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Original Article

A multinational report on SARS-CoV-2 infection outcomes in people with CF and *Aspergillus* infection or ABPA

Jacob D. Bradbury [a,b,1], Emily Chesshyre [a,c,1], Annalisa Orenti [d], Andreas Jung [e], Adilia Warris [a,f,*], European Cystic Fibrosis COVID project group

[a] MRC Centre for Medical Mycology, University of Exeter, EX4 4QD, UK
[b] Department of Pharmacology, University of Oxford, OX1 3QT, UK
[c] Department of Paediatrics, Royal Devon University Healthcare NHS Foundation Trust, EX2 5DW, UK
[d] Department of Clinical Sciences and Community Health, Laboratory of Medical Statistics, Biometry and Epidemiology G.A. Maccacaro, University of Milan, Milan 20122, Italy
[e] Paediatric Pulmonology, University Children's Hospital Zurich, Ramistrasse 102, Stadtkreis 7 8006, Zurich, Switzerland
[f] Department of Paediatric Infectious Diseases, Great Ormond Street Hospital, London, WC1N 3JH, UK

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ABSTRACT

Background: *Aspergillus* infection is known to be associated with worse respiratory outcomes in people with CF (pwCF) and is a well-recognised complication of severe SARS-CoV-2 infection. The aim of this observational cross-sectional study was to examine the association of pre-existing *Aspergillus* infection and/or allergic bronchopulmonary aspergillosis (ABPA) in pwCF and severity of COVID-19.

Methods: Data on SARS-CoV-2 infections in pwCF from January 2020 to June 2021 were collected by the European Cystic Fibrosis Society Patient Registry. The primary outcome was COVID-19 severity measured by hospitalisation comparing those with *Aspergillus* infection and/or ABPA in the 12 months preceding COVID-19 and those without.

Results: In total, 1095 pwCF were diagnosed with SARS-CoV-2 and information on pre-existing *Aspergillus*/ABPA status was available from 807. PwCF and SARS-CoV-2 in the *Aspergillus*/ABPA group (n = 153), in comparison to the non-*Aspergillus*/ABPA group (n = 654), were more likely to be hospitalised (adjusted OR 1.79 (1.19 to 2.85); p = 0.005) and their disease course was more likely to be complicated by sepsis (adjusted OR 7.78 (1.78 to 49.43); p = 0.008). The association with hospital admission was no longer significant after excluding patients with ABPA. Secondary analysis comparing pwCF who received antifungal treatment (n = 18), versus those who did not (n = 474) during COVID-19, showed a higher rate of hospitalisation ($p < 0.001$); intensive care unit admission ($p < 0.001$), and requirement for invasive ventilation ($p < 0.001$) in the antifungal treated group.

Conclusion: We show that pre-existing *Aspergillus*/ABPA is associated with increased rates of hospitalisation and sepsis during COVID-19 in pwCF.

1. Introduction

Patients with severe pneumonia caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) are susceptible to fungal co-infections, in particular pulmonary aspergillosis [1]. Coronavirus disease 2019 (COVID-19) associated pulmonary aspergillosis (CAPA) has been shown to significantly impact the outcomes of patients admitted to the ICU, with increased length of hospital stay and increased mortality rates compared to those without *Aspergillus* co-infection [1–3]. A qualitative review including 21 observational studies with mortality data (n = 3777), showed a mortality rate of 46.2 % in CAPA patients (n = 539) versus 31.3 % in the non-CAPA group ($n = 3238$) ($p < 0.001$) [1]. Over 600 cases of proven or probable CAPA have been reported in patients with COVID-19, reflecting an incidence rate of 10.9 % [1]. Only scarce data is available on the impact of antifungal therapy on survival in CAPA patients, but no significant difference was found in survival in those specifically treated for CAPA and those who were not [1,2,4].

People with CF (pwCF) were assumed to be highly vulnerable to SARS-CoV-2 from early on in the COVID-19 pandemic, and therefore most countries advised 'shielding' to minimise the risk for infection.

* Corresponding author at: MRC Centre for Medical Mycology at the University of Exeter, GP-building Rm 318, Stocker Road, Exeter, EX4 4QD, United Kingdom.
[1] Shared first authors

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Previous studies using data from the European Cystic Fibrosis Society Patient Registry (ECFSPR) have shown that SARS-CoV-2 infection has worse outcomes in pwCF compared to the general population of the same age in terms of increased morbidity and hospitalisation [5,6].

Infection and disease caused by *Aspergillus* spp. is a common complication in pwCF and is observed in up to 60 % of adult patients [7]. Allergic responses to *Aspergillus* spp., presenting as allergic bronchopulmonary aspergillosis (ABPA), have shown to worsen long-term outcomes [8–10]. The impact of non-allergic *Aspergillus* infection on lung function is less clear, but some recent studies have shown that *Aspergillus* infection in pwCF is associated with lung function decline and structural lung damage [11–13].

It is likely that pwCF who are already colonised with *Aspergillus* will be more susceptible to CAPA during SARS-CoV-2 infection and may therefore experience worse COVID-19 outcomes. We used prospectively collected data from the ECFSPR during the COVID-19 pandemic to determine the relationship between pre-existing *Aspergillus* infection and/or ABPA and COVID-19 outcomes in pwCF.

2. Methods

2.1. Study design and study population

This cohort study was conducted using anonymised data on pwCF, who had SARS-CoV-2 infection (positive PCR test) between 1st January 2020 and 30th June 2021, from the countries who participated in the European Cystic Fibrosis Society Patient Registry (ECFSPR) COVID-19 data collection (see Supplemental file). Anonymised patient data was provided from 2 time points: data on clinical characteristics and outcomes after SARS-CoV-2 infection; and data from these patients' annual review in the year preceding SARS-CoV-2 infection, with information on demographics and CF disease characteristics. The ECFSPR (www.ecfs.eu/ecfspr) is a patient registry which collects demographic and clinical data from consenting pwCF in Europe and neighbouring countries and is subject to local ethical approval and data governance [14]. PwCF who contribute data do so with informed consent and the retrieval of data for research is to be approved by each country separately [15].

The primary outcome of this study was hospitalisation for COVID-19 and the secondary outcomes were mortality, Intensive Care Unit (ICU) admission, oxygen and ventilation requirement, and COVID-19 related complications. Variables were defined where possible according to ECFSPR standards (www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions). Specifically, *Aspergillus* infection was defined as a positive microbiology sample at least once as reported in the previous annual review data. A diagnosis of ABPA was up to the treating physician providing the data.

The total number of patients were grouped based on the presence or absence of *Aspergillus* infection and/or ABPA in the preceding 12 months of the SARS-CoV-2 infection. The aim was to assess whether pre-existing *Aspergillus* infection and/or ABPA in pwCF is associated with more severe COVID-19. As a secondary analysis, the cohort was grouped by whether the patients received antifungal treatment during COVID-19 to assess the association between antifungal treatment during COVID-19 and disease severity.

2.2. Statistical analysis

Characteristics of pwCF before SARS-CoV-2 infection, with and without *Aspergillus* infection or ABPA, were summarized using descriptive statistics. Missing data in the groups are specified in the tables if exceeding 10 %. Fisher exact test and Wilcoxon test were used to compare values of categorical and numerical variables respectively between the two groups. Logistic regression models were used to assess the association between pre-existing *Aspergillus* infection and/or ABPA and COVID-19 severity, complications, and outcomes. Where numbers allowed the models were adjusted for age at SARS-CoV-2 infection, value of FEV_1 percent of predicted ($ppFEV_1$), and lung transplant status. Two sensitivity analyses were undertaken to ensure the validity of the main study results. The first after exclusion of lung transplant recipients, and the second after exclusion of ABPA patients. All results are presented as adjusted odds ratios (OR) with 95 % confidence intervals (CI) and p-values. P-values were considered significant when < 0.05.

For the secondary analysis pwCF and SARS-CoV-2 were grouped according to who received antifungal treatment and descriptive analysis was completed with the same methods. A sensitivity analysis was undertaken on the non-transplant cohort. Logistic regression models were used to measure the association between antifungal treatment and COVID-19 severity, complications, and outcomes. Each model was fitted only if at least 5 events for each explanatory variable were available. Results are presented as odds ratios (OR) with 95 % confidence intervals (CI) and p-values. P-values were considered significant when < 0.05.

The statistical analyses were performed using SAS, version 9.4, (SAS Institute Inc., Cary, NC, USA) and R software, version 4.2.2.

3. Results

3.1. Study population

1095 pwCF were diagnosed with a SARS-CoV-2 infection between January 2020 and June 2021. Information was available on the presence or absence of *Aspergillus* infection or ABPA in the preceding 12 months for 807 pwCF (73.7 %), and these cases were included in the study. *Aspergillus* infection or ABPA was present in 153 (19.0 %) in the preceding 12 months before SARS-CoV-2 infection (table 1). Of these 11 had both ABPA and *Aspergillus* infection, 115 had *Aspergillus* infection only, and 27 had ABPA only. Overall, the median age of the study participants was 23 years (range 0.25 – 83 years) and 412 (51.1 %) were female. Eighty (11.6 %) participants had a $ppFEV_1$ below 40 %, 322 (46.7 %) between 40 % and 80 % and 287 (41.7 %) over 80 %. Seventy-six (9.4 %) had received a lung transplant, and 190 (26.3 %) were on CFTR modulator therapy.

3.2. Baseline (pre-COVID-19) characteristics of Aspergillus/ABPA group and non-Aspergillus/ABPA group

The *Aspergillus*/ABPA group was older than the non-*Aspergillus*/ABPA group, median age 25 versus 21.3 years, respectively ($p < 0.001$). The proportion of those with ppFEV1 < 40 was similar in the 2 groups (11.7 % versus 11.5 %). The *Aspergillus*/ABPA group had a higher proportion of patients with ppFEV1 40–80, 53.4 % versus 44.9 %, but overall lung function was not significantly different between the 2 groups. There was no significant difference in BMI z-scores ($p = 0.24$), genotype ($p = 0.14$), and the number of pwCF who had received a lung transplant ($p = 0.54$) between the two groups. The prevalence of CF-related diabetes (CFRD) was significantly higher in the Aspergillus/ABPA group (30.2 % versus 21.0 %, $p = 0.02$).

The *Aspergillus*/ABPA group had significantly higher rates of co-infection with *Pseudomonas aeruginosa* ($p = 0.008$) and non-tuberculous mycobacteria (NTM) ($p = 0.01$) (Table 1). Infection rates with *Staphylococcus aureus* and *Burkholderia cepacia* did not differ significantly between the two groups.

Oral azithromycin, inhaled antibiotics and inhaled steroids were significantly more commonly used during the 12 months prior to SARS-CoV-2 infection in the *Aspergillus*/ABPA group (table 1). Oral antibiotics, other than azithromycin, and oral steroids did not differ significantly between the two groups. Previous treatment with non-steroidal anti-inflammatory medication (NSAIDs) was significantly less common in the *Aspergillus*/ABPA group versus the non-*Aspergillus*/ABPA group ($p < 0.001$).

Table 1
Baseline (pre-COVID-19) characteristics of people with Cystic Fibrosis included in the study.

	Total N = 807 (%)	Non-*Aspergillus*/ ABPA group N = 654 (%)	*Aspergillus*/ ABPA group N = 153 (%)	p-value
Sex				
Male	395 (48.95)	314 (48.01)	81 (52.94)	0.282
Female	412 (51.05)	340 (51.99)	72 (47.06)	
Age class				
0–11 years	166 (20.57)	157 (24.01)	9 (5.88)	< 0.001
12–17 years	120 (14.87)	97 (14.83)	23 (15.03)	
18–29 years	264 (32.71)	199 (30.43)	65 (42.48)	
30–39 years	139 (17.22)	105 (16.06)	34 (22.22)	
40–49 years	88 (10.90)	70 (10.70)	18 (11.76)	
50+ years	30 (3.72)	26 (3.98)	4 (2.61)	
BMI z-score (median, range)				
Min	−30.5	−30.2	−4.5	0.242
Q1	−1.0	−1	−1	
Q2	−0.2	−0.2	−0.3	
Q3	0.5	0.5	0.3	
Max	2.5	2.5	2	
Underweight (z-score <−2)	57 (7.44)	45 (7.28)	12 (8.11)	0.728
Genotype				
ΔF508 Homozygous	271 (33.58)	209 (31.96)	62 (40.52)	0.138
ΔF508 Heterozygous	337 (41.76)	279 (42.66)	58 (37.91)	
Other	199 (24.66)	166 (25.38)	33 (21.57)	
ppFEV1				
> 80	287 (41.65)	235 (43.44)	52 (35.14)	0.159
40–80	322 (46.73)	243 (44.92)	79 (53.38)	
< 40	80 (11.61)	63 (11.65)	17 (11.49)	
CF related diabetes	170 (22.64)	129 (20.98)	41 (30.15)	0.024
CFTR Modulator Use	190 (26.32)	151 (26.03)	39 (27.47)	0.750
Lung Tx	76 (9.42)	64 (7.93)	12 (1.49)	0.540
Oxygen therapy pre-COVID				
Oxygen	24 (4.95)	23 (5.41)	1 (1.67)	0.346
NIPPV*	9/483 (1.86)	9/423 (2.13)	0/60 (0.00)	0.610
Antibiotic therapy pre-COVID				
Oral (excluding Azithromycin)*	134/548 (24.45)	109/461 (23.64)	25/87 (28.74)	0.341
Inhalation*	281/638 (44.04)	216/538 (40.15)	65/100 (65.00)	< 0.001
Azithromycin	285 (35.58)	208 (31.95)	77 (51.33)	< 0.001
Pre-COVID treatments				
Oral steroids*	45/408 (11.03)	40/359 (11.14)	5/49 (10.20)	1.000
Inhaled steroids	305 (38.85)	223 (34.90)	82 (56.16)	< 0.001
NSAID	402 (55.22)	354 (60.21)	48 (33.37)	< 0.001
Other immunosuppressive therapy*	30/411 (7.30)	29/361(8.03)	1/50 (2.00)	0.154
Pre-COVID infections				
S. aureus	493 (65.91)	388 (64.56)	105 (71.43)	0.121
*B. cepacia**	32/685 (4.67)	27 (4.73)	5/114 (4.39)	1.000
P. aeruginosa	355 (46.04)	272 (43.66)	83 (56.08)	0.008
NTM*	8/471 (1.70)	4/412 (0.97)	4/59 (6.78)	0.011

Categorical variables: Numbers (%). Continuous variables given in ranges: Numbers (%). BMI z scores interquartile ranges and minimum/maximum given. *If missing data is ≥ 10 % for specific variable, total number is specified. BMI; body mass index, $ppFEV_1$; percentage predicted Forced Expiratory Volume in 1 s, CFTR; cystic fibrosis transmembrane conductance regulator, Tx; transplantation; NIPPV; non-invasive positive pressure ventilation, NSAID: non-steroidal anti-inflammatory drug, NTM; non-tuberculous mycobacteria.

3.3. *Aspergillus* infection or ABPA and COVID-19 disease severity

i) COVID-19 Severity Outcomes

PwCF in the *Aspergillus*/ABPA group were significantly more likely to be hospitalised with COVID-19 compared to the non-*Aspergillus*/ABPA group (32.0 % versus 20.8 % (OR 1.79 (1.19–2.85); p = 0.005)). There were similar rates of ICU admissions, oxygen requirement, non-invasive ventilation and invasive ventilation. Covid-19 associated mortality was low and no significant difference was observed between the two groups (table 2).

ii) Treatments during SARS-CoV-2 infection There was significantly higher use of antifungals in the *Aspergillus*/ABPA group versus non-*Aspergillus*/ABPA group (8.5 % versus 2.8 % (OR 3.21 (1.26 to 15.91); p = 0.016). The use of other treatments such as antiviral therapy, antibiotic therapy and systemic steroids did not differ significantly between the two groups.

iii) Complications of COVID-19 There was a significant association of sepsis during COVID-19 in the *Aspergillus*/ABPA group, versus non-*Aspergillus*/ABPA group (6.9 % versus 0.9 % (adjusted OR 7.78 (1.78 to 49.43); p = 0.008). However, numbers were small with only 4 cases of sepsis in each group (table 2). Occurrence of CF pulmonary exacerbations and bacterial pneumonia was comparable in both groups. Multi-organ failure was rare in both groups. Acute respiratory distress syndrome (ARDS) was rare and was observed in 7 patients in the non-*Aspergillus*/ABPA group only.

*iv) Sensitivity analyses.*The sensitivity analysis in the non-transplant group showed that the baseline characteristics of pwCF with or without *Aspergillus*/ABPA were comparable to the total cohort, and that the associations between preceding *Aspergillus* infection and/or ABPA and hospitalisation (adjusted OR 1.69 (1.03 to 2.63); p = 0.035) and sepsis (adjusted OR 5.55 (0.96 to 32.26); p = 0.045) remain significantly different, with a higher use of antifungals (7.0 % versus 1.7 %; p = 0.03) during COVID-19 (Supplemental Table 1–2). In contrast, excluding pwCF and ABPA from the cohort showed that the prevalence of CFRD and pre-COVID-19 infection with *P. aeruginosa* was no longer significantly different between the group with or without preceding *Aspergillus* infection. No significant impact of previous *Aspergillus* infection in pwCF on COVID-19 associated hospitalisation (p = 0.084) and antifungal use (p = 0.05) was observed (Supplemental Table 3–4). The development of sepsis (6.9 % versus 0.9 %; p = 0.006) remained significantly higher in the *Aspergillus* infection group.

Table 2
Characteristics of COVID-19 in patients with Cystic Fibrosis in the presence or absence of *Aspergillus* infection or ABPA.

	Total N = 807 (%)	Non-*Aspergillus* / ABPA group N = 654 (%)	*Aspergillus* /ABPA group N = 153 (%)	Adjusted[&] OR (95 % CI)	Adjusted[&] p-value[1]
COVID Severity Outcomes					
Community treated	612 (77.08)	510 (79.19)	102 (68.00)	0.56(0.35 - 0.84)	0.005
Hospital admission	182 (22.92)	134 (20.81)	48 (32.00)	1.79(1.19 - 2.85)	0.005
ICU admission	30 (3.72)	26 (3.98)	4 (2.61)	0.65(0.20 - 1.96)	0.534
Oxygen requirement	92 (11.54)	77 (11.96)	15 (9.80)	0.80(0.34 - 1.23)	0.214
Non-invasive ventilation	23 (3.11)	18 (2.80)	5(3.27)	1.25(0.34 - 2.92)	0.876
Invasive ventilation	17 (2.30)	13 (2.16)	4 (2.96)	1.39(0.39 - 4.80)	0.521
Death	13 (1.61)	10 (1.53)	3 (1.95)	1.29(0.30 - 5.38)	0.619
Treatment during COVID infection					
Antiviral therapy*	32/485 (6.60)	31/426 (7.28)	1/59(1.70)	n.a.	n.a.
Antibiotic therapy (oral & IV)*	355/711 (49.93)	285/584(48.8)	70 (55.12)	1.29(0.84 – 1.90)	0.266
Systemic Steroids*	125/701 (17.83)	96 (16.64)	29 (23.39)	1.53(0.80 – 2.20)	0.250
Hydroxychloroquine*	16/487 (3.29)	12/428 (2.80)	4/59 (6.78)	2.52(0.65 – 7.85)	0.146
Vitamin C*	50/486 (10.29)	47/427 (11.01)	3/59 (5.09)	0.43(0.08 – 1.06)	0.103
Immunomodulators*	5/419 (1.19)	4/370 (1.08 %)	1/49 (2.04)	n.a.	n.a.
Antifungal therapy*	17/487 (3.49)	12/428 (2.80)	5/59 (8.48)	3.21(1.26 – 15.91)	0.016
Complications of COVID					
Sepsis*	8/482 (1.66)	4/424 (0.94)	4/58 (6.90)	7.78(1.78 – 49.43)	0.008
Multiorgan failure	5 (0.62)	4 (0.61)	1 (0.66)	n.a.	n.a.
CF pulmonary exacerbation*	103/806 (14.65)	78/653 (11.95)	25/153 (16.34)	1.62(0.84 – 2.43)	0.167
ARDS*	7/480 (1.46)	7/422 (1.66)	0/59 (0.0)	n.a.	n.a.
Bacterial Pneumonia*	14/480 (2.92)	11/422 (2.61)	3/58 (5.17)	2.04(0.45 – 8.02)	0.282

All variables: Numbers (%). *If missing data is ≥ 10 % for specific variable, total number is specified. [&]Odds ratio with 95 % confidence interval and p-value$_1$ adjusted for age at SARS-CoV-2 infection, pre-infection value of percentage predicted FEV_1, status of lung transplant. ICU; intensive care unit, ARDS; acute respiratory distress syndrome. N.a; not applicable.

3.4. Antifungal treatment during SARS-CoV-2 infection and severity of COVID-19 disease

Of the 1095 pwCF and SARS-CoV-2 infection, data on antifungal treatment was recorded in 492 (45.0 %), and 18 (3.7 %) received antifungal treatment during SARS-CoV-2 infection (Supplementary Table 5). . There were no significant differences between these 2 groups with respect to gender, age, BMI, lung function, genotype and *Aspergillus* infection or ABPA in the preceding year. Those having had a lung transplant were 11 times more likely to be treated with antifungals during COVID-19 (38.9 % versus 5.5 %; $p < 0.001$). Oral antimicrobial and immunomodulatory treatments prior to COVID-19 were significantly associated with receiving antifungal treatment during COVID-19.

COVID-19 outcomes were much worse in pwCF who received antifungal treatment during COVID-19, compared to those who did not (Supplementary Table 6). This is shown by a significantly increased rates of hospitalisation, (83.3 % versus 17.4 %; $p < 0.001$), ICU admission (33.3 % versus 2.3 %; $p < 0.001$), oxygen requirement (55.6 % versus 9.8 %; $p < 0.001$), invasive ventilation (22.2 % versus 1.5 %; $p < 0.001$) and mortality (16.7 % versus 1.3 %; $p < 0.001$). In addition, the complications of sepsis (16.7 % versus 0.9 %; $p < 0.001$) and ARDS (22.2 % versus 0.6 %; $p < 0.001$) were much more frequent in the antifungal treated group PwCF who received antifungals, were significantly more likely to be treated with antivirals, antibiotics and steroids

Sensitivity analysis by excluding the lung transplant patients showed that the baseline characteristics of pwCF treated antifungals during COVID-19 were comparable to those not having received antifungal. The significant associations between treatment with antifungals during COVID-19 and hospitalisation ($p < 0.001$), ICU admission ($p = 0.005$), oxygen requirement ($p < 0.001$), development of sepsis ($p = 0.001$) or ARDS ($p < 0.001$), and mortality ($p = 0.001$) remained in non-transplant cohort.

4. Discussion

This study aimed to evaluate the impact of *Aspergillus* infection and ABPA combined on COVID-19 outcomes in pwCF. Although their immunopathogenesis differs, they represent different disease phenotypes caused by *Aspergillus* spp. Our results show a significant association between pre-existing *Aspergillus* infection and ABPA in pwCF and COVID-19 disease severity reflected in increased rates of hospitalisation and sepsis; but no association with other markers of COVID-19 disease severity such as ICU admission and oxygen requirement. The sensitivity analysis, after excluding patients with ABPA, showed that the increased rate of hospitalisation was largely driven by pre-existing ABPA. The development of sepsis remained significantly higher in the *Aspergillus* group after excluding ABPA. Separate analyses on pwCF with ABPA only were not performed due to the low numbers (n = 27) in this group.

Our observations confirm and extend the results from an earlier ESCFSPR study assessing outcomes of COVID-19 in pwCF showing that ABPA was associated with hospitalisation [6]. ABPA as a risk factor for more severe COVID-19 was unfortunately not included in the multivariable model in that study due to > 10 % missing data for this variable [6]. A French CF Registry study showed that pwCF with pre-existing ABPA were significantly more likely to be diagnosed with SARS-CoV-2 infection, but pre-existing ABPA was not associated with worse COVID-19 outcomes [16]. A global study assessing the characteristics and outcomes of COVID-19 in 105 children with CF, showed that ABPA was positively associated with hospitalisation, with five out of 8 children (63 %) with ABPA and COVID-19 needing hospitalisation [17].

To assess the role of pre-existent *Aspergillus*/ABPA more precisely on COVID-19 outcomes, we adjusted our analyses for the factors known to be associated with worse outcomes shown in earlier studies. Age at SARS-CoV-2 infection, pre-infection value of $ppFEV_1$, and lung transplant status have been shown to be associated with worse outcomes of SARS-CoV-2 infection in pwCF [6,18–21]; as well as worse outcomes of COVID-19 in the non-CF population [22–24]. The pwCF in the

Aspergillus/ABPA group were older than the non-*Aspergillus*/ABPA group as anticipated, as rates of *Aspergillus* infection and ABPA increase with age in pwCF [25]. These differences remained when patients with ABPA were excluded. There were no significant differences between the groups at baseline in terms of lung function or lung transplant status. Our results show that after adjustment for known confounders, pre-existing *Aspergillus*/ABPA remain associated with worse outcomes of COVID-19 in pwCF. The statistical significance of the association with hospital admission was lost when focussing on *Aspergillus* infection only, although a higher number of pwCF and *Aspergillus* infection were hospitalised (27.4 % versus 20.8 %), but development of sepsis remained significantly higher in the *Aspergillus* infection only group (6.9 % versus 0.9 %; $p = 0.006$) during COVID-19. An explanation for this might be the absence of a clear definition for *Aspergillus* infection, and how to differentiate infection from colonisation. As the total number of respiratory samples positive for *Aspergillus*/year is not captured by the ECFSPR, it was not possible to differentiate between a 'one off' positive sample and persistent (≥ 2) positive samples per year. Furthermore, the type of respiratory sample from which *Aspergillus* was cultured is not captured, with sensitivity and specificity varying between sputum, cough, throat and bronchoalveolar lavage samples [26]. In addition, it is likely the culture techniques vary across the participating countries, with high-volume cultures being more sensitive than standard culture based-techniques in detecting *Aspergillus* [26].

As previous data have indicated that lung transplant is an independent risk factor for more severe COVID-19 [18], we performed a sensitivity analysis by excluding patients who received a lung transplant, but did had no effect on the significant associations found with respect to hospitalisation and development of sepsis during COVID-19.

When taking into account surrogate markers of CF disease severity including CFRD, *P. aeruginosa* infection, NTM infection, the use of inhaled antibiotics, inhaled steroids and azithromycin, significant differences were observed at baseline between the *Aspergillus*/ABPA group, which remained significantly different when either excluding patients with ABPA (with exception of CFRD and *P. aeruginosa* infection) and those who had a received a lung transplant.

In our study, 51.3 % of the *Aspergillus*/ABPA group versus 32.0 % of the non-*Aspergillus*/ABPA group ($p < 0.001$) received chronic azithromycin therapy before SARS-CoV-2 infection. Observational studies have shown an association between azithromycin and *Aspergillus* colonisation in pwCF which authors argue could be due to the anti-inflammatory effect of azithromycin pre-disposing to *Aspergillus* infection CF [27,28]. Jung et al. [6] identified that in pwCF and COVID-19, chronic azithromycin treatment, after adjustment for confounders, was as a risk factor for hospitalisation ($p = 0.02$) and oxygen therapy ($p = 0.002$). Colombo [19] also identified it as a risk factor for hospitalisation after adjustment for age and pancreatic insufficiency ($p = 0.0009$). It is likely that chronic azithromycin therapy is indicative of recurrent bacterial infections, particularly chronic *P. aeruginosa*, thus is a surrogate marker for worse lung disease in pwCF. This is supported by the findings in our study of an association between *Aspergillus*/ABPA and chronic inhaled antibiotic therapy ($p < 0.001$), which remained a significant finding after excluding patients with ABPA or lung transplant. In our study lung function was included as a predictor in the multivariable model, thus precluding the inclusion of azithromycin due to lack of independence from lung function..

In this study 30.2 % of the *Aspergillus*/ ABPA group versus 21.0 % of the non-*Aspergillus*/ABPA group had CF related diabetes (CFRD) ($p = 0.024$). CF registry studies from France [16] Italy [19] Europe [6] and worldwide [18] have shown association between CFRD and more severe COVID-19 outcomes. In the non-CF population, type 1 and 2 diabetes is an important risk factor for COVID-19 mortality as shown in a meta-analysis of 42 global studies [24], and in a meta-analysis of 88 European cohort studies [23]. CFRD differs from diabetes in the non-CF population in that it is not associated with macrovascular complications in the same way, nor obesity, both of which are associated with worse COVID 19 outcomes [23,24]. However, the common features of hyperglycaemia causing impaired immunity; and immune dysregulation impacting response to SARS-CoV-2 are likely to be important in CFRD, as well as non-CF diabetes. In addition, CFRD is a marker of disease severity in pwCF, which develops as the disease progresses, which may also account for the association shown with *Aspergillus*/ ABPA.

The secondary analysis comparing pwCF treated with antifungals, to those not treated with antifungals during COVID-19, shows that antifungal treatment is positively associated with disease severity and increased rates of mortality (16.7 % versus 1.3 %), hospitalisation, ICU admission, oxygen therapy, non-invasive ventilation, ARDS and bacterial pneumonia in the antifungal group. These association remained significant when focussing on the non-transplant cohort only. Antifungal treatment administered to pwCF during COVID-19 is clearly associated with clinical markers of disease severity of both CF and COVID-19 as well as higher mortality compared to those who did not receive antifungals. Our observation reflects the clinical guidance in which antifungal treatment is reserved for severe COVID-19 in ICU patients [29, 30] and may therefore not represent a causative factor, but rather confounding. Pre-existent *Aspergillus*/ABPA was not associated with the administration of antifungals during COVID-19 treatment, as only 9.4 % (6/64) with pre-existent *Aspergillus* infection or ABPA were treated with antifungals. Unfortunately, our study was limited by lack of information available on CAPA, and how this might have impacted antifungal treatment and outcome.

There are several limitations to this study. Firstly, not all countries participating in the ECFSPR participated in the COVID-19 data collection, which might have introduced a bias. Furthermore, the high proportion of missing data > 10 % for certain variables, such as sepsis as a complication of COVID-19 (missing data as specified in all tables with an asterix), is a potential source of bias. In addition, annual review data on antifungal treatment prescribed prior to SARS-CoV-2 infection was not available.

This European observational cohort study is the first to consider the specific importance of pre-existing *Aspergillus* infection and ABPA, on outcomes of COVID-19 in pwCF. The strong association shown between pre-existing *Aspergillus*/ABPA, but not *Aspergillus* infection only, and hospitalisation from COVID-19 is likely due to a combination of the detrimental impact of *Aspergillus*/ABPA on CF lung disease before SARS-CoV-2 infection; the immunological impact of *Aspergillus*-SARS-CoV-2 co-infection; as well as the association of *Aspergillus*/ABPA with other markers of CF disease severity, including CFRD and chronic inhaled antibiotics and azithromycin treatment. Whilst this study shows an association of pre-existing *Aspergillus*/ABPA and sepsis in COVID-19, no association was shown with ICU admission or oxygen or ventilation requirements. In conclusion this study highlights the importance of *Aspergillus*/ABPA in pwCF, showing it to be an important risk factor for disease severity in COVID-19.

Collaborators

We would like to thank the people who provided the data and the members of the ECFSPR Scientific Committee:

Albania

Irena Kasmi, "Mother Thereza" Hospital Centre, Department of Paediatrics, Tirana

Armenia

Satenik Harutyunyan, Yerevan University CF Centre, Muratsan Hospital, Yerevan

Austria

Sabine Burghart, Andrea Lakatos-Krepcik, Abteilung für Atmungs- und Lungenerkrankungen, Krankenhaus Hietzing, Vienna

Johannes Eder, Zertifiziertes CF Zentrum für Kinder, Jugendliche und Erwachsene, Medizinische Universität Innsbruck, Innsbruck

Peter Jaksch, Dagmar Liebhart, Sabina Seehofer, Medizinische Universität, Allgemeines Krankenhaus Wien, Austria

Katharina Kainz, Abteilung für Kinder- und Jugendheilkunde mit Ambulanz, Wilhelminenspital, Vienna

Margit Kallinger, Monika Pell, Abteilung für Kinder- und Jugendheilkunde und Abteilung für Lungenheilkunde, Landeskrankenhaus Steyr, Steyr

Alexander Leitner, Klinikum Wels-Grieskirchen, Abteilung für Lungenkrankheiten, Wels, Austria

Marta Mozdzen, Abteilung für Lungenkrankheiten, Klinikum Wels-Grieskirchen, Wels

Andreas Pfleger, Department of Pediatrics and Adolescent Medicine, Division of paediatric Pulmonology and Allergology, Medical University of Graz, Graz

Sabine Renner, Nicole Strasser, Klinik für Kinder- und Jugendheilkunde, Cystische Fibrose Ambulanz, Medizinische Universität Wien, Vienna

Martin Stadlinger, Klinik für Lungenheilkunde/ Pneumologie, Kepler Universität Klinikum, Linz

Christina Thir, Univ. Klinik für Kinder- und Jugendheilkunde, Kepler Universitätsklinikum, Linz

Belgium

Hedwige Boboli, Department of Pediatrics, paediatric Pulmonology, University Hospital Liège, Liège

Elke De Wachter, Department of Paediatric Pulmonology, Universitair ziekenhuis Brussel, Brussels

Lieven Dupont, Department of Pneumology, University Hospitals Leuven, Leuven

Sophie Gohy, Department of Pulmonology Cliniques Universitaires Saint-Luc UCL, Brussels & Cystic Fibrosis Reference centre Cliniques Universitaires Saint-Luc UCL, Brussels

Laurence Hanssens, CF centre, Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Brussels; Institut de mucoviscidose de l'université libre de Bruxelles (ULB), hôpital universitaire des enfants Reine Fabiola - ULB, Brussels

Christiane Knoop, Institut de mucoviscidose de l'université libre de Bruxelles (ULB), hôpital universitaire Erasme - ULB, Brussels

Elise Lammertijn*, Cystic Fibrosis Europe, Brussels; Association Muco A.S.B.L. – Mucovereniging V.Z.W., Brussels

Vicky Nowé, Department of Pulmonology, GZA Sint-Vincentius Hospital, Antwerp

Jessica Pirson, Service de Pneumologie, CHR Citadelle, Liège

Matthieu Thimmesch, Service de Pédiatrie, CHC Clinique du MontLégia, Liège

Eva Van Braeckel, Cystic Fibrosis Reference Centre, Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium & Department of Internal Medicine and Pediatrics, Ghent University, Ghent

Kim Van Hoorenbeeck, Department of Pediatrics, Antwerp University Hospital, Edegem

Eef Vanderhelst, Respiratory Division, University Hospital UZ Brussel, Brussels

Croatia

Duška Tješić-Drinković, Andrea Vukić Dugac, Ivan Bambir, University Hospital Centre Zagreb, Cystic Fibrosis Centre - Paediatrics and Adults, Zagreb

Czech Republic

Alena Bilkova, Pavel Drevinek, Cystic Fibrosis Centre, Department of Pneumology, Dept. of Preventive Care, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague

Milan Macek Jr*, Department of Biology and Medical Genetics, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague

Denmark

Hanne Vebert Olesen, Department of Pediatrics and Adolescent Medicine, Cystic Fibrosis centre, Aarhus University Hospital, Aarhus

Tania Pressler, Copenhagen Cystic Fibrosis Centre, Rigshospitalet, Copenhagen

France

Pierre- Régis Burgel, Respiratory Medicine and National Cystic Fibrosis Reference centre, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Université de Paris, Institut Cochin, INSERM U1016, Paris

Harriet Corvol, Sorbonne Université, Centre de Recherche Saint-Antoine, Inserm UMR_S938, Assistance Publique-Hôpitaux de Paris, Hôpital Trousseau, paediatric Pulmonology Department and Cystic Fibrosis centre, Paris, France

Lydie Lemonnier-Videau, Vaincre la Mucoviscidose, Paris

French Cystic Fibrosis Reference Network study group:

Michel Abely, Centre Hospitalier Universitaire de Reims, Reims

Carole Bailly Piccini, Centre Hospitalier Universitaire de Nice, Nice

Chantal Belleguic, Centre Hospitalier Universitaire de Rennes - Hôpital Pontchaillou, Rennes

Tiphaine Bihouee, Centre Hospitalier Universitaire de Nantes, Nantes

Yves Billon, Centre Hospitalier Régional Universitaire de Nancy, Nancy

Stéphanie Bui, Centre Hospitalier Universitaire Bordeaux, Bordeaux

Boubou Camara, Centre Hospitalier Universitaire de Grenoble, La Tronche

Marie-Christine Cheraud, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand

Raphael Chiron, Centre Hospitalier Universitaire de Montpellier, Montpellier

Emmanuelle Coirier Duet, Centre Hospitalier de Versailles, Le Chesnay-Rocquencourt

Laure Cosson, Centre Hospitalier Régional Universitaire de Tours - Clocheville Hospital, Tours

Marie-Laure Dalphin, Centre hospitalier universitaire de Besançon, Besançon

Isabelle Danner Boucher, Centre Hospitalier Universitaire de Nantes, Nantes

Sandra De Miranda, Hôpital Foch, Suresnes

Eric Deneuville, Centre Hospitalier Universitaire de Rennes - Hôpital Sud, Rennes

Jean-Christophe Dubus, Hôpitaux Universitaires de Marseille, Marseille

Isabelle Durieu, Centre Hospitalier Lyon-Sud, Pierre-Bénite

Ralph Epaud, Hôpital Intercommunal de Créteil, Créteil

Michèle Gerardin, AP-HP - Hôpital Robert-Debré, Paris

Dominique Grenet, Hôpital Foch, Suresnes

Véronique Houdouin, AP-HP - Hôpital Robert-Debré, Paris

Frédéric Huet, Centre Hospitalier Universitaire de Dijon Bourgogne, Dijon

Kanaan Reem, AP-HP Hôpital Cochin, Paris

Romain Kessler, Hôpitaux Universitaires de Strasbourg, Strasbourg

Jeanne Languepin, Centre Hospitalier Universitaire de Limoges, Limoges

Muriel Laurans, Centre Hospitalier Universitaire de Caen, Caen

Sylvie Leroy, Centre Hospitalier Universitaire de Nice, Nice

Cathie Llerena, Centre Hospitalier Universitaire de Grenoble, La Tronche

Julie Macey, Centre Hospitalier Universitaire de Bordeaux - Hôpital Haut-Lévêque, Pessac

Julie Mankikian, Centre Hospitalier Régional Universitaire de Tours – Bretonneau, Tours

Christophe Marguet, Centre Hospitalier Universitaire de Rouen, Rouen

Clémence Martin, AP-HP Hôpital Cochin, Paris

Laurent Mely, Hospices Civils de Lyon - Hôpital Renée Sabran, Giens-Hyères

Marie Mittaine, Centre Hospitalier Universitaire de Toulouse - Hôpital des Enfants, Toulouse

Marlène Murris-Espin, Centre Hospitalier Universitaire de Toulouse -

Hôpital Larrey, Toulouse

Caroline Perisson, Centre Hospitalier Universitaire de La Réunion sites Sud, Saint-Pierre

Anne Prevotat, Centre Hospitalier Universitaire de Lille, Lille

Sophie Ramel, Fondation ILYDS, Roscoff

Cinthia Rames, Centre Hospitalier Universitaire Amiens-Picardie, Amiens

Philippe Reix, Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Bron

Marine Revillon, Centre Hospitalier Universitaire de Lille, Lille

Martine Reynaud-Gaubert, Hôpitaux Universitaires de Marseille, Marseille

Bénédicte Richaud-Thiriez, Centre hospitalier universitaire de Besançon, Besançon

Jean-Luc Rittie, Centre Hospitalier Universitaire de La Réunion - site Felix Guyon, Saint-Denis

Manuëla Scalbert-Dujardin, Centre Hospitalier Dunkerque, Dunkerque

Isabelle Sermet-Gaudelus, AP-HP - Hôpital Necker Enfants malades, Paris

Véronique Storni, Centre hospitalier Bretagne-Atlantique, Vannes

Aurélie Tatopoulos, Centre Hospitalier Régional Universitaire de Nancy, Nancy

Guillaume Thouvenin, AP-HP Hôpital Armand-Trousseau, Paris, France

Françoise Troussier, Centre hospitalier universitaire d'Angers, Angers

Laurence Weiss, Hôpitaux Universitaires de Strasbourg, Strasbourg

Nathalie Wizla, Centre Hospitalier Universitaire de Lille, Lille

Germany

Eva-Susanne Behl, Klinikum Westbrandenburg, Klinik für Kinder- und Jugendmedizin, Potsdam

Folke Brinkmann, Universitätsklinikum der Ruhr-Universität Bochum, St. Josef-Hospital am Katholischen Klinikum Bochum, Klinik für Kinder- und Jugendmedizin, Christiane Herzog Centrum Ruhr, Bochum

Martin Claßen, Klinikverbund Bremen gGmbH, Klinikum Links der Weser, Christiane Herzog-Ambulanz für Mukoviszidose, Bremen

Ute Graepler-Mainka, Department of General Pediatrics, hematology and Oncology, Children's Hospital, Eberhard-Karls-University, Tübingen

Matthias Griese, Ludwig-Maximillian Klinikum der Universität München, Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital, Christiane-Herzog-Ambulanz, München

Armin Grübl, Klinik für Kinder- und Jugendmedizin München, Klinik Schwabing und Harlaching, München

Jutta Hammermann, Universitätsklinikum Carl-Gustav Carus, Klinik und Poliklinik für Kinder- und Jugendmedizin, Universitäts Mukoviszidose-Centrum „ Christiane Herzog", Dresden

Helge Hebestreit, Universitäts-Kinderklinik, Christiane–Herzog-Anmbulanz für Mukoviszidose, Würzburg

Andrea Heinzmann, Universitätsklinikum Freiburg, Klinik für Allgemeine Kinder- und Jugendmedizin, Ambulanz und Arbeitsgruppe Pneumologie, Allergologie und Mukoviszidose, Freiburg

Alexander Herz, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Klinik für Kinder- und Jugendmedizin, Pädiatrische Pneumologie, Lübeck

Alexander Kiefer, KUNO Klinik St. Hedwig, Regensburg

Birte Kinder, Dietrich Bonhoeffer Klinikum Neubrandenbrurg, Klinik für Kinder- und Jugendmedizin, Neubrandenburg

Holger Köster, Klinikum Oldenburg, Oldenburg

Stefan Kuhnert, Universitätsklinikum Gießen und Marburg GmbH, Medizinische Klinik und Poliklinik II, Giessen

Jochen Mainz, Brandenburg Medical School (MHB), University, Klinikum Westbrandenburg,

Brandenburg an der Havel

Angelika Mayer, Robert-Bosch-Krankenhaus, Klinik Schillerhöhe, Pneumologie, Gerlingen

Susanne Naehrig, Medizinische Klinik V (Pneumology), LMU University of Munich, Pneumology, Medizinische Klinik Innenstadt, University of Munich, Munich

Tim Niehues, Helios Klinikum Krefeld, Zentrum für kinder- und Jugendmedizin, Mukoviszidose-Zentrum, Krefeld

Thomas Nüßlein, Gemeinschaftsklinikum Mittelrhein - Klinik für Kinder- und Jugendmedizin, Koblenz, Koblenz

Krystyna Poplawska, Universitätskinderklinik Mainz, Pädiatrische Pneumologie und Allergologie, Mukoviszidose, Mainz

Felix Ringshausen, Medizinische Hochschule Hannover, Klinik für Innere Medizin, Pneumologische Ambulanz, Hannover

Markus Rose, Klinikum Stuttgart, Olgahospital- paediatric Pulmonology, Stuttgart, Germany

Josef Rosenecker, Fachkliniken Wangen, Wangen

Renate Ruppel, Kinderklinik des Universitätsklinikums Erlangen, Erlangen

Anette Scharschinger, Paediatric and Adolescent Medicine, University Medical centre Augsburg, Augsburg

Christian Schropp, Children's Hospital Dritter Orden, Passau

Carsten Schwarz, Department of paediatric Pneumology, Immunology and Intensive Care Medicine, Cystic Fibrosis centre, Charité - Universitätsmedizin Berlin, Berlin

Christina Smaczny, Universitätsklinikum Frankfurt, Goethe-Universität, Christiane Herzog CF-Zentrum für Kinder, Jugendliche und Erwachsene, Frankfurt

Olaf Sommerburg, Universitätsklinikum Heidelberg, Sektion Pädiatrische Pneumologie, Allergologie und Mukoviszidose-Zentrum, Heidelberg

Sivagurunathan Sutharsan, Ruhrlandklinik, Pneumologie, Essen

Simone Stolz, Klinik für Kinder- und Jugendmedizin, Carl-Thiem-Klinikum gGmbH, Cottbus

Wolfgang Thomas, Klinikum Mutterhaus der Borromäerinnen, Kinder- und Jugendmedizin, Trier

Sabine Wege, Department of Pneumology and Critical Care Medicine, Thoraxklinik at the University Hospital Heidelberg, Heidelberg

Britta Welzenbach, Josefinum hospital for children and adolescents, Augsburg

Bettina Wollschläger, Martin-Luther-University Halle, Clinic for Internal Medicine, Halle

Greece

Filia Diamantea, Adult Cystic Fibrosis Unit, Sismanoglio General Hospital of Attica, Athens

Elpis Hatziagorou, Cystic Fibrosis Unit, Hippokration General Hospital, Aristotle University of Thessaloniki, Thessaloniki

Katerina Manika, Pulmonary Dept, Aristotle University of Thessaloniki, G Papanikolaou Hospital, Thessaloniki

Ireland

Des Cox, Children's Health Ireland, Crumlin, Dublin

Basil Elnazir, Children's Health Ireland, Tallaght University Hospital, Dublin

Godfrey Fletcher, The Cystic Fibrosis Registry of Ireland, Dublin

Cedric Gunaratnam, Department of Respiratory Medicine, Beaumont Hospital, Dublin

Edward F. McKone, St. Vincent's University Hospital & University College Dublin School of Medicine, Dublin

Barry J. Plant, Cork Adult CF Centre, Cork University Hospital, University College, Cork

Israel

Malena Cohen-Cymberknoh, paediatric Pulmonology Unit and Cystic Fibrosis centre, Hadassah Medical centre and Faculty of Medicine, Hebrew University of Jerusalem

Michal Gur, paediatric Pulmonary Institute and CF centre, Rappaport Children's Hospital, Rambam Health Care Campus, Haifa

Galit Livnat, Carmel CF centre, Technion-Israel Institute of

Technology, Haifa

Meir Mei-Zahav, Pulmonary Institute, Schneider Children's Medical centre of Israel, Petah Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv

Italy

Annalisa Amato and Gianluca Ferrari, technical board of ICFR, Italian Cystic Fibrosis Ligue, Rome

Raffaele Badolato and Piercarlo Poli, Department of Pediatrics, Regional support Centre for Cystic Fibrosis, Children's Hospital – ASST Spedali Civili Pz. le Spedali Civili, University of Brescia, Brescia

Fiorella Battistini and Valentina Donati, CF Referral centre Emilia-Romagna Region, Cesena

Elisabetta Bignamini and Anna Folino, CF Referral centre Piemonte and Valle D'Aosta Regions, Ospedale Infantile Regina Margherita – Sant' Anna, Torino

Vincenzo Carnovale, Adult CF Referral centre Campania Region, Naples

Carlo Castellani and Rosaria Casciaro, CF Referral centre Liguria Region, IRCCS Istituto Giannina Gaslini Genova

Carla Colombo, Giovanna Pizzamiglio, Cystic Fibrosis Reference centre of Lombardia Region, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Department of Pathophysiology and Transplantation, Milan

Giuseppe Cimino, CF Referral centre Lazio Region, Rome

Marco Cipolli and Francesca Lucca, CF Referral centre Veneto Region, Azienda Ospedaliera Universitaria Integrata di Verona, Verona

Mirella Collura and Francesca Ficili, CF Referral centre Sicily Region, Palermo

Valeria Daccò, Vanessa Gagliano and Giovanna Pizzamiglio, CF Referral centre Lombardia Region, Fondazione IRCCS Cà Granda - Ospedale Maggiore Policlinico, Milan

Valeria Mencarini and Nicola Palladino, CF Referral centre Umbria Region, Gubbio

Salvatore Leonardi and Novella Rotolo, CF Support centre Sicily Region, Catania

Maria Cristina Lucanto and Ester Quattromano, CF Referral centre Sicily Region, Messina

Vincenzina Lucidi, Fabio Majo, Federico Alghisi and Fabiana Ciciriello, CF UOC, Paediatric Hospital "Bambino Gesù", Rome

Antonio Manca and Giuseppina Leonetti, CF Referral centre Puglia Region, Bari

Massimo Maschio, CF Referral centre Friuli-Venezia Giulia Region, IRCCS Materno Infantile Burlo Garofolo, Trieste

Barbara Messore, Adult CF Centre Torino, Pulmonolgy Dept, Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano

Stefano Pantano, CF Referral centre Abruzzi and Molise Region, Teramo

Giovanna Pisi and Cinzia Spaggiari, CF Referral centre Emilia-Romagna Region, Parma

Valeria Raia and Caterina Laezza, CF paediatric Referral centre Campania Region, Naples

Mirco Ros, Veneto Region CF Support centre of Treviso, Ospedale Ca' Foncello, Treviso

Donatello Salvatore, Cystic Fibrosis centre, Hospital San Carlo, Potenza

Marco Salvatore, Undiagnosed Rare Diseases Interdepartmental Unit, National centre Rare Diseases, Istituto Superiore di Sanità, Rome

Giovanni Taccetti and Michela Francalanci, Cystic Fibrosis centre, Toscana Region, Florence, Italy

Pamela Vitullo, CF Support centre Puglia Region, Cerignola

Latvia

Elina Aleksejeva, Department of Pneumology, Children's Clinical University Hospital, Rīga Stradinš University, Riga

Luxembourg

Anna-Maria Charatsi, Michael Sieren, Centre Hospitalier de Luxembourg, Luxembourg

Hélène De la Barrière, Department of Pulmonology, Hôpitaux Robert Schuman, Luxembourg

Netherlands

Josje Altenburg, Department of Pulmonology, Amsterdam University Medical centre, Amsterdam

Michiel Bannier, Department of paediatric Pulmonology, University Medical centre Maastricht, Maastricht

Harry Heijerman, Department of Pulmonology, University Medical centre Utrecht, Utrecht

Hettie Janssens, Department of paediatric Pulmonology, Erasmus Medical centre Rotterdam, Rotterdam

Gerard Koppelman, Department of paediatric Pulmonology, University Medical centre Groningen, Groningen

Renske van der Meer, Department of Pulmonology, Haga Ziekenhuis Den Haag, Den Haag

Peter Merkus, Department of paediatric Pulmonology, Radboud University Medical centre Nijmegen, Nijmegen

Domenique Zomer-van Ommen, Vincent Gulmans, Jacquelien Noordhoek, Dutch Cystic Fibrosis Foundation (NCFS), Baarn

Marianne Nuijsink, Department of paediatric Pulmonology, Haga Ziekenhuis Den Haag, Den Haag

Suzanne Terheggen, Department of paediatric Pulmonology, Amsterdam University Medical centre, Amsterdam

Hester van der Vaart, Department of Pulmonology, University Medical centre Groningen, Groningen

Geert-Jan Wesseling, Department of Pulmonology, University Medical centre Maastricht, Maastricht

Karin de Winter, Department of paediatric Pulmonology, University Medical centre Utrecht, Utrecht

Rep. of North Macedonia

Ivana Arnaudova Danevska, Tatjana Jakovska Maretti, Centre for cystic fibrosis, Children and adults, Institute for respiratory diseases in children, Kozle

Poland

Daria Dziecichowicz-Latała, St. Louis Regional Specialised Children's Hospital, Krakow

Irena Wojsyk-Banaszak, Karol Jonscher University Hospital of Poznan University of Medical Sciences, Poznan

Lukasz Wozniacki, Warsaw Cystic Fibrosis Centre, Dziekanow Lesny Paediatric Hospital, Warsaw

Portugal

Adelina Amorim, Centro Hospitalar S. João, Pulmonology Department, Porto

Ana Sofia Araújo Santos, Susana Castanhinha, Centro Hospitalar Lisboa Centro, Hospital Dona Estefânia, Lisbon

Fernanda Gamboa and Teresa Reis Silva, Centro Hospitais da Universidade de Coimbra, Pulmonology Department, Coimbra

Fabienne Gonçalves, Centro Hospitalar do Porto Materno-Infantil, Porto

Sónia Silva, Inês Azevedo, Department of Pediatrics, Centro Hospitalar Universitário de São João, Porto

Romania

Ioana Ciuca, Liviu Pop, National Cystic Fibrosis Centre, Timisoara

Szabo Csilla-Enikö, Cluj-Napoca, Regional CF Centre, Cluj

Iustina Stan, Bukarest Mother and Child Health institute, Bucharest

Russian Federation

Elena Amelina, Cystic Fibrosis Department, Pulmonology Research Institute of the Federal Medical and Biological Agency of Russia, Moscow

Evgeniya Boitcova, Department of propaedeutics of children's diseases. Federal state budgetary Educational Institution of Higher Eductation "St. Petersburg State paediatric Medical University" Ministry of Healthcare of the Russian Federation, Moscow

Yuliya Gorinova, centre for rare disease в National Medical Research centre for Children's Health, Moscow

Stanislav Krasovskiy, Cystic Fibrosis Department, Pulmonology

Research Institute of the Federal Medical and Biological Agency of Russia, Moscow

Maria Mukhina, Medical and genetic Department, cystic fibrosis office of the State budgetary healthcare institution "Morozovskaya Children's Municipal Clinical Hospital" Moscow

Victoria Sherman, Clinical research department of cystic fibrosis "Research Centre for Medical Genetics", Moscow

Olga Simonova, centre for rare disease в National Medical Research centre for Children's Health, Moscow, Russia; Morozov State paediatric Teaching Hospital, Moscow Healthcare Department; I.M. Sechenov First Moscow State Medical University (Sechenov University), Healthcare Ministry of Russia, Moscow

Nataliya Kashirskaya, Laboratory of genetic epidemiology, "Research Centre for Medical Genetics", Moscow

Elena Kondratyeva, Elena Zhekaite Clinical research department of cystic fibrosis «Research Centre for Medical Genetics», Moscow

Slovakia

Eva Bérešová, Centrum cystickej fibrozy pre dospelych FNSP FDR, Banská Bystrica

Nina Bližnáková, pracovisko Podunajské Biskupice, Klinika detskej pneumologie SZU UN Bratislava, Bratislava

Slovenia

Barbara Salobir, University Medical Centre Ljubljana, Department of Pulmonology and Allergy, Ljubljana

Julij Šelb, University Clinic of Pulmonary and Allergic Diseases, Golnik

Spain

Antonio José Aguilar Fernandez, Materno Infantil, Las Palmas

Antonio Alvarez Fernàndez, Adult Cystic Fibrosis unit, Hospital Universitario Vall d'Hebron, Barcelona Oscar Asensio de la Cruz, Unitat de Pneumologia Pediátrica i Unitat de Fibrosi Quística, Parc Taulí Hospital Universitario, Hospital de Sabadell, Barcelona

Félix Baranda García, Ainhoa García Bonilla, Servicio de Neumología y Fibrosis Quística, Osakidetza, Hospital Universitario Cruces, Bizkaia

Marina Blanco Aparicio, Servicio de Neumología, Hospital Universitario A Coruña, A Coruña

Silvia Castillo Corullón, Unidad de Fibrosis Quística Pediátrica, Hospital Clínico Universitario de Valencia, Valencia

Isidoro Cortell-Aznar, Inés Pérez, Unidad de Trasplante Pulmonar y Fibrosis Quística, Hospital Universitario y Politécnico La Fe, Valencia

Jordi Costa i Colomer, María Cols Roig, Unitat de Pneumologia Pediátrica i Fibrosi Quística, Hospital Sant Joan de Déu, Barcelona

Isabel Delgado Pecellín, Esther Quintana, Unidad de Fibrosis Quística, Hospital Universitario Virgen del Rocío, Sevilla

Layla Diab Cáceres, Carmen Luna Paredes, Unidad de Fibrosis Quística, Hospital 12 de Octubre, Madrid

Silvia Gartner, Unidad Fibrosis Quística y Neumología Pediátrica, Hospital Vall d'Hebron, Barcelona Estela González Castro, Servicio de Neumología, Hospital Universitario Torrecárdenas, Almería

José Ramón Gutiérrez Martínez, Unidad de Fibrosis Quística, Hospital Universitario Central de Asturias, Oviedo

Inés Herrero Labarga, Unidad de Neumología y Fibrosis Quística (Adultos), Hospital Universitario Miguel Servet, Zaragoza, Zaragoza

Rosa Maria Girón-Moreno, Neumología Adultos, Hospital Universitario La Princesa, Madrid

Esperanza Jiménez Nogueira, Neumología Pediatrica, Hospital Universitario Torrecárdenas, Almería

Adelaida Lamas Ferreiro, Alejandro López Neyra, Enrique Blitz Castro, Unidad de Fibrosis Quística Neumología Pediátrica, Servicio de Pediatría Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) Hospital Universitario Ramón y Cajal, Madrid

Laura Moreno Galarraga, Navarra Institute for Health Research (IdisNa); Department of Pediatrics, Complejo Hospital de Navarra, Pamplona

Carlos Martin de Vincente, Unidad de Neumología Pediátrica y Fibrosis Quística, Hospital Universitario Miguel Servet, Zaragoza

Silvia Merlos Navarro, Servicio de Neumología, Hospital Universitario Virgen de las Nieves, Granada Pedro Mondejar Lopez, paediatric Pulmonology and Cystic Fibrosis Unit, Virgen de la Arrixaca Clinic University Hospital, Murcia

Rosa Nieto-Royo, Unidad de Fibrosis Quística, Hospital Universitario de Ramón y Cajal, Madrid

Casilda Olveira Fuster, Unidad Fibrosis Quística Adultos, Hospital Regional Universitario de Málaga, Málaga

Maria Dolores Pastor, Unidad de Fibrosis Quística, Hospital Universitario Cruces, Bizkaia Carlos Peñalver Mellado, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia

Estela Pérez-Ruiz, Pilar Caro-Aguilera, Unidad de Fibrosis Quística Pediátrica, Hospital Regional Universitario de Málaga, Málaga

Concepción Prados-Sánchez, Unidad de Fibrosis Quistica Adultos, Servicio de Neumología, Hospital Universitario La Paz, Madrid

Isabel Ramos Cancelo, Hospital Clínico Universitario de Valladolid, Vallalodid

Marta Ruiz de Valbuena, Sección de Neumología Pediátrica, Unidad de Fibrosis Quística Pediátrica, Hospital Infantil La Paz, Madrid

José R. Villa Asensi, Veronica Sanz Santiago, Patricia Fernández García, Sección de Neumología Pediátrica, Unidad de Fibrosis Quística, Hospital Niño Jesús, Madrid

Sweden

Adrienn Banki, Stockholm CF centre, Karolinska University Hospital, Karolinska Institutet, Stockholm Stefanie Diemer & Christine Hansen, Lunds university hospital, Lund

Marita Gilljam, Gothenburg CF centre, Sahlgrenska University Hospital, Gothenburg

Christina Krantz, Department of Women's and Children's Health, Research Group; Paediatric Inflammation, Metabolism and Child Health Research, Uppsala University, Uppsala

Ulrika Lindberg, Department of Respiratory Medicine and Allergology, Lund CF centre, Skane University Hospital, Lund

Anders Lindblad*, Gothenburg CF Centre, Queen Silvia Children's Hospital, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg

Switzerland

Christian Clarenbach, Carolin Steinack, René Hage, Macé Schuurmans, Klinik für Pneumologie, Adultes CF Zentrum, Universitätsspital Zürich, Zürich

Reta Fischer, Lindenhofspital Quartier Bleu, Bern

Rachel Kusche, Kantonsspital Aarau AG, Klinik für Kinder und Jugendliche, Abteilung pädiatrische Pneumologie, Allergologie und Immunologie, Aarau

Isabelle Rochat, Département femme-mère-enfant, Service de pédiatrie, Unité de pneumologie et mucoviscidose pédiatrique, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne

Macé Schuurmans, Klinik für Pneumologie, Adultes CF Zentrum, Universitätsspital Zürich, Zürich

Anna-Lena Walter, Lungenzentrum, Zentrum für Cystische Fibrose für Erwachsene, Kantonsspital St. Gallen, St. Gallen

Turkey

Dilber Ademhan Tural and Ugur Ozcelik, Department of paediatric Pulmonology, Hacettepe University Faculty of Medicine, Ankara

Pelin Asfuroğlu, Tuğba Şişmanlar Eyüboğlu and Ayse Tana Aslan, Department of paediatric Pulmonology, Gazi University Faculty of Medicine, Ankara

Ayşen Bingöl, Division of paediatric Pulmonology, Allergy and Immunology, Faculty of Medicine, Akdeniz University, Antalya

Nazan Çobanoğlu and Gizem Ozcan, Division of paediatric Pulmonology, Faculty of Medicine, Ankara University, Ankara

Deniz Dogru, Cystic Fibrosis Registry of Turkey, Ankara (ORCID ID: https://orcid.org/0000–0001–9931–9473).

Yasemin Gökdemir, Division of paediatric Pulmonology, Marmara University Faculty of Medicine, Istanbul

Mehmet KÖSE, Department of Pediatrics, Division of paediatric

Pulmonology, Erciyes University, Kayseri
Sevgi Pekcan, Division of paediatric Pulmonology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya
United Kingdom:
Siobhán B. Carr*, Department of Respiratory Paediatrics, Royal Brompton Hospital; NHLI, Imperial College, London
*The ECFSPR Scientific Committee

CRediT authorship contribution statement

Jacob D. Bradbury: Writing – original draft. **Emily Chesshyre:** Conceptualization, Methodology, Formal analysis, Writing – original draft. **Annalisa Orenti:** Methodology, Formal analysis, Writing – review & editing. **Andreas Jung:** Supervision, Writing – review & editing. **Adilia Warris:** Conceptualization, Supervision, Writing – review & editing.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.10.017.

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