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Characterisation of fatigue and its substantial impact on health status in a large cohort of patients with chronic pulmonary aspergillosis (CPA)☆

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ABSTRACT

Introduction: Fatigue is a prominent disabling symptom in several pulmonary diseases. Its impact on health status in patients with chronic pulmonary aspergillosis (CPA) has not been investigated.
Methods: A total of 151 CPA patients attending the National Aspergillosis Centre completed Manchester COPD Fatigue Scale (MCFS), St. George's Respiratory Questionnaire (SGRQ) and Medical Research Council (MRC) dyspnoea score. Lung function and BMI were measured. Univariate, multivariate linear and binary analyses, and principal component analysis (PCA) were used.
Results: Female patients accounted for 44%. The mean (range) of age was 59.6 (31–83) years, FEV_1% was 64 (14–140), BMI was 23.6 (16.3–43.4), SGRQ total score was 56 (4–96.2) and MCFS total score was 30.6 (0–54). PCA showed that 27 items of MCFS loaded on three components; physical, psychosocial and cognitive fatigue, explaining 78.4% of fatigue variance. MCFS score correlated strongly with total SGRQ score ($r = 0.83$, $p < 0.001$). Using linear multivariate analysis, fatigue was the strongest factor (beta = 0.7 $p < 0.0001$) associated with impaired health status, after adjusting for age, BMI, FEV1%, and MRC dyspnoea score. Using patients' 5 self-assessment grades of their health, one-way ANOVA showed that those with "very poor" health status had the highest fatigue scores (45 (±6) ($p < 0.001$)). Logistic regression analysis showed that fatigue score (OR = 0.9, 95% CI 0.84–0.97; $p = 0.005$) and FEV_1% (OR = 1.03, 95% CI 1.01–1.07, $p = 0.02$) are significantly associated with self-assessed impaired health status after correcting for age, gender and DLCO%.
Conclusion: Fatigue is a major component of impaired health status of CPA patients.

1. Introduction

Chronic pulmonary aspergillosis (CPA) is a progressive, infectious, non-communicable disease [1–3] that is manifest by pulmonary cavities, fibrosis or aspergilloma formation; it may be bilateral [3,4]. Patients with CPA commonly present with breathlessness, weight loss, fatigue, cough, haemoptysis [1,5], and/or limited physical activity and impaired health status [1,6]. For instance, in an early case series, Denning et al. assessed 18 patients with CPA and found that at least 28% of the studied cases reported fatigue as a principal symptom [1]. However, the true impact of fatigue on health status of CPA patients is poorly understood, and further investigation of this disabling symptom is necessary.

Abbreviations: BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; CPA, Chronic pulmonary aspergillosis; FEV_1, Forced Expiratory Volume over 1 Second; FVC, Forced Vital Capacity; IQR, Interquartile range; MCFS, Manchester COPD fatigue scale; MRC scale, Medical Research Council Scale; NAC, National Aspergillosis Centre; ROC, Receiver Operating Characteristic; SGRQ, St Georges Respiratory Questionnaire.

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Fatigue is common in other chronic respiratory diseases such as COPD, asthma, bronchiectasis and cystic fibrosis [7–11]. It can impede functional performance in daily activities and significantly impacts on health status [12–14]. Several generic scales such as the 40-item Piper Fatigue Scale, the 20-item Multi-dimensional Fatigue Inventory and the 40-item Impact Fatigue Scale have been used in assessing fatigue and its burden in chronic respiratory illnesses [15–19]. Importantly, no tool has been validated in examining fatigue in patients with CPA. The recently developed Manchester COPD fatigue scale (MCFS) is a respiratory-specific scale [11]. It has shown a high level of validity and reliability in comprehensively assessing fatigue as well as its psychosocial, physical, and cognitive dimensions [11,20].

The pathophysiology of fatigue in chronic progressive respiratory illnesses is not adequately understood, and is probably multifactorial. The important factors are thought to include poor lung function, physical deconditioning, muscle wasting and dysfunction, dyspnoea, anxiety, and depression [10,12–14,20–23]. In CPA many of these factors are present [6,24] and the impact of fatigue on health status of CPA patients is probably highly significant.

Using a reasonably large cohort of CPA patients, we first investigated the validity and reliability of MCFS in examining fatigue and defining its context in CPA. Then we studied factors associated with fatigue in CPA, and quantified the impact on health status of CPA patients.

2. Methods

2.1. Sample and measurements

One hundred and fifty one CPA patients attending the National Aspergillosis Centre (NAC) were studied. The NAC is a tertiary specialist centre, caring for patients with CPA, which receives about 100 referrals annually from all over the United Kingdom. An opportunistic sample of patients attending clinics, who also had pulmonary function testing performed, were identified and asked to complete Manchester COPD fatigue scale (MCFS) and the St George's Respiratory Questionnaire (SGRQ).

The MCFS is a 27-item respiratory-specific scale which was developed using a standardized well-structured framework [11,20]. It has a high level of validity and reliability in assessing fatigue in chronic progressive respiratory illness (namely COPD) [11,20]. It is a self-administered scale, and measures total fatigue as well as specific psychosocial, physical and cognitive domains. The total score ranges from 0 to 54; a higher score signifies more fatigue. To examine the test-retest reliability of the MCFS in CPA, 14 clinically stable patients were randomly selected and they filled in the questionnaire twice two weeks apart.

Patients also completed the SGRQ which is a highly valid and reliable scale that has been widely used in assessing health status (also called health-related quality of life) in several chronic respiratory illnesses. We have recently reported on the significant validity and reliability of the SGRQ in assessing health status in patients with CPA [6]. A high score indicates worse health status.

Dyspnoea was assessed using the original Medical Research Council scale [25]. Lung function was measured by trained respiratory physiologists and technicians in our centre. Data on body mass index and demographic characteristics were also collected. Approximate CPA severity was assessed using our recently published classification ranged from band 1 to 3, where the higher band indicates more disease severity and complexity, as previously described [6,26]. Per UK National Research Ethics Service guidance, ethical approval or institutional review board approval is not required for this kind of work.

2.2. Statistical analysis

Exploratory Principal Component Analysis (PCA) was performed to examine the structure of the scale. Briefly; we used Kaiser's criterion of eigenvalue >1 and Catell's scree test to determine the number of components [27]. We conducted both orthogonal and oblique rotation techniques and the outcome from oblique (Direct Oblimin) is presented [11]. The Pearson correlation coefficient was used to test the correlation between total and dimensional fatigue scores with SGRQ total and domain scores except with SGRQ activity domain where Spearman correlation was used. The difference between total and dimensional fatigue scores amongst different degrees of health status, bands of disease severity, and degrees of MRC dyspnoea was examined using ANOVA. Paired T-tests were employed to test the difference between total and dimensional fatigue scores for patients who completed the questionnaire twice over two-weeks. We also used Receiver Operating Characteristic (ROC) curves to test the sensitivity of the MCFS in discriminating between different health status categories. The ROC curve is defined by the sensitivity values (true positive cases) and specificity values (true negative cases) [28]. The analysis included the comparison of the areas under the curve (AUC); an AUC $\geq$0.7 indicating a good predictive ability of the questionnaire [29]. Multivariable linear and logistic regression analyses also were conducted. SPSS version 20 (SPSS Inc, USA) was used throughout.

3. Results

3.1. Patients' characteristics

A cohort of 151 patients with CPA was examined; mean (range) age was 59.6 (31–83) years, and 64 (44%) were women. Overall lung function was moderately obstructed, and the patients were dyspnoeic on moderate functional performance, as assessed by a median MRC dyspnoea score of three (Table 1). Patients generally reported high total and dimensional SGRQ scores indicating marked health status impairment (Table 1).

3.2. The structure of the MCFS in CPA

The 27-item MCFS was subjected to an exploratory principal component analysis (PCA). PCA showed three components with eigen values >1, explaining 76.3% of fatigue variance as demonstrated in Table S1 (in the e-supplement). The decision to retain

Table 1
Baseline characteristics of the cohort.

Descriptive	Mean (range)
Age, yrs	59.6 (31–83)
Female (n, %)	64 (44%)
FEV_1 (L)	1.8 (0.41–3.7)
FEV_1%	64 (14–140)
FVC (L)	2.9 (0.76–4.81)
FVC %	84.8 (28–135)
FEV_1/FVC	61.9 (20–99)
Height (cm)	167 (142–186)
Weight (kg)	68 (31.6–129.8)
BMI (kg/m^2)	23.6 (16.3–43.4)
MRC dyspnoea score	3 (1–5)
SGRQ total score	56 (4–96.2)
SGRQ (symptom domain) score	63.9 (0–100)
SGRQ (activity domain) score (median, range)	79 (0–100)
SGRQ (impact domain) score	47 (0–97.5)

BMI = Body Mass Index; FEV_1% = Forced Expiratory Volume over 1 s of predicted; FVC = Forced Vital Capacity; MRC dyspnoea score: Medical Research Council dyspnoea score; SGRQ = Saint George's Respiratory Questionnaire.

Table 2
Correlation between the total and dimensional fatigue scores.

	Psychosocial dimension	Physical dimension	Cognitive dimension
Psychosocial dimension	1		
Physical dimension	0.87	1	
Cognitive dimension	0.72	0.68	1
Total fatigue score	0.96	0.96	0.78

All presented correlations have a p value <0.001.

Table 3
Correlations between total and dimensional fatigue scores and the SGRQ total and dimensional scores (Pearson correlation coefficient was presented unless otherwise stated).

	Total SGRQ	Symptom	Activity	Impact
Total fatigue score	0.83	0.53	0.71*	0.82
Psychosocial dimension	0.76	0.50	0.60*	0.75
Physical dimension	0.85	0.54	0.76*	0.82
Cognitive dimension	0.59	0.35	0.54*	0.60

All presented correlations have a p value <0.001. *Spearman correlation coefficient. SGRQ = St George's Respiratory Questionnaire.

three components was also supported by Scree test scores, (Fig. S1 in the e-supplement). The oblimin rotation revealed the presence of a simple structure with three major dimensions (components) in the data (psychosocial, physical and cognitive) with many items showing strong loadings (items loading >0.4 on the components are shown in Table S1).

A high correlation was found between different domains of fatigue ($r > 0.67$; $p < 0.001$ for all correlations). The impact of psychosocial and physical domains was greater than the cognitive domain (Table 2).

3.3. The burden of fatigue on health status

Patients who were more fatigued experienced considerable health status impairment. This burden was seen on all dimensions of health status (Table 3). A stronger relationship was seen between higher fatigue scores and both activity and impact domains of the SGRQ; correlations between symptoms and all fatigue scores varied from only 0.35 to 0.54. Likewise the cognitive domain of the MCFS had the lowest correlations with the SGRQ ($r = 0.35–0.6$), compared with the psychosocial and physical domains ($r = 0.5–0.85$).

We found that total fatigue score explained 69% of the variance of total SGRQ ($p < 0.0001$) as demonstrated in Fig. 1.

Using total SGRQ score as a dependent variable, multivariate linear analysis showed that total MCFS and MRC dyspnoea scores were significantly correlated with impaired health status, but age was not. When FEV_1% and BMI were added to the model, only the total MCFS score correlated significantly with poor health status (standardized coefficient $\beta = 0.7$; $p < 0.001$) this model explained 73% of the variance of health status impairment.

More severely ill patients experienced higher fatigue scores. Using the self-reported health status grades (very good, good, fair, poor and very poor) of the SGRQ, patients who reported worse health status suffered higher total and dimensional fatigue scores.

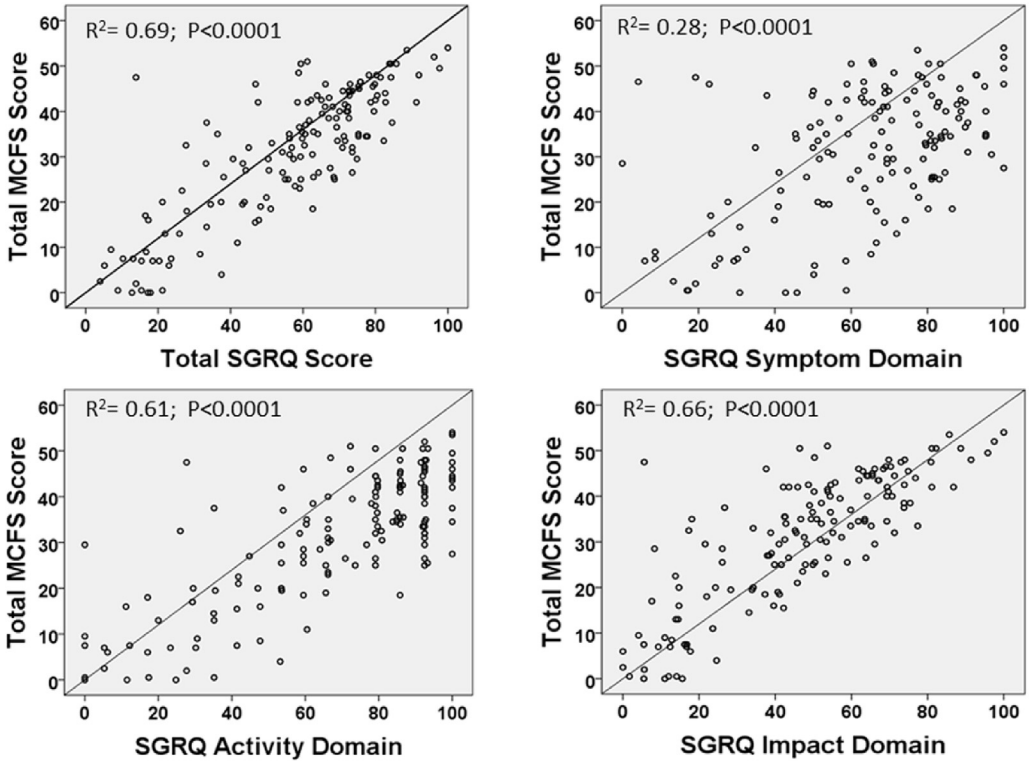

Fig. 1. The correlation between total MCFS score and SGRQ total and dimensional scores.

Table 4
Mean and (SD) Manchester COPD Fatigue Scale scores in groups defined according to self-reported health status grades, complexity band and MRC dyspnoea grades.

		n	Total fatigue score	Psychosocial dimension score	Physical dimension score	Cognitive dimension score
Self-reported health status	Very good	2	0	0	0	0
	Good	31	16 (12)	7.8 (5.8)	7 (6)	1 (1.3)
	Fair	50	31 (10)	14.2 (4.6)	15 (5)	2.4 (1.5)
	Poor	42	37 (10)	16.6 (4)	17.9 (3.9)	2.9 (1.7)
	Very poor	15	45 (6)	19.7 (3.4)	21.9 (2.3)	3.8 (1.3)
	P value	-	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
CPA bands	Band 1	56	26.7 (15)	12.6 (7)	12.1 (7)	2 (1.8)
	Band 2	75	31.8 (14)	14.1 (6)	15.2 (7)	2.5 (1.7)
	Band 3	13	40 (10)	17.2 (4)	19.5 (4)	3.2 (1.4)
	P value	-	*0.006*	*0.06*	*0.001*	*0.04*
MRC dyspnoea grades	Grade 1	16	13.9 (11)	7.4 (6)	5.6 (5)	1 (1)
	Grade 2	33	25.7 (12)	12.1 (5)	11.7 (6)	1.9 (1.6)
	Grade 3	24	31.3 (14)	13.7 (6)	15.3 (7)	2.3 (1.7)
	Grade 4	18	40.7 (7)	17.9 (3.4)	19.5 (4)	3.3 (1.3)
	Grade 5	20	40.8 (8)	17.7 (4.4)	19.8 (3)	3.3 (1.5)
	P value	-	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*

This correlation was consistently seen throughout different levels of impaired health (Table 4). Moreover, patients with more complex and severe CPA disease as assessed by their banding experienced more fatigue. For instance, patients with band 3 almost all had double the fatigue scores of patients with band 1. Patients who are more short of breath reported considerably higher total and dimensional fatigue scores. Patients with grade 4 MRC dyspnoea had fatigue scores approximately twice those of grade 2 (Table 4).

When the cohort was split into two groups of health status (very poor and poor) versus (fair, good and very good), the receiver operating characteristic (ROC) curve analysis indicated considerable ability of MCFS and its components to detect variation in health status (area under the curve (AUC) for the total MCFS score = 0.81 and for psychosocial, physical and cognitive fatigue dimensions 0.78, 0.8 and 0.72 respectively, $p < 0.0001$) as demonstrated in Fig. 2.

Using the same binary split of health status as in the ROC analyses as a dependent variable, logistic regression analysis showed that only total fatigue score (OR = 0.9, 95% CI 0.84–0.97; p = 0.005) and FEV_1% (OR = 1.03, 95% CI 1.01–1.07, p = 0.02) are significantly associated with impaired health status after correcting to age, gender, and DLCO%.

3.4. Fatigue, lung function, gender and age

A low correlation was seen between total fatigue and physical dimension with FEV1 (L), FVC (L) and DLCO values (r = −0.27 to −0.4; P < 0.05). Although female patients reported slightly higher fatigue scores, this did not reach statistical significance. A weak correlation was observed between physical fatigue with age (r = 0.2; P = 0.03).

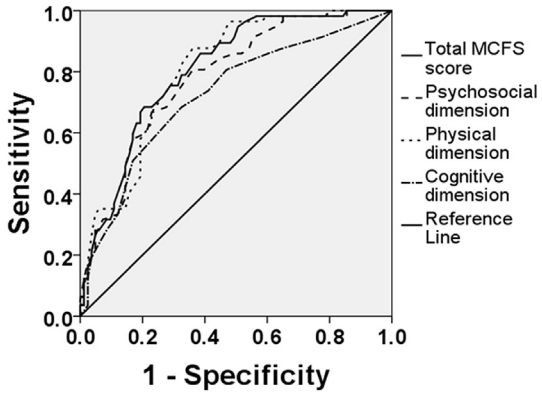

Fig. 2. ROC curve of total and dimensional fatigue score in defining different health status grades.

3.5. Reliability of the MCFS in CPA

When the reliability of the MCFS was examined, Cronbach's alpha values of the internal consistency of the total fatigue, psychosocial, physical and cognitive dimensions are 0.98, 0.96, 0.97 and 0.93, respectively. For test-retest reliability the intra-class correlation coefficients for the scale and its psychosocial, physical and cognitive dimensions were 0.95, 0.94, 0.95 and 0.77, respectively. The difference of the mean scores (SD) of total MCFS and the 3 dimensions at both visits was minimal as shown in Table 5.

4. Discussion

This is the first study examining structure, validity, and reliability of a respiratory-specific fatigue scale in assessing fatigue in CPA. This directly implicates fatigue as a major factor affecting the health status of patients with this chronic progressive respiratory disease. PCA showed that the MCFS is reliable in examining overall fatigue and its domains. Patients with poorer health status, more severe illness or more breathlessness experienced significantly more fatigue. Multivariate analysis showed that fatigue, dyspnoea and poor lung function are strongly associated with impaired health status in CPA.

PCA showed that the MCFS explained 78.4% of the variance of fatigue supporting the ability of the scale to define the concept of fatigue and capture its main characteristics in CPA. Patients with CPA clearly found that fatigue has a major impact on different aspects of their health such as; psychosocial wellbeing and interactions, physical activity, and cognitive performance. This may explain the strong association between this inhibiting phenomenon and impaired total and dimensional health status as measured by SGRQ. Multivariate analysis demonstrated that fatigue, followed by dyspnoea and poor lung function are correlated with impaired health status of patients with this debilitating fungal infection. Fatigue and dyspnoea are the most prominent disabling symptoms in other chronic progressive respiratory illnesses such as COPD [30,31].

Our finding of a pivotal role of fatigue in contributing to poor health after adjusting for dyspnoea, lung function limitation [32], age (24) and low body mass on health status (1, 24) is not surprising for several reasons. First, CPA is a dysregulated inflammatory

Table 5
Comparison of mean (SD) scores of total MCFS and its dimensions at both visits (2–3 weeks interval) (n = 14).

	Mean score (SD) 1st completion	Mean score (SD) 2nd completion	Mean difference (SD)	P Value
Total fatigue score	21.4 (13.5)	23.3 (14.8)	1.8 (4.8)	0.17
Psychosocial dimension	10.1 (5.8)	10.7 (6.5)	0.5 (2.2)	0.4
Physical dimension	9.6 (6.8)	10.4 (7.3)	0.75 (2.1)	0.2
Cognitive dimension	1.6 (1.4)	2.2 (1.6)	0.61 (1)	0.048

disease with poorly controlled persistent inflammation. It is well-known that inflammation induces "behavioural sickness" [33]. Several cytokines such as TNF and several other cytokine play a role in the mechanism of sickness perception. This includes the perception of lethargy and tiredness [34]. Infection caused by bacteria or fungi, results in the production of inflammatory biomarkers including cytokines that would induce a feeling of being ill [34,35]. The effect of these cytokines is interpreted as a feeling of general fatigue, decreased inclination to undertake physical activity, lack of appetite and sleep disturbance as discussed in detail by Kelley et al. [34]. Recently, it has been reported that increased inflammatory proteins such as C-reactive protein is a valuable predictor of mortality in CPA [24] as had previously been reported in COPD [36].

Second, it is likely that other physiological factors contribute to the considerable burden of fatigue on health status. For instance, CPA patients generally have impaired lung function [6], and we observed a mild correlation of fatigue with lung function parameters, consistent with the literature where fatigue had mild negative correlation with FEV1 ($r = -0.32$, $p < 0.05$) in COPD [12]. Additionally, we recently reported a modest correlation of SGRQ with FEV1 in CPA [6], in line with findings in bronchiectasis [37]. The work of breathing may contribute to fatigue given the strong association with dyspnoea [21,23,38].

Fatigue has multi-dimensional effects and contributes to the long-term extra-pulmonary burden of CPA. In recent years, there is a growing body of evidence showing the burden of non-pulmonary manifestations of chronic lung diseases. A better understanding of the disabling burden of fatigue in chronic respiratory illnesses is clinically important, taking into account its association with physical activity limitation [30,39–41], poor exercise performance [14], depression [12,23], sleep disturbance [40,42,43], exacerbation frequency [23] and impaired health status [12,31]. Indeed, these findings reflect the clinical importance of fatigue as a novel target for therapeutic intervention for two reasons. Firstly, fatigue has been reported to be one of the most inhibiting symptoms preventing physical activity in chronic respiratory conditions such as COPD [12,30]. Regular physical activity in COPD is associated with reduced hospital admission and mortality [44]. Secondly, fatigue (as measured by fatigue dimension of the Chronic Respiratory Questionnaire (CRQ)) improved after pulmonary rehabilitation in COPD [45].

Our study has limitations. The MCFS has been developed and validated in COPD. However, the MCFS is a respiratory-specific scale and has shown significant validity and reliability and enabled definition of 78.4% of the variance of fatigue in CPA, a comparable performance to that in COPD [11]. CPA is generally an uncommon infection complicating many different underlying diagnoses [5,46]. We have not been able to assess the relative contribution of the underlying diagnoses to fatigue, which would be valuable. However, this is the first study to examine fatigue and its significant burden in CPA thoroughly and we anticipate further exploratory and interventional studies directed at fatigue using the MCFS. Additionally, we do not have a full dataset for some of the variables of interest, a common limitation in convenience sampling in clinical environments.

In conclusion, the MCFS is a valid and reliable scale for use in assessing fatigue in CPA and has strong correlations with well-established objective and subjective measures. Fatigue contributes a substantial burden on physical activity and health status in CPA. Further studies to investigate this disabling phenomenon and possible therapeutic interventions are required.

Authors contribution

Khaled Al-shair, study design, data collection, entry and analysis, and manuscript writing and drafting. Eavan G. Muldoon, manuscript editing and reviewing. Julie Morris, statistical revision and manuscript editing and reviewing. Graham Atherton, data collection and entry, and manuscript editing and reviewing. Chris Kosmidis, manuscript editing and reviewing. David Denning, study design, manuscript editing and reviewing.

Statement of disclosure

All the authors have no financial or other potential conflicts of interest to disclose.

Dr Denning holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, North-West Lung Centre Charity, Medical Research Council, Global Action Fund for Fungal Infections and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Basilea and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.03.020.

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