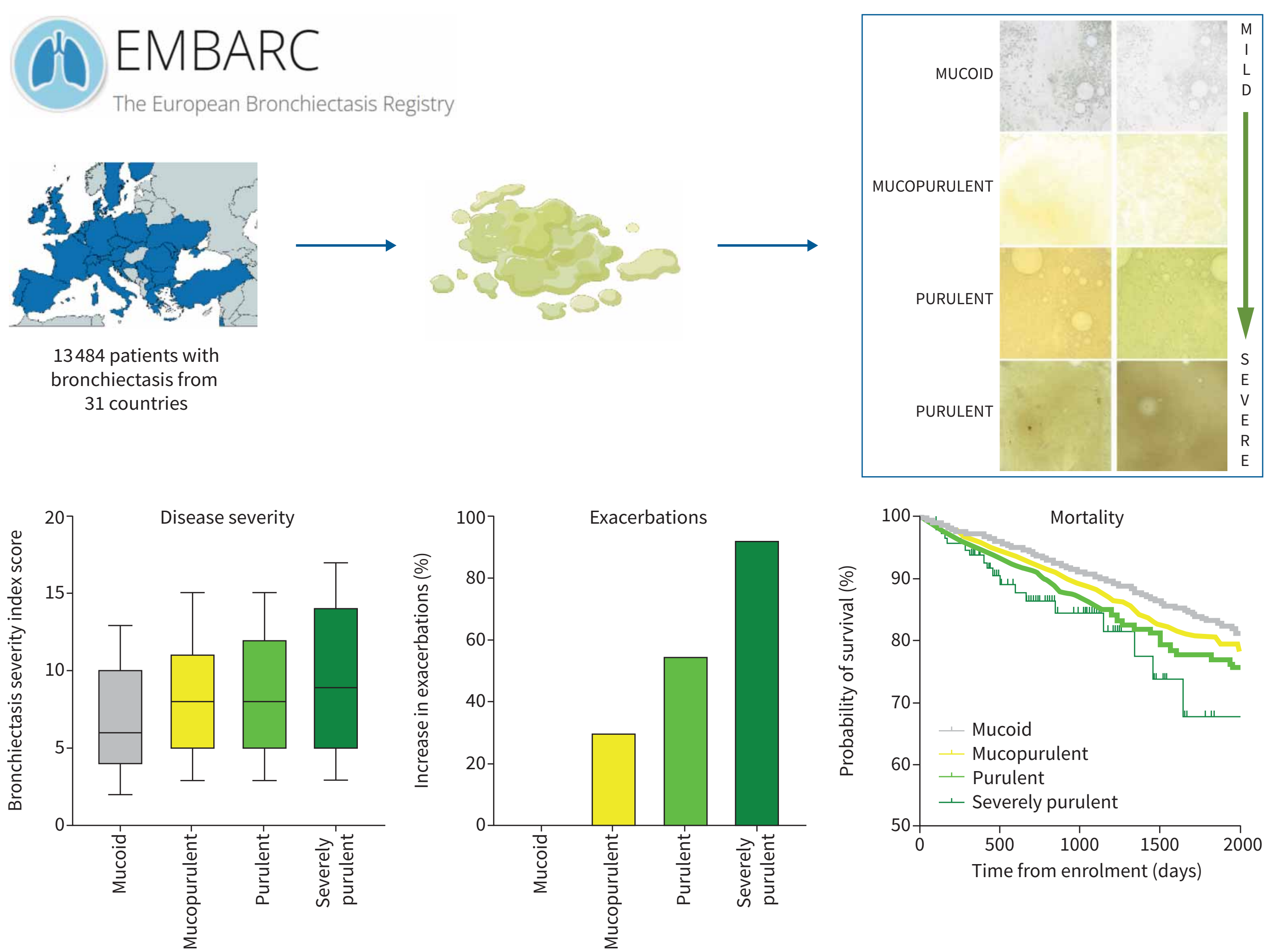

GRAPHICAL ABSTRACT We enrolled 13 484 patients with bronchiectasis from 31 countries. Assessment of sputum colour at baseline was used to investigate the relationship with disease severity and outcomes. We show a strong relationship between sputum colour and exacerbations and hospitalisation for severe exacerbations. Increasing sputum purulence is a marker of disease outcome in bronchiectasis.

https://doi.org/10.1183/13993003.01554-2023

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Shareable abstract (@ERSpublications)
Sputum colour is a simple non-invasive marker of airway inflammation that identifies patients with bronchiectasis at higher risk of exacerbation, hospitalisation and mortality https://bit.ly/3HczGxO

Cite this article as: Aliberti S, Ringshausen FC, Dhar R, *et al*. Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). *Eur Respir J* 2024; 63: 2301554 [DOI: 10.1183/13993003.01554-2023].

This article has an editorial commentary: https://doi.org/10.1183/13993003.00152-2024

Received: 13 Sept 2023
Accepted: 2 Jan 2024

Abstract

Background A validated 4-point sputum colour chart can be used to objectively evaluate the levels of airway inflammation in bronchiectasis patients. In the European Bronchiectasis Registry (EMBARC), we tested whether sputum colour would be associated with disease severity and clinical outcomes.

Methods We used a prospective, observational registry of adults with bronchiectasis conducted in 31 countries. Patients who did not produce spontaneous sputum were excluded from the analysis. The Murray sputum colour chart was used at baseline and at follow-up visits. Key outcomes were frequency of exacerbations, hospitalisations for severe exacerbations and mortality during up to 5-year follow-up.

Results 13 484 patients were included in the analysis. More purulent sputum was associated with lower forced expiratory volume in 1 s (FEV_1), worse quality of life, greater bacterial infection and a higher bronchiectasis severity index. Sputum colour was strongly associated with the risk of future exacerbations during follow-up. Compared to patients with mucoid sputum (reference group), patients with mucopurulent sputum experienced significantly more exacerbations (incident rate ratio (IRR) 1.29, 95% CI 1.22–1.38; p<0.0001), while the rates were even higher for patients with purulent (IRR 1.55, 95% CI 1.44–1.67; p<0.0001) and severely purulent sputum (IRR 1.91, 95% CI 1.52–2.39; p<0.0001). Hospitalisations for severe exacerbations were also associated with increasing sputum colour with rate ratios, compared to patients with mucoid sputum, of 1.41 (95% CI 1.29–1.56; p<0.0001), 1.98 (95% CI 1.77–2.21; p<0.0001) and 3.05 (95% CI 2.25–4.14; p<0.0001) for mucopurulent, purulent and severely purulent sputum, respectively. Mortality was significantly increased with increasing sputum purulence, hazard ratio 1.12 (95% CI 1.01–1.24; p=0.027), for each increment in sputum purulence.

Conclusion Sputum colour is a simple marker of disease severity and future risk of exacerbations, severe exacerbations and mortality in patients with bronchiectasis.

Introduction

Bronchiectasis is a chronic inflammatory disease [1, 2]. Although it is recognised that bronchiectasis is composed of multiple phenotypes and endotypes, inflammation has classically been regarded as neutrophilic and patients with higher levels of neutrophilic inflammation have been shown to have worse clinical outcomes [3–5].

Although there are composite severity and prognostic assessment tools for bronchiectasis, there are currently no direct measures of inflammation [5–7]. Direct measurement of neutrophilic inflammation is currently only possible in the research sphere and is difficult to implement in clinical practice [4, 8].

Therefore the most accessible measure of neutrophilic inflammation in bronchiectasis is thought to be the assessment of sputum colour [9, 10]. The green colour associated with sputum purulence in chronic inflammatory lung diseases is thought to result from accumulation of myeloperoxidase (MPO) released from granulocytes. The increase of sputum purulence therefore provides a non-invasive assessment of the extent of neutrophilic inflammation [11, 12].

Since colour perception is subjective, the assessment of sputum colour in clinical practice requires to be standardised. In 2009, Murray *et al*. [9] developed a sputum colour chart for bronchiectasis patients based on sputum photographs which classifies samples into four groups. This study demonstrated an association between sputum colour and the presence of bacterial infection [9]. Goeminne *et al*. [10] extended these findings, demonstrating that neutrophilic inflammation and protease activity in sputum was directly related to sputum colour using this method. Existing data have, however, been derived from single-centre studies with small sample sizes. Prior studies did not investigate a possible correlation between the sputum colour chart and patients' clinical outcomes. Prior studies are therefore insufficient to establish that sputum colour assessment could be used for patient phenotyping in routine clinical practice.

To investigate the value of sputum colour assessment in identifying positive airway bacterial cultures, disease severity and risk of future exacerbations, we incorporated baseline and annual assessment of sputum colour using a standardised sputum colour chart into the data collected as part of the European

Bronchiectasis Registry (EMBARC) [13]. We tested whether a single assessment of sputum colour could identify the risk of airway infection, severity of disease and risk of future exacerbations.

Methods

EMBARC is a prospective observational study of patients with computed tomography (CT)-confirmed bronchiectasis conducted across more than 30 countries worldwide [13, 14]. The registry includes European Union (EU) countries, non-EU European countries and several non-European countries (Israel, India, Kyrgyzstan and Pakistan) [14, 15]. The study is approved by the ethical committee in the host country (UK) and by institutional review boards or ethics committees in all countries and regions in which the study is conducted. A detailed protocol of the study and baseline patient characteristics have been previously published [13, 14].

Data collection

Patient enrolment commenced in January 2015 and recruitment is open-ended and ongoing. Patients enrolled up to April 2022 were included for the purposes of this analysis. Patient data were collected annually using a standardised case report form. Comprehensive clinical data incorporating demographics, comorbidities, medications, aetiological testing, microbiology, radiology, lung function and disease history were recorded. Spirometry was performed according to American Thoracic Society/European Respiratory Society standards [16]. Aetiology was recorded by the investigators and verified using data on results of aetiological testing. Microbiology data from clinically indicated sputum samples sent during clinical stability and exacerbation were collected and patients classified according to whether they had specific bacteria isolated in any sample in the 12 months prior to the baseline visit. Radiological severity was evaluated in the patient's most recent CT scan using the modified Reiff score as previously described [17]. Disease severity was evaluated using the bronchiectasis severity index (BSI) with a sensitivity analysis performed using the FACED tool [7]. Exacerbations were defined as use of antibiotics for acute respiratory symptoms and were recorded from a combination of patient history, hospital and prescription records [18]. Severe exacerbations were defined as exacerbations requiring hospitalisation. Symptoms were evaluated using the Quality of Life Questionnaire-Bronchiectasis (QOL-B) version 3.1 using validated translations [19, 20].

Sputum colour assessment

Baseline and annual follow-up visits were performed during clinical stability. Sputum samples from these visits were used for sputum colour assessment by either the physician or patient using the chart developed by Murray *et al*. [9] (figure 1). The study user guide asked the physicians to make an assessment of sputum colour on a fresh sputum sample wherever possible. If this was not possible, patients were asked to report the most common/typical colour of their sputum during stable state (away from both exacerbations and antibiotic courses). The reliability of this scoring system for assessment by both patients and physicians was established in the original validation study with an intraclass correlation coefficient of 0.83. The online data collection tool provided the sputum colour chart (figure 1) to allow scoring by investigators at sites. A numerical scoring system from 1 (mucoid) to 4 (severely purulent) was used as originally described.

For the purposes of this analysis any patient unable to produce sputum at baseline was excluded, but data from this subgroup are shown for comparison.

Long-term clinical outcomes

Data are collected for up to 5 years on an annual basis for calculation of clinical outcomes. Since patient enrolment began in 2015, patients have up to 5 years of follow-up at the time of writing, although the dataset includes patients enrolled through to 2021/2022 who have not yet had a follow-up visit. Statistical analysis of relevant end-points takes account of the duration of follow-up. Relevant clinical outcomes were survival, exacerbation frequency and risk of hospitalisation due to severe exacerbations.

Statistical analysis

Summary data are presented as median (interquartile range (IQR)). Comparisons of more than two groups were performed by the Kruskal–Wallis test. Exacerbation frequency and frequency of severe exacerbations requiring hospital admission over time were studied using a negative binomial model with time in study as an offset. Survival analysis was performed using Cox proportional hazards regression [14]. The proportional hazards assumption was assessed with log–log plots.

We observed a strong relationship between sputum colour and *Pseudomonas aeruginosa* infection and so present adjusted analyses of these models with *P. aeruginosa* infection included as a covariate. In addition, an analysis was performed adjusting the negative binomial model for prior exacerbations to determine if sputum

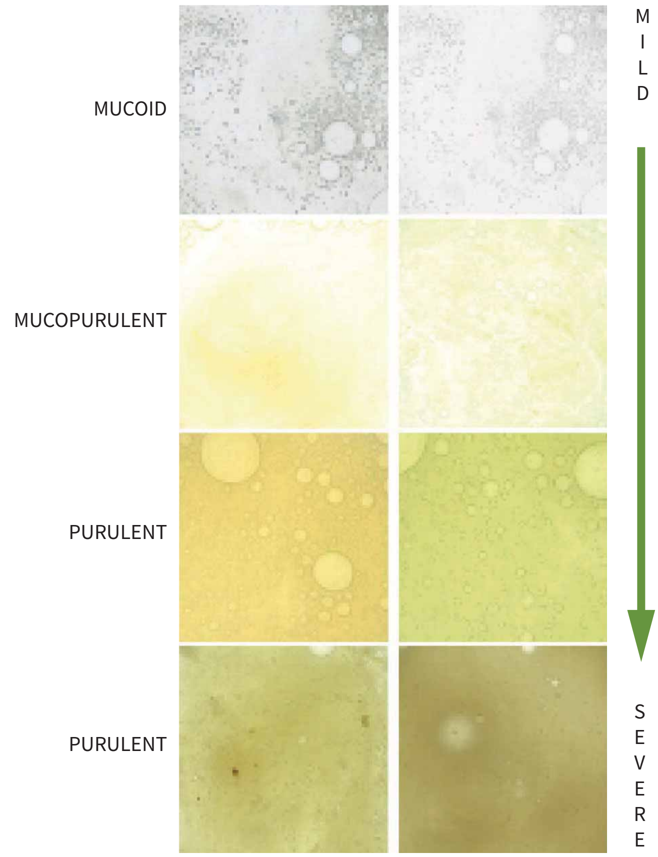

FIGURE 1 The Murray sputum colour chart. Reproduced from [9] with permission.

colour was associated with exacerbation risk after adjusting for prior exacerbation history. All analyses utilised SPSS version 27 (IBM, Armonk, NY, USA) or Prism version 9 (GraphPad, Boston, MA, USA).

Results

19 324 patients were enrolled from 31 countries. 13 484 patients reported daily sputum expectoration, had a sputum colour grade using the Murray chart performed and were, therefore, included in the analysis. This is shown in figure 2; a detailed description of the cohort is reported elsewhere [14]. Table 1 shows the characteristics of the patients at enrolment according to sputum colour at baseline (visit 1) including the characteristics of patients excluded as they did not regularly produce sputum.

Patients with more purulent sputum have a higher daily sputum volume, a higher modified Medical Research Council dyspnoea score, and a greater likelihood of prescription of macrolides, long-term antibiotics and inhaled antibiotics. No strong relationship was found between sputum colour and age, smoking status, or the presence of asthma or COPD as underlying conditions (table 1). Supplementary table S1 shows the relationships with aetiology, where the most common aetiologies did not have a greater odds of having purulent sputum compared to idiopathic bronchiectasis. Patients with primary ciliary dyskinesia or immunodeficiency had significantly higher odds of purulent sputum (supplementary table S1).

Relationship between sputum colour and severity of disease

Figure 3 shows the association between sputum colour and cross-sectional markers of bronchiectasis disease severity using the BSI. The BSI increased with increasing sputum colour from median (IQR) 6 (4–10) in patients with mucoid sputum to 8 (5–11) in patients with mucopurulent sputum, 8 (5–12) in patients with purulent sputum and 9 (5–14) in patients with severely purulent sputum. Similar results were seen with the FACED score (supplementary figure S1). Examining severity groups, we included 12 229 patients with complete data for analysis. Severe bronchiectasis classified by the BSI was observed in 1531 (31.5%) patients with mucoid sputum, 1992 (41.0%) patients with mucopurulent sputum, 1091 (46.3%) patients

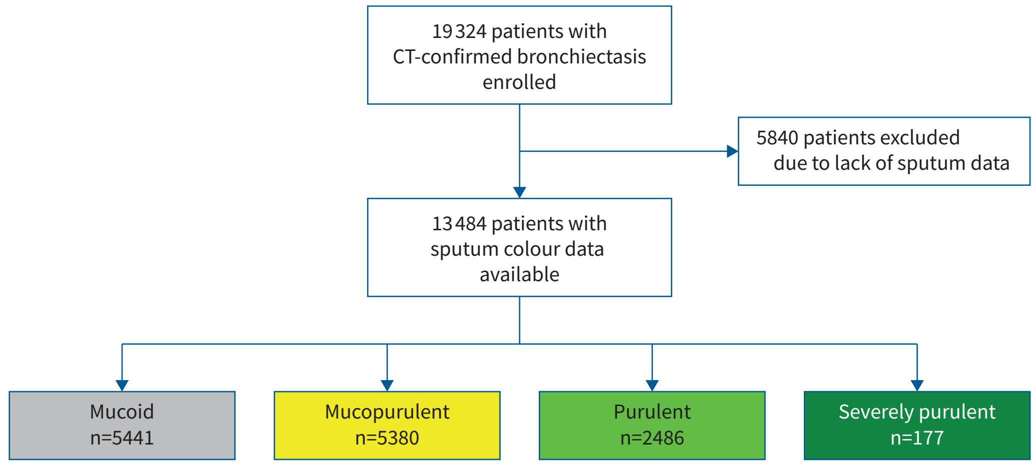

FIGURE 2 Flow of patients through the study. CT: computed tomography.

with purulent sputum and 81 (51.3%) patients with severely purulent sputum (supplementary table S2). Differences in disease severity were all statistically significant (p<0.0001).

Forced expiratory volume in 1 s (FEV_1) percentage predicted was significantly lower in patients with more purulent sputum, with median values of 75.7%, 70.2%, 65.9% and 70.4% (p<0.0001) for mucoid, mucopurulent, purulent and severely purulent sputum, respectively (figure 3b). There were less obvious differences in radiological severity, with a median Reiff radiological severity score of 3 in patients with mucoid sputum and 4 in patients with mucopurulent to severely purulent sputum (p<0.0001) (figure 3c). The median (IQR) values of the QOL-B respiratory symptoms score were also strongly related to sputum colour, with patients with mucoid sputum having the best quality of life (66.7 (48.1–77.8)), followed by patients with mucopurulent sputum (55.6 (40.7–70.4)), purulent sputum (48.1 (33.3–63.0)) and severely purulent sputum (44.4 (25.9–64.9)) (p<0.0001) (figure 3d). Patients with purulent sputum also reported a larger daily sputum volume. Median (IQR) sputum volume was 10 (5–20) mL in patients with mucoid sputum and 15 (10–30), 20 (10–50) and 30 (10–66) mL in patients with mucopurulent, purulent and severely purulent sputum, respectively.

Relationship between sputum colour and sputum culture

12 229 patients with complete data were included in this analysis. There was an increase in the percentage of patients with sputum samples positive for bacteria as sputum purulence increased. Figure 4 shows the frequency of the most common bacteria isolated in sputum at baseline. The frequency of additional pathogens is shown in supplementary table S3. 1279 (26.3%) patients with mucoid sputum had a positive sputum for bacteria compared to 1863 (38.4%) with mucopurulent sputum, 1026 (43.5%) with purulent sputum and 84 (53.2%) with severely purulent sputum (p<0.0001). Approximately a third of patients with purulent sputum and severely purulent sputum had isolation of *P. aeruginosa*. The EMBARC registry includes a data field for chronic *P. aeruginosa* infection and this also showed a clear increase with increasing sputum purulence, from 797 (16.4%) in patients with mucoid sputum to 57 (36.1%) in patients with severely purulent sputum (p<0.0001).

Significant differences were observed across sputum purulence categories for *P. aeruginosa* (p<0.0001), *Haemophilus influenzae* (p<0.0001), *Moraxella catarrhalis* (p=0.01), Enterobacteriaceae (p<0.0001), *Staphylococcus aureus* (p<0.0001) and *Streptococcus pneumoniae* (p<0.0001). *Aspergillus* species were observed in 110 (2.3%) patients with mucoid sputum, 129 (2.7%) with mucopurulent sputum, 98 (4.2%) with purulent sputum and five (3.2%) with severely purulent sputum (p<0.0001).

Relationship between sputum colour and exacerbations in the previous year

In the 12 months prior to the baseline visit there were 33 724 exacerbations in 12 229 patients with a valid sputum colour measurement and 6298 severe exacerbations requiring hospitalisation. The median (IQR) exacerbation frequency was 2 (1–4) per year.

Compared to patients with mucoid sputum (reference group), exacerbation rates were increased with increasing sputum purulence, with rate ratios of 1.23 (95% CI 1.17–1.29), 1.38 (95% CI 1.31–1.47) and

TABLE 1 Patient characteristics according to baseline sputum colour[#]

	Grade 1 (mucoid)	Grade 2 (mucopurulent)	Grade 3 (purulent)	Grade 4 (severely purulent)	Non-sputum-producing patients
Patients	5441 (28.2)	5380 (27.8)	2486 (12.9)	177 (0.9)	5840 (30.2)
Demographics					
Age (years)	66 (55–74)	66 (55–74)	66 (56–73)	67 (57–75)	65 (53–73)
Female	3039 (55.9)	3123 (58.0)	1425 (57.3)	97 (54.8)	3712 (63.6)
BMI ($kg \cdot m^{-2}$)	24.6 (21.4–28.4)	24.4 (21.4–28.2)	24.2 (21.0–28.0)	23.7 (20.7–28.5)	24.4 (21.4–28.3)
Never-smoker	3038 (55.8)	3000 (55.8)	1367 (55.0)	89 (50.3)	3325 (56.9)
Ex-smoker	2031 (37.3)	2052 (38.1)	989 (39.8)	77 (43.5)	2156 (36.9)
Current smoker	372 (6.8)	328 (6.1)	130 (5.2)	11 (6.2)	359 (6.1)
Comorbidity					
Cardiovascular disorders	1685 (31.0)	1729 (32.1)	773 (31.1)	64 (36.2)	1672 (28.6)
Stroke	169 (3.1)	185 (3.4)	73 (2.9)	11 (6.2)	171 (2.9)
Diabetes	593 (10.9)	573 (10.7)	261 (10.5)	22 (12.4)	595 (10.2)
Liver disease	36 (0.7)	24 (0.4)	16 (0.6)	3 (1.7)	43 (0.7)
Chronic renal failure	181 (3.3)	184 (3.4)	102 (4.1)	9 (5.1)	218 (3.7)
COPD	1428 (26.2)	1450 (27.0)	712 (28.6)	49 (27.7)	1243 (21.3)
Asthma	1665 (30.6)	1666 (31.0)	732 (29.4)	46 (26.0)	1655 (28.3)
Osteoporosis	649 (11.9)	713 (13.3)	337 (13.6)	30 (16.9)	634 (10.9)
Depression	654 (12.0)	763 (14.2)	392 (15.8)	48 (27.1)	617 (10.6)
Solid tumour	515 (9.5)	530 (9.9)	270 (10.9)	19 (10.7)	547 (9.4)
Aetiology					
Idiopathic	1934 (35.5)	1964 (36.5)	876 (35.2)	66 (37.3)	2117 (36.3)
Post-infective	1173 (21.6)	1193 (22.2)	571 (23.0)	29 (16.4)	1200 (20.5)
Tuberculosis	538 (9.9)	396 (7.4)	149 (6.0)	10 (5.6)	533 (9.1)
Immunodeficiency	177 (3.3)	201 (3.7)	110 (4.4)	4 (2.3)	214 (3.7)
ABPA	179 (3.3)	177 (3.3)	79 (3.2)	7 (4.0)	226 (3.9)
Rheumatoid arthritis	112 (2.1)	159 (3.0)	63 (2.5)	8 (4.5)	148 (2.5)
Others	1328 (24.4)	1290 (24.0)	638 (25.7)	53 (29.9)	1402 (24.0)
Clinical status					
Sputum volume ($mL \cdot day^{-1}$)	10 (5–20)	15 (10–30)	20 (10–50)	30 (10–66)	0 (0–0)
mMRC dyspnoea score[¶]					
0	1425 (26.2)	1069 (19.9)	416 (16.7)	34 (19.2)	1864 (31.9)
1	1776 (32.6)	1727 (32.1)	759 (30.5)	42 (23.7)	1945 (33.3)
2	1188 (21.8)	1343 (25.0)	595 (23.9)	34 (19.2)	1172 (20.1)
3	710 (13.0)	859 (16.0)	457 (18.4)	37 (20.9)	560 (9.6)
4	279 (5.1)	338 (6.3)	219 (8.8)	30 (16.9)	207 (3.5)
Treatment					
Long-term macrolide treatment	768 (14.1)	995 (18.5)	547 (22.0)	36 (20.3)	733 (12.6)
Other long-term oral antibiotic treatment	228 (4.2)	292 (5.4)	202 (8.1)	13 (7.3)	196 (3.4)
Inhaled antibiotic treatment	313 (5.8)	523 (9.7)	357 (14.4)	31 (17.5)	167 (2.9)
Inhaled corticosteroids	2900 (53.3)	3008 (55.9)	1376 (55.3)	86 (48.6)	2739 (46.9)

Data are presented as n (%) or median (interquartile range). BMI: body mass index; ABPA: allergic bronchopulmonary aspergillosis; mMRC modified Medical Research Council. [#]: all variables measured at baseline visit. [¶]: totals for mMRC dyspnoea score do not add up to 100% due to missing data.

1.51 (95% CI 1.26–1.81) for mucopurulent, purulent and severely purulent sputum, respectively. For severe exacerbations the relationship was even stronger, with rate ratios of 1.28 (95% CI 1.19–1.37), 1.63 (95% CI 1.50–1.77) and 1.68 (95% CI 1.31–2.15) for patients with mucopurulent, purulent and severely purulent sputum, respectively. This is shown in figure 5a.

At baseline, across the whole cohort, 2579 (21.1%) patients had no exacerbations, 2242 (18.3%) had 1 exacerbation per year, 2138 (17.5%) patients had 2 exacerbations per year and 5270 (43.1%) had ⩾3 exacerbations per year. The proportion of patients with ⩾3 exacerbations per year markedly increased with increasing sputum purulence from 36.0% (n=1751) in patients with mucoid sputum to 45.8% (n=2225) in patients with mucopurulent sputum, 51.0% (n=1202) in patients with purulent sputum and 58.2% (n=92) in patients with severely purulent sputum (p<0.0001).

Sputum colour and long-term clinical outcomes

Long-term clinical outcomes were evaluated over a cumulative total of 29 830 years of patient follow-up (range 0–5 years per patient).

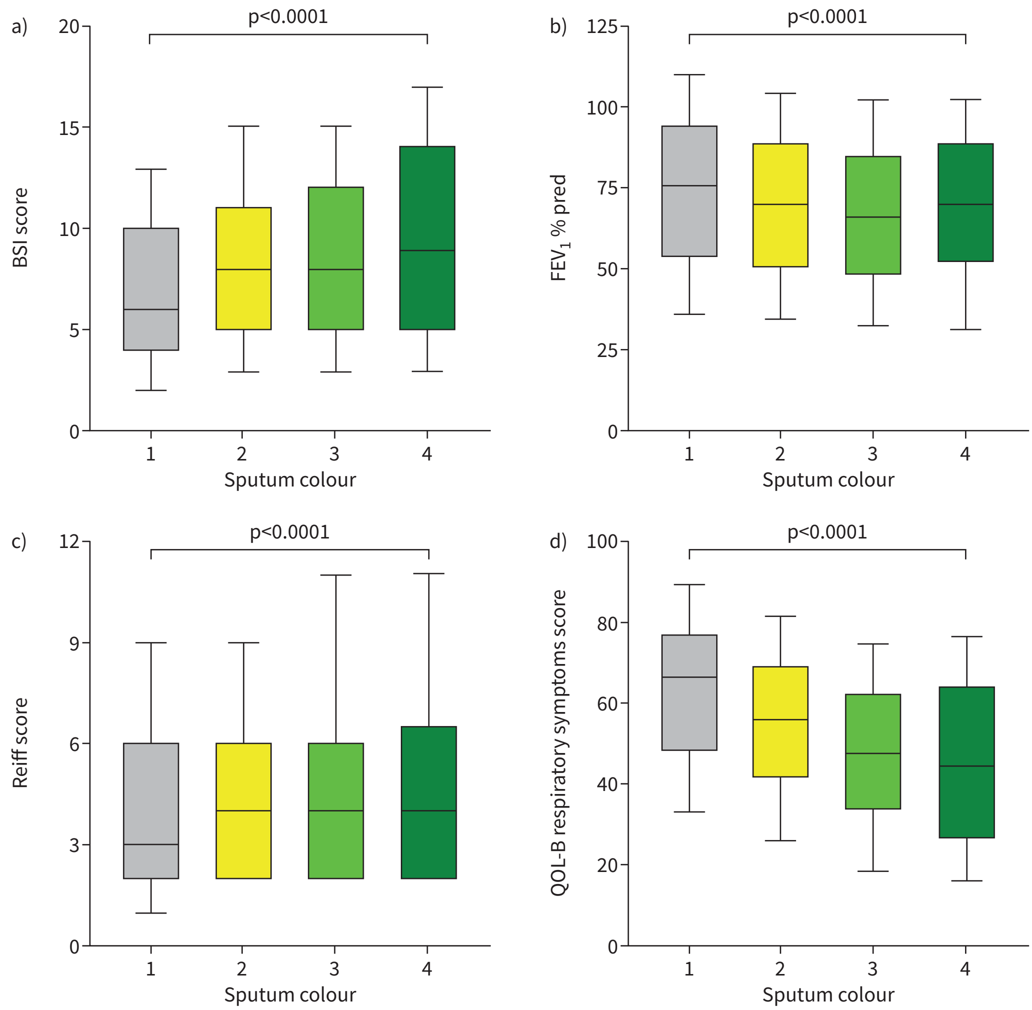

FIGURE 3 Disease severity and its relationship with sputum colour: a) bronchiectasis severity index (BSI) score, b) forced expiratory volume in 1 s (FEV_1) percentage predicted, c) Reiff score and d) Quality of Life Questionnaire-Bronchiectasis (QOL-B) respiratory symptoms score. Sputum colour is graded as 1=mucoid, 2=mucopurulent, 3=purulent and 4=severely purulent. Box plots show median and interquartile range with whiskers at the 10–90th percentiles.

Sputum colour was strongly associated with the risk of future exacerbations. Compared to patients with mucoid sputum (reference group), patients with mucopurulent sputum experienced significantly more exacerbations (incident rate ratio (IRR) 1.29, 95% CI 1.22–1.38; p<0.0001), while the rates were even higher for patients with purulent sputum (IRR 1.55, 95% CI 1.44–1.67; p<0.0001) and severely purulent sputum (IRR 1.91, 95% CI 1.52–2.39; p<0.0001) (figure 5b). The relationship between sputum colour and exacerbations was evaluated in subgroups of patients based on disease severity using the BSI, *P. aeruginosa* infection status, baseline FEV_1 and prior exacerbation history, showing clear associations between increasing sputum purulence and increasing exacerbations independent on these other criteria (supplementary table S4).

For hospitalisation, increasing sputum colour was also associated with worse clinical outcomes with rate ratios (compared to patients with mucoid sputum) of 1.41 (95% CI 1.29–1.56; p<0.0001), 1.98 (95% CI 1.77–2.21; p<0.0001) and 3.05 (95% CI 2.25–4.14; p<0.0001) for patients with mucopurulent, purulent and severely purulent sputum, respectively (figure 5b).

We performed a number of sensitivity analyses. Sputum colour remained strongly associated with future exacerbations even after adjustment for prior exacerbations. Compared to the reference group (mucoid sputum) the adjusted rate ratios for exacerbation frequency were 1.21 (95% CI 1.14–1.29), 1.31 (95% CI

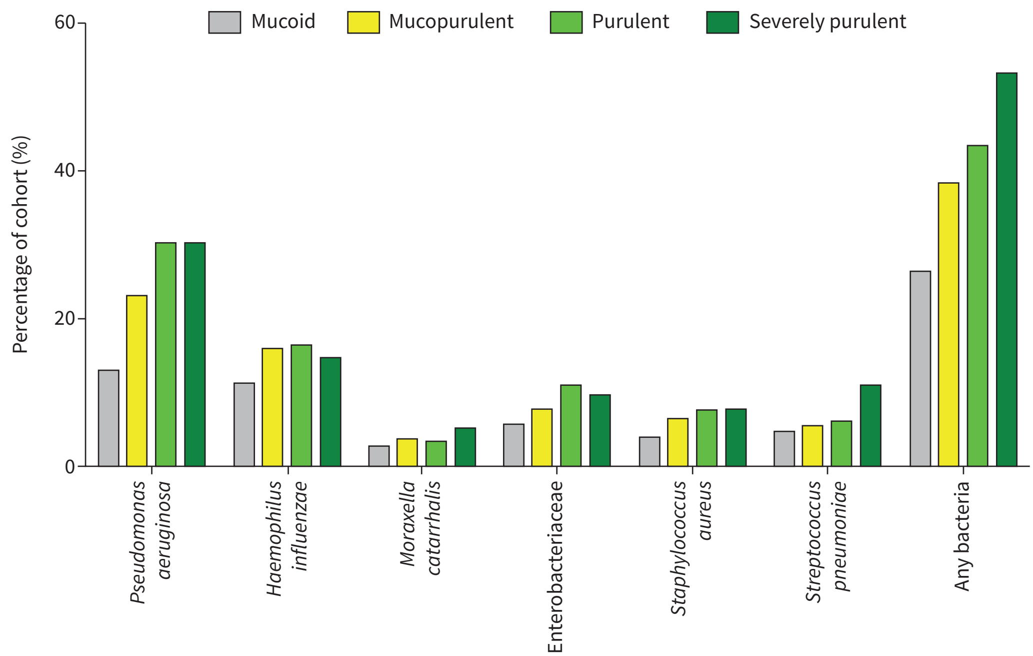

FIGURE 4 Percentage of all patients with positive sputum cultures for selected respiratory pathogens or any bacteria at baseline.

1.21–1.42) and 1.68 (95% CI 1.33–2.11) for mucopurulent, purulent and severely purulent sputum, respectively. Sputum colour was also clearly associated with future exacerbation risk in patients using long-term macrolide or inhaled antibiotics at baseline (supplementary table S4). Since *P. aeruginosa* is a strong predictor of future hospitalisation and sputum purulence was strongly associated with *P. aeruginosa* infection, an analysis was conducted adjusting for *P. aeruginosa* in the negative binomial model. This shows rate ratios of 1.20 (95% CI 1.10–1.30), 1.53 (95% CI 1.39–1.68) and 1.74 (95% CI 1.33–2.29) for mucopurulent, purulent and severely purulent sputum, respectively. In an additional analysis, sputum colour was also associated with a shorter time to the first severe exacerbation following baseline (supplementary table S5).

There were 582 deaths during follow-up. Mortality was significantly increased with increasing sputum purulence (hazard ratio 1.12, 95% CI 1.01–1.24; p=0.027), indicating a 12% increased risk of death for each 1-point increase in sputum purulence. For patients with purulent sputum at baseline compared to patients with mucoid sputum the corresponding hazard ratios were 1.02 (95% CI 0.85–1.23) for mucopurulent sputum, 1.26 (95% CI 1.01–1.57; p=0.039) for purulent sputum and 1.60 (95% CI 0.90–2.86; p=0.11) for severely purulent sputum. The Kaplan–Meier survival curve is shown in figure 5c.

Visit-to-visit repeatability of sputum colour

7632 patients were included in the analysis of repeated sputum colour assessment over time, on the basis of having at least two assessments 12 months apart. Sputum colour showed a degree of stability from visit to visit in the stable state within individuals. We analysed the levels of agreement between baseline and year 1 sputum colour assessments within individuals. Of those with mucoid sputum at baseline, 89.3% of patients had mucoid sputum at their next follow-up visit. The corresponding figures were 88.2% for mucopurulent sputum at both visits, 78.6% for purulent sputum and 79.7% for severely purulent sputum. The Sankey diagram is shown in supplementary figure S2.

Discussion

Bronchiectasis is a chronic inflammatory disorder [10]. Airway inflammation in bronchiectasis is a key component of the vicious vortex of disease and is believed to play a key role in disease progression [21]. Sputum colour represents a potentially clinically useful, simple and non-invasive marker of airway inflammation [9, 10]. Our study shows that sputum colour as determined by a validated sputum colour chart is strongly associated with disease severity measured by the BSI, lower FEV_1, worse quality of life and greater radiological severity. Patients with purulent sputum are more likely to have positive sputum

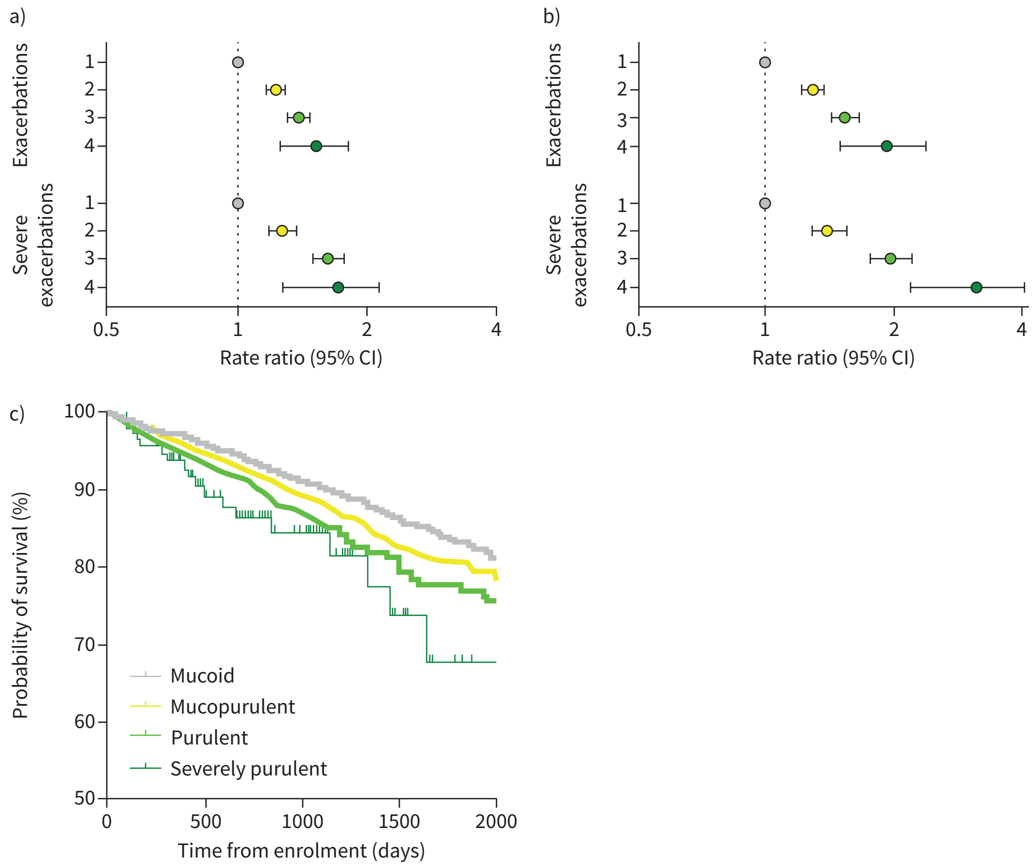

FIGURE 5 a, b) Forest plots of the frequency of exacerbations and severe exacerbations across the four sputum colour groups (1=mucoid sputum (reference group), 2=mucopurulent sputum, 3=purulent sputum and 4=severely purulent sputum): a) in the previous year and b) during follow-up. c) Kaplan–Meier survival curve.

cultures for multiple bacteria and particularly *P. aeruginosa*, an organism that is known to be associated with greater risk of hospitalisation, mortality and FEV_1 decline [22]. Patients with greater sputum purulence experience more frequent exacerbations and a higher risk of severe exacerbations during follow-up. Importantly, this increased risk is seen even when patients are matched for severity of disease or prior exacerbation history. When we examined subgroups of patients defined by their prior exacerbation history (0, 1, 2 or ⩾3 exacerbations in the previous year), patients with more purulent sputum still experienced more exacerbations. Similar results were observed for severe exacerbation risk. Finally, survival was also lower for patients with increased sputum purulence. Taken together our results suggest that sputum purulence can be used as a relatively simple risk stratification tool in clinical practice to identify patients at greater risk of severe disease, positive sputum cultures and future exacerbations.

Our study is observational and it cannot prove that any of these relationships are causal. It is unlikely that the presence of purulent sputum, in itself, is causing any of these poor outcomes. It is most likely that purulent sputum is a reflection of underlying lung inflammation and that this inflammation directly contributes to lung injury, while the resulting exacerbations contribute to disease progression [12, 23]. Sputum colour therefore represents a potentially clinically useful and non-invasive marker of airway inflammation.

Previous work has shown that sputum purulence reflects the presence of neutrophilic inflammation [11, 12]. MPO, an enzyme contained within the azurophilic granules of neutrophils, is responsible for the green colour in purulent sputum. MPO itself generates the toxic metabolite hypochlorite which contributes to oxidative stress and inflammation in the airways [24]. MPO is a key component of neutrophil extracellular traps (NETs) which are believed to be the dominant mechanism of neutrophilic inflammation in the bronchiectasis airway and which have also been linked with disease severity and future risk of exacerbations [12, 25]. NETs release multiple granule and cytoplasmic proteins associated with DNA and histones which together amplify lung inflammation and protease-mediated degradation of lung tissue [12]. Neutrophil elastase, which has been strongly linked to disease progression in bronchiectasis, is released from the same granules as MPO and increases with increasing sputum purulence [3, 8]. The relationships between neutrophilic inflammation and exacerbations and survival seen in this study mirror those seen with laboratory assays of neutrophilic inflammation such as elastase and NETs, and confirm, in a much larger cohort, that neutrophilic inflammation is a key prognostic marker in bronchiectasis.

Recognition that bronchiectasis is an inflammatory disease has led to the development of novel anti-inflammatory treatment strategies including dipeptidyl peptidase-1 inhibition, a treatment that reduces neutrophilic inflammation by blocking neutrophil serine protease activation in the bone marrow [26]. This was shown to prolong the time to first exacerbation in a phase 2 trial [26]. A phase 3 trial is ongoing. In that trial, sputum purulence was used as an inclusion criteria in an effort to enrol patients with significant neutrophilic inflammation and a higher risk of exacerbations. Our data would support that sputum colour can be used as such a marker for trials and may in future be useful to identify patients for anti-inflammatory treatment.

There is a strong relationship between sputum purulence and airway infection, which is the major driver of neutrophil recruitment to the airway, and this was clearly shown in our data where positive sputum cultures greatly increased as sputum purulence increased. Given this relationship, sputum purulence may be a promising biomarker to identify patients that would respond to antibiotic treatment. In an analysis of the AIR-BX trials of inhaled aztreonam, sputum purulence was significantly reduced during the on-cycles of treatment [27]. More importantly, patients with purulent sputum (identified on self-reported questionnaire) had a significant improvement in quality of life on treatment, while patients without sputum purulence did not [27]. Conversely, patients without sputum purulence had a significantly increased frequency of exacerbations and adverse events with inhaled antibiotic treatment [27]. This suggests that antibiotic treatment is most likely to be effective in patients with higher levels of neutrophilic inflammation and bacterial load, a concept now supported by several studies in bronchiectasis [28–31].

Sputum colour identifies patients at increased risk but it is clear from our data that patients with mucoid sputum can still experience exacerbations, including severe exacerbations, and may have severe bronchiectasis. It is increasingly recognised that bronchiectasis is a heterogeneous disease with multiple endotypes [21]. Endotyping of this subgroup of patients without clear neutrophilic inflammation is important. Recent data suggest around 20% of bronchiectasis patients without asthma have eosinophilic inflammation, which would not be expected to produce sputum purulence and may therefore explain some of the burden of disease in the subgroup [28, 32–34]. Other treatable traits are likely to be identified in this subgroup through ongoing research into inflammatory endotypes [35].

Our study has unique strengths, including the very large sample size, systematic collection of data and inclusion of a large number of countries. Limitations of this analysis include the real-life nature of the data collection. Although the sputum colour chart was provided to all sites through the online data collection system, monitoring how this was used across so many sites is not feasible and variation in practice is inevitable. Sputum characteristics may vary by time of day, or depending on airway clearance techniques or other interventions [36]. Sputum cultures were not mandatory and so the analysis of sputum bacteria is limited by whether or not patients had sputum cultures performed for clinical reasons. The frequency of bacteria in our study therefore likely underestimates the true prevalence of pathogens. Other sputum parameters such as plugging on CT and rheology parameters such as viscosity may provide additional information but were not evaluated in this study.

In summary we show that sputum colour is a clinically useful non-invasive inflammatory biomarker that is associated with disease severity and identifies patients at risk of future exacerbations.

Conflict of interest: S. Aliberti reports grants or contracts from Insmed Incorporated, Chiesi, Fisher & Paykel and GlaxoSmithKline, royalties or licences from McGraw Hill, consulting fees from Insmed Incorporated, Insmed Italy, Insmed Ireland Ltd, Zambon SpA, AstraZeneca UK Ltd, AstraZeneca Pharmaceutical LP, CSL Behring GmbH, Grifols, Fondazione Internazionale Menarini, Moderna, Chiesi, MCD Italia Srl, Brahms, PhysioAssist SAS and GlaxoSmithKline SpA, payment or honoraria for lectures, presentations, manuscript writing or educational events from GlaxoSmithKline SpA, Thermofisher Scientific, Insmed Italy, Insmed Ireland, Zambon and Fondazione Internazionale Menarini, and participation on a data safety monitoring board or advisory board for Insmed Incorporated, Insmed Italy, AstraZeneca UK Ltd and MSD Italia Srl. F.C. Ringshausen reports grants or contracts from the German Center for Lung Research (DZL), German Center for Infection Research (DZIF), IMI (EU/EFPIA),

iABC Consortium (including Alaxia, Basilea, Novartis and Polyphor), Mukoviszidose Institute, Novartis, Insmed Germany, Grifols, Bayer and InfectoPharm, consulting fees from Parion, Grifols, Zambon, Insmed and Helmholtz-Zentrum für Infektionsforschung, payment or honoraria for lectures, presentations, manuscript writing or educational events from I!DE Werbeagentur GmbH, Interkongress GmbH, AstraZeneca, Insmed, Grifols and Universitätsklinikum Frankfurt am Main, payment for expert testimony from Social Court Cologne, support for attending meetings and/or travel from the German Kartagener Syndrome and Primary Ciliary Dyskinesia (PCD) Patient Advocacy Group Mukoviszidose eV, participation on a data safety monitoring board or advisory board for Insmed, Grifols and Shionogi, and leadership or fiduciary roles as Coordinator of the ERN-LUNG Bronchiectasis Core Network, Chair of the German Bronchiectasis Registry PROGNOSIS, Member of the SteerCo of the European Bronchiectasis Registry EMBARC, Member of the SteerCo of the European Nontuberculous Mycobacterial Pulmonary Disease Registry EMBARC-NTM, Co-Speaker of the Medical Advisory Board of the German Kartagener Syndrome and PCD Patient Advocacy Group, Speaker of the Respiratory Infections and TB group of the German Respiratory Society (DGP), Speaker of the Cystic Fibrosis group of German Respiratory Society (DGP), PI of the German Center for Lung Research (DZL), Member of the Protocol Review Committee of the PCD-CTN, and Member of the Physician Association of the German Cystic Fibrosis Patient Advocacy Group; F.C. Ringshausen has other financial or non-financial interests with AstraZeneca, Boehringer Ingelheim, Celtaxsys, Corbus, Insmed, Novartis, Parion, University of Dundee, Vertex and Zambon. R. Dhar reports payment or honoraria for lectures, presentations, manuscript writing or educational events from LUPIN, CIPLA and Glenmark. C.S. Haworth reports payment or honoraria for lectures, presentations, manuscript writing or educational events from 30 Technology, CSL Behring, Chisi, Insmed, Janssen, LifeArc, Meiji, Mylan, Pneumagen, Shionogi, Vertex and Zambon. M.R. Loebinger reports consulting fees from Armata, 30T, AstraZeneca, Parion, Insmed, Chiesi, Zambon, Electromed, Recode, AN2 and Boehringer Ingelheim, payment or honoraria for lectures, presentations, manuscript writing or educational events from Insmed, and a leadership or fiduciary role as ERS Infection Group Chair. K. Dimakou reports payment or honoraria for lectures, presentations, manuscript writing or educational events from Novartis, Boehringer Ingelheim, GlaxoSmithKline, Norma Hellas, Chiesi, AstraZeneca and Zambon, support for attending meetings and/or travel from Novartis, Boehringer Ingelheim, GlaxoSmithKline, Norma Hellas, Chiesi, AstraZeneca and Menarini, and participation on a data safety monitoring board or advisory board for Novartis, GlaxoSmithKline and Chiesi. M.L. Crichton reports consulting fees from Boxer Capital LLC. A. De Soyza reports grants or contracts from AstraZeneca, Pfizer, GlaxoSmithKline and Novartis, consulting fees from AstraZeneca, Insmed, GlaxoSmithKline, Boehringer, 30T and Bayer, and payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, Pfizer, GlaxoSmithKline and Novartis. M. Vendrell reports grants or contracts from Chiesi, payment or honoraria for lectures, presentations, manuscript writing or educational events from Insmed and Publi Creation, support for attending meetings and/or travel from Zambon, Chiesi, Novartis, Behring and Gebro, participation on a data safety monitoring board or advisory board for Insmed, and receipt of equipment, materials, drugs, medical writing, gifts or other services from Insmed and Novartis. P-R. Burgel reports grants or contracts from GlaxoSmithKline and Vertex, consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, Insmed, MSD, Vertex, Viatris and Zambon, and support for attending meetings and/or travel from AstraZeneca and Chiesi. S. Skrgat reports honoraria for educational events, invited lectures and presentations supported by Sanofi, AstraZeneca, Medis, Berlin-Chemie and Chiesi, and participation on a data safety monitoring board or advisory board for AstraZeneca. A. de Roux reports consulting fees from Adboard Insmed, payment or honoraria for lectures, presentations, manuscript writing or educational events from Insmed, AstraZeneca, GlaxoSmithKline, Berlin-Chemie and Boehringer Ingelheim, support for attending meetings and/or travel from AstraZeneca, and advisory board participation with Insmed. A. Bossios reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Chiesi, and leadership or fiduciary roles as Secretary of ERS Assembly 5 (Airway diseases, asthma, COPD and chronic cough), Vice-chair of the Nordic Severe Asthma Network (NSAN)-NORDSTAR and on the Steering Committee of ERS CRC Severe Asthma (SHARP). P. 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Amorim reports payment or honoraria for lectures, presentations, manuscript writing or educational events from Zambon Group, and support for attending meetings and or/travel from Zambon Group, Boehringer Ingelheim and Novartis Farma. E. Van Braeckel reports grants or contracts from Insmed, Boehringer Ingelheim and Zambon. A. Shoemark reports consulting fees from Spirovant and Translate Bio, payment or honoraria for lectures, presentations, manuscript writing or educational events from Translate Bio, Ethris and Insmed, leadership or fiduciary roles in ERS CRCs (EMBARC, BEATPCD, AMR). M. Shteinberg reports consulting fees from GlaxoSmithKline, Boehringer Ingelheim, Kamada and Zambon, payment or honoraria for lectures, presentations, manuscript writing or educational events from Insmed,

Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Teva, Novartis, Kamada and Sanofi, support for attending meetings and/or travel from Novartis, Actelion, Boehringer Ingelheim, GlaxoSmithKline and Rafa, participation on a data safety monitoring board or advisory board for Bonus Therapeutics, Israel, leadership or fiduciary roles in EMBARC, Israel Pulmonology Society, and Israel Society for TB and Mycobacterial Diseases, receipt of equipment, materials, drugs, medical writing, gifts or other services from Trudell Medical International, and is Associate Editor of the *American Journal of Respiratory and Critical Care Medicine*. P.C. Goeminne reports payment or honoraria for lectures, presentations, manuscript writing or educational events from Insmed, GlaxoSmithKline and Chiesi, support for attending meetings and/or travel from Chiesi, and participation on a data safety monitoring board or advisory board for Boehringer, GlaxoSmithKline and Pfizer. T. Welte reports grants from the German Ministry of Research and Education (BMBF), consulting fees and lecture honoraria from AstraZeneca, Chiesi, Grifols, GlaxoSmithKline, Insmed, MSD, Novartis, Pfizer and Sanofi, leadership roles for the German Center for Lung Research (DZL) – Board of Directors, Novartis Foundation – Board of Directors, Chairman of the Board of Trustees for CAPNETZ Foundation, German Lung Foundation, German Sepsis Foundation, and is Past President of the ERS, German Society of Pneumology and German Sepsis Society. F. Blasi reports grants or contracts from AstraZeneca, Chiesi, GlaxoSmithKline and Insmed, consulting fees from Menarini, GlaxoSmithKline and Om Pharma, and payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, Chiesi, GlaxoSmithKline, Guidotti, Grifols, Insmed, Menarini, Novartis, OM Pharma, Pfizer, Sanofi, Viatris, Vertex and Zambon. E. Polverino reports grants or contracts from Grifols, consulting fees from Insmed, Bayer, Chiesi and Zambon, payment or honoraria for lectures, presentations, manuscript writing or educational events from Bayer, Chiesi, Grifols, GlaxoSmithKline, Insmed, Menarini and Zambon, and support for attending meetings and/or travel from Insmed, Pfizer and Moderna. J.D. Chalmers reports grants or contracts from AstraZeneca, Boehringer Ingelheim, Genentech, Gilead Sciences, GlaxoSmithKline, Grifols, Insmed, LifeArc and Novartis, and consulting fees from AstraZeneca, Chiesi, GlaxoSmithKline, Insmed, Grifols, Novartis, Boehringer Ingelheim, Pfizer, Janssen, Antabio and Zambon, and is Chief Editor of the *European Respiratory Journal*. The remaining authors have no potential conflicts of interest to disclose.

Support statement: This work was supported by the Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations companies under the European Commission-funded Horizon 2020 Framework Program and by Inhaled Antibiotic for Bronchiectasis and Cystic Fibrosis (grant 115721). EMBARC3 is funded by the European Respiratory Society through the EMBARC3 Clinical Research Collaboration. EMBARC3 is supported by project partners Armata, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Grifols, Insmed, Janssen, Lifearc and Zambon. J.D. Chalmers is supported by the GlaxoSmithKline/Asthma and Lung UK Chair of Respiratory Research. Funding information for this article has been deposited with the Crossref Funder Registry.

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