Predictors of massive haemoptysis after a first episode of mild-to-moderate haemoptysis in patients with cystic fibrosis.

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To the Editor:

The main cause of death of cystic fibrosis (CF) patients is respiratory disease due to secondary infections, haemoptysis, pneumothorax, and respiratory failure [1]. In a study of 129 French CF patients who died between 2007 and 2010 without receiving lung transplantation, 8.5% of deaths were due to haemoptysis [2]. Factors associated with an increased risk of haemoptysis in CF patients include older age, advanced lung disease (forced expiratory volume in 1 s (FEV_1) <70% predicted), airway colonisation by *Pseudomonas aeruginosa* [3], CF-related diabetes, portal hypertension, and liver cirrhosis [4]. To our knowledge, there have been no studies of the risk factors for the development of massive haemoptysis (MH) in CF patients who have previously experienced an episode of mild-to-moderate haemoptysis.

We retrospectively analysed data from all adult CF patients seen at the Lille CF Centre between 2008 and 2018 who had a history of at least one mild-to-moderate haemoptysis episode. All individuals gave written informed consent. Approval for the use of these data was provided by the Institutional Review Board of the French Learned Society for Pulmonology (CEPRO 2015-004). The patients were followed up from the time of mild-to-moderate haemoptysis (or from the first episode for those with >1 mild-to-moderate haemoptysis) until they experienced an MH event ("with MH" group) or until the end of follow-up ("without MH" group). Clinicopathological data were collected from medical records. Mild-to-moderate haemoptysis was defined as an episode resulting in 5–240 mL externalised blood. MH was defined as: 1) >240 mL externalised blood in 24 h, 2) >100 mL externalised blood over ⩾2 days [5], or 3) any externalised blood loss causing abnormal gas exchange/airway obstruction or haemodynamic instability [6]. Haemoptysis was treated according to the CF Foundation Consensus Conference Report [7], and patients with MH received concomitant therapy with intravenous (*i.v.*) antibiotics. Long-term drug therapy was defined as medication prescribed for >3 months. The cumulative incidence of MH was estimated using the Kaplan–Meier method by censoring patients lost to follow-up at the last available visit. The median follow-up time from first mild-to-moderate haemoptysis episode was calculated using the reverse Kaplan–Meier method. Associations between baseline characteristics and MH occurrence were analysed using univariable Cox proportional hazard regression models. The log–linearity assumption for continuous factors was checked by examining Martingale residual plots and using restricted cubic spline functions, and the proportional hazard assumption for each potential predictive factor was checked by examining the Schoenfeld residuals. Mild-to-moderate haemoptysis recurrence rates were calculated as the number of episodes per 100 person-months from the time of first mild-to-moderate haemoptysis episode to MH or, for patients without MH, to the last annual review. All statistical tests were performed at a two-tailed α level of 0.05.

A total of 85 CF patients experienced at least one episode of mild-to-moderate haemoptysis; of these, 23 were excluded for missing data (no follow-up after the episode of mild-to-moderate haemoptysis, transfer to

another unit, lung transplant, or otherwise not indicated) and the remaining 62 patients were included in the study. 15 (24.2%) of the 62 patients experienced MH during follow-up (median 73 months, interquartile range 37–132 months). Baseline characteristics obtained at the most recent annual review after mild-to-moderate haemoptysis (when the patients were stable) are shown in table 1. Univariate analysis indicated that allergic bronchopulmonary aspergillosis (ABPA), CF-related diabetes and treatment with triazoles were significantly associated with subsequent MH. Positive and negative association trends were detected between MH and severe malnutrition and body mass index (BMI), respectively, but they did not reach the level of significance. Interestingly, MH occurred in four of the five patients with liver cirrhosis and three of the four patients with thrombocytopenia (including two patients with liver cirrhosis) at 24–55 months and 24–103 months, respectively, after the first mild-to-moderate haemoptysis episode. However, the small number of patients with these conditions precluded statistical analysis of possible associations. Mild-to-moderate haemoptysis recurrence was more common among patients who did *versus* those who did not experience MH (mild-to-moderate haemoptysis rate 16.5 and 5.9 per 100 patient-months, respectively). MH was not significantly associated with any other baseline characteristic. Among the 15 patients who had MH, 11 (73.3%) were treated with terlipressin, 11 (73.3%) underwent bronchial artery embolisation (BAE), and nine (60%) received both treatments. Despite appropriate management, three (20%) of the 15 patients died from the MH event. There were no deaths among patients who did not experience MH.

THOMPSON *et al.* [3] reported that haemoptysis is more common in CF individuals with advanced lung disease (FEV_1 <70% predicted). Although we did not detect an association between FEV_1 and MH in our

TABLE 1 Univariate analysis of the association between baseline characteristics and massive haemoptysis (MH) occurrence in patients with cystic fibrosis

Characteristic	Patients without MH	Patients with MH	Hazard ratio (95% CI)	p-value
Subjects n	47	15		
Age years median (IQR)	22.0 (20.5–30.0)	19.0 (16.0–22.0)	1.01 (0.96–1.04)	0.93
Male	28 (59.6%)	6 (40.0%)	0.97 (0.33–2.85)	0.96
Homozygous ΔF508/ΔF508	18 (38.3%)	6 (40.0%)	1.04 (0.36–3.01)	0.94
Heterozygous ΔF508	18 (38.3%)	5 (33.3%)	1.62 (0.53–4.97)	0.40
Body mass index $kg \cdot m^{-2}$	20.1±2.2	18.5 ±2.75	0.79 (0.61– 1.02)	0.075
Severe malnutrition	8 (17.0%)	7 (46.7%)	2.69 (0.94–7.68)	0.064
FEV_1 % predicted	57.3±24.6	71.9 ±19.8	1.01 (0.98–1.03)	0.55
FVC % predicted	74.8±20.6	79.7 ±19.6	0.99 (0.96–1.03)	0.69
EPI	41 (87.2%)	12 (80.0%)	1.12 (0.25–5.04)	0.88
ABPA	12 (25.5%)	9 (60.0%)	6.03 (1.97–18.45)	**0.002**
Liver cirrhosis	1 (2.1%)	4 (25.0%)		ND
Osteoporosis	4 (8.5%)	1 (6.7%)		ND
Diabetes	1(2.1%)	5 (33.3%)	5.66 (1.84–17.42)	**0.002**
Thrombocytopenia	1 (2.1%)	3 (20.0%)		ND
Bacteriology				
Pseudomonas aeruginosa	34 (72.3%)	8 (53.3%)	0.46 (0.15–1.38)	0.17
MSSA	22 (46.8%)	8 (53.3%)	1.53 (0.53–4.42)	0.43
MRSA	9 (19.1%)	1 (6.7%)	1.17 (0.14–9.41)	0.88
Aspergillus	10 (21.3%)	2 (13.3%)	0.88 (0.20–3.96)	0.87
Stenotrophomonas	3 (6.4%)	1 (6.7%)		ND
Achromobacter	2 (4.3%)	1 (6.7%)		ND
Long-term treatment				
RhDNase	37 (78.7%)	13 (86.7%)	2.19 (0.28–16.85)	0.45
Inhaled tobramycin	9 (19.1%)	3 (20.0%)	1.26 (0.34–4.71)	0.73
Inhaled colimycin	12 (25.5%)	4 (25.0%)	1.05 (0.33–3.36)	0.93
Triazole	9 (19.1%)	6 (40.0%)	4.13 (1.41–12.07)	**0.009**
>4 *i.v.* antibiotic courses	11 (23.9%)	3 (20.0%)	1.08 (0.30–3.90)	0.90
Exacerbations per year n (range)	2 (0–3)	1 (0–3)	1.07 (0.85–1.35)	0.57

Data are presented as mean±SD or n (%), unless otherwise stated. Hazard ratios were calculated using Cox regression models. Multivariate analysis was not performed due to the limited sample size and MH event number. Bold font indicates statistically significant p-values. Genotype was known for 61 out of the 62 patients. IQR: interquartile range; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; EPI: exocrine pancreatic insufficiency; ABPA: allergic bronchopulmonary aspergillosis; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus;* RhDNase: recombinant human deoxyribonuclease (dornase alfa); ND: not done.

cohort, consistent with a report by BARBEN et al. [4], our study was limited by its retrospective design, the small number of patients, the high proportion of excluded patients, and the difficulty in precisely quantifying haemoptysis-associated blood loss. Current practices recommend cessation of recombinant human deoxyribonuclease (RhDNase) aerosols during haemoptysis due to their irritant effects. In our study, RhDNase use was not significantly associated with MH, supporting the findings of a Cochrane review in which haemoptysis was not a significant adverse effect of RhDNase [8].

ABPA infection is a frequent complication in adult patients with CF and is generally associated with poorer clinical condition. In the present study, ABPA was significantly associated with MH, consistent with previous studies by others [9] and by us [10]. The latter study was a retrospective, case–control, multicentre study in France of 21 adult patients with CF and showed that ABPA and recurrent mild haemoptysis are associated with MH [10]. However, triazole treatment was prescribed for 15 of the 21 patients with ABPA in the present study and was also significantly associated with MH, suggesting that it did not prevent MH. In our cohort, two of the five patients who had been treated with BAE for the first mild-to-moderate haemoptysis went on to experience MH; although this suggests that BAE was not effective in preventing MH, it is possible that it could have delayed the time to MH. ANTONELLI et al. [11] reported a significant reduction in mild-to-moderate haemoptysis recurrence in eight CF patients during the 3 years after BAE, although the severity of recurrent mild-to-moderate haemoptysis was not specified. We did not determine whether MH was associated with haemoptysis treatment with tranexamic acid here because many CF patients with scant haemoptysis self-medicate with this agent without reporting it to their clinician. It would be of interest to assess the potential protective effect of tranexamic acid on MH occurrence [12].

The prognostic value of nutritional status for MH occurrence in CF patients remains unclear. In the present study, we detected a trend towards an association between low BMI and MH occurrence. EFRATI et al. [13] found no significant association between BMI and haemoptysis in 40 CF patients, whereas VIDAL et al. [14] reported that low BMI was significantly associated with increased risk of death or lung transplantation in their study of 57 CF patients with haemoptysis. We note that the small sample size in our study may have precluded detection of some associations [14].

Nevertheless, our findings do concur with other observations by EFRATI et al. [13], including that diseases such as CF-related diabetes, cirrhosis and portal hypertension are more common among patients with a history of haemoptysis than those without (57.5% versus 5.2%) [14]. Here, we detected a significant association between CF-related diabetes and MH occurrence, and four of the five patients with liver cirrhosis experienced MH.

In conclusion, ABPA, metabolic disorders and recurrent mild-to-moderate haemoptysis may predict MH occurrence in CF patients with at least one mild-to-moderate haemoptysis episode. Whether optimal management of these events would help to reduce the risk of MH remains to be determined.

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