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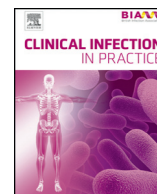


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Risk factors for relapse of chronic pulmonary aspergillosis after discontinuation of antifungal therapy

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ABSTRACT

Objectives: We aimed to identify the frequency and risk factors for disease relapse following cessation of antifungal therapy in CPA.

Methods: This retrospective audit at the National Aspergillosis Centre, Manchester, UK assessed outcomes for patients with CPA who had received antifungal treatment and for whom therapy was discontinued for at least one month between August 2009 and May 2017. We defined relapse as a deterioration in two of the following parameters: clinical, radiological, serological or sputum microbiological markers of CPA activity.

Results: Therapy was discontinued in 102 patients. Age distribution was 63.7 ± 11.5 years. Therapy was recommenced in 43 (42%) patients of whom 21 met our definition of relapse – 31% of those with bilateral and 11% of those with unilateral disease. Patients with bilateral disease and those with ≥ 1 aspergillomas were more likely to relapse on univariate analysis. In a multivariable logistic regression analysis, bilateral disease was the only independent risk factor for relapse (OR: 3.0; 95% CI: 1.0–8.8; $p = .044$).

Conclusions: Bilateral CPA is a risk factor for relapse after treatment discontinuation. A longer duration of treatment may be associated with a lower rate of relapse in extensive CPA, whereas more limited disease may respond to shorter courses.

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1. Introduction

Chronic pulmonary aspergillosis (CPA) refers to a spectrum of syndromes characterised by slowly progressive destruction of lung parenchyma with the creation of new cavities or expansion of existing ones. CPA manifests with prominent respiratory and/or systemic symptoms and is associated with significant morbidity and mortality [1].

Long-term oral triazole therapy is the mainstay of treatment for most patients, with the exception of some with localised disease who may be offered surgery [1,2]. However, acquired resistance during therapy, drug-related side effects and disease recurrence after cessation of treatment are the major management challenges [3–6].

Recurrence is thought to be common in CPA following discontinuation of triazole maintenance therapy. However, very few studies, often involving small numbers of patients, have investigated this. Clinical, mycological, serological and radiological parameters, all or in combination have been used in clinical trials and case series to evaluate the

efficacy of oral and parenteral antifungals [6–11] and in documentation of disease recurrence [5,12–15]. Nevertheless, there are no consensus definitions on what constitutes disease relapse in CPA. The optimal duration of treatment in CPA is also not known, and it is thought that treatment for only 6 months may be associated with recurrence [12]. Recent guidance suggests extending the course to at least 9 months, and considering long-term treatment [1] in an effort to prevent recurrence. Our practice is to continue antifungal treatment for longer than 1 year, if tolerated, especially in patients with extensive disease. However, prolonged treatment is often associated with high cost and toxic side effects.

Identifying patients at low risk of relapse could allow earlier treatment discontinuation. In this study, we aim to identify risk factors for disease relapse following cessation of antifungal therapy in CPA.

2. Materials and methods

2.1. Patients

This audit involved retrospective review of data of patients with CPA at the National Aspergillosis Centre (NAC), Manchester, UK. Patients on antifungal treatment for whom therapy was discontinued for at least

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one month between August 2009 and May 2017 were enrolled. The patients were followed for a minimum period of 4 months and a maximum of 12 months and their outcome evaluated. When less than 12-month follow-up was available, patients were censored at the time of last follow-up. All patients met previously described CPA diagnostic criteria involving a combination of characteristics: pulmonary disease lasting at least 3 months with a consistent appearance in thoracic imaging (preferably by CT), direct evidence of *Aspergillus* infection or an immunological response to *Aspergillus* spp. and exclusion of some alternative diagnoses [1,2].

2.2. Data collection and retrieval

Collected data for each patient included: 1) Baseline information: age, sex, key underlying pulmonary and systemic conditions, radiological findings at the time of discontinuation of therapy; 2) type and duration of prior antifungal therapy; 3) reason for discontinuation of antifungal therapy (intolerance, therapy failure, resistance, patient preference); 4) Relapse, as defined below, within 12 months of stopping treatment; and 5) death.

The drug information (date of discontinuation, dose, and reason for discontinuation), pertinent clinical information, *Aspergillus* serology, sputum microbiology (microscopy, PCR, galactomannan and culture), radiographic findings and antifungal treatment information were extracted from the patients' notes.

2.3. Definitions

Relapse was defined as a deterioration in two of the following parameters: clinical, radiological, serological, or sputum microbiological markers of CPA activity. Clinical deterioration was any deterioration in systemic or respiratory symptoms, as reported by the patient and documented in the patient's notes. Radiological deterioration was defined as a worsening of respiratory imaging, either chest X-ray or chest CT scan, according to the reporting radiologist. Clinical and radiological deterioration should not have been attributable to other disease processes, notably concurrent pulmonary infection (e.g. bacterial super-infection or non-tuberculous mycobacterial infection), overt deterioration in underlying disease (e.g. sarcoidosis, rheumatoid arthritis or lung cancer) or toxicity of non-antifungal drugs. Serological deterioration was defined as any increase in *Aspergillus* IgG. Microbiological deterioration was defined as a new positive culture of *Aspergillus* from respiratory secretions or a positive *Aspergillus* PCR or galactomannan, deemed in the opinion of the treating physician to represent a significant result. The clinical decision of the treating physician to re-institute antifungal therapy was used as a surrogate marker of relapse.

2.4. Statistical analysis

Results were presented in terms of means, ranges and standard deviations for continuous data and medians and ranges for non-normally distributed variables. Pearson's chi-squared tests and Fisher's exact probability tests were performed as appropriate for categorical variables to assess for associations between relapse, radiological and clinical (co-morbidities), demographic characteristics, previous triazole therapy and reasons for discontinuation of treatment. Duration of therapy before discontinuation was assessed using Mann-Whitney *U* test and age was assessed using an independent *t*-test. Logistic regression analyses were performed with multiple covariates to determine independent predictors. Odds ratios and 95% confidence intervals (CIs) were recorded. Kaplan-Meier analyses and log-rank tests were used to assess the relationship between baseline variables of interest and the time to relapse for variables that had a significant difference in the rates of relapse. Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA). All tests were two-tailed and a $p \leq .05$ was considered statistically significant.

2.5. Ethics

As this study was a retrospective service evaluation, patient consent was waived. All the principles of confidential transfer and handling of patients' identifiable information were observed.

3. Results

Antifungal therapy was discontinued in 102 patients during the audit period. Demographics and underlying disorders are shown in Table 1. At the time of diagnosis, 45 (44%) patients were found to have bilateral disease on lung imaging, and 76 (75%) patients presented with (an) aspergilloma(s) within the cavity(ies). Of the 76 patients with aspergillomas, 42 (55%) had multiple aspergillomas, and the remaining 34 (45%) had a single aspergilloma.

The median duration of continuous triazole therapy before discontinuation of therapy was 19 (range: 1–106) months. At the time of discontinuation of therapy, 61 (60%) patients were on voriconazole, 31 (30%) on posaconazole, 8 (8%) on itraconazole and 2 (2%) patients were on isavuconazole for maintenance therapy. Two (2%) patients

Table 1
Demographic, clinical, radiological, and antifungal therapy data of the 102 CPA patients whose therapy was discontinued.

Characteristics	Number (percent)
Male	61 (60)
Female	41 (40)
Age (years) (mean \pm SD)	63.7 \pm 11.5
Primary underlying conditions	
Chronic obstructive pulmonary disease	26 (26)
Tuberculosis	21 (21)
Non-tuberculous mycobacterial infection	9 (9)
Allergic bronchopulmonary aspergillosis	8 (8)
Pneumothorax	8 (8)
Lobectomy	7 (7)
Rheumatoid arthritis	7 (7)
Asthma without ABPA or SAFS	5 (5)
Sarcoidosis	3 (3)
Asbestosis	2 (2)
Sub-acute invasive pulmonary aspergillosis	2 (2)
Community acquired pneumonia	1 (1)
Severe asthma with fungal sensitisation (SAFS)	1 (1)
None	2 (2)
Previous antifungal (prior to discontinuation)	
Itraconazole	75 (75)
Voriconazole	92 (92)
Posaconazole	35 (35)
Isavuconazole	2 (2)
Reasons for discontinuation	
Adverse events	71 (71)
Resistance	20 (20)
Resistance and adverse events	5 (5)
Clinical failure	5 (5)
Clinical stability	1 (1)
Re-commencement of antifungal therapy over 12 months (n = 102)	
No	59 (58)
Yes	43 (42)
Antifungals re-commenced (n = 43)	
Itraconazole	2 (5)
Voriconazole	2 (5)
Posaconazole	26 (60)
Isavuconazole	8 (19)
Intravenous antifungals	5 (12)
Relapse criteria (n = 43)	
Clinical	34 (33)
Radiological	12 (12)
Serological	9 (9)
Microbiological	6 (6)
≥ 2 of the above criteria	21 (21)

had been treated with all four azoles, 26 (26%) patients with 3 agents, 41 (40%) patients with 2 agents, and 33 (32%) patients had been treated with only one antifungal agent. The reasons for discontinuation of therapy are listed in Table 1.

Of the 102 patients, 59 (58%) remained off therapy for the whole 12-month follow-up period. Of the remaining 43 (42%) patients whose therapies were re-commenced, 34 (33%) had significant clinical deterioration, 12 (12%) patients had worsening radiological parameters, 9 (9%) patients had serological deterioration, and 6 (6%) patients had mycological relapse. Twenty-one (21%) patients met our definition of relapse, 31% of those with bilateral and 11% of those with unilateral disease (Table 2). Posaconazole was commenced in 26 of the 43 patients (60%), isavuconazole in 8 (19%) patients, voriconazole and itraconazole in 2 (5%) each, and 5 (12%) were initiated on short-course intermittent intravenous antifungal agents (Table 1). The median duration patients were off therapy before re-commencement of therapy was 4 (range: 1–11) months.

The demographic, clinical, radiological characteristics and antifungal therapy data of the 102 patients stratified to relapse and non-relapse

Table 2
Univariate analysis for risk factors for relapse of chronic pulmonary aspergillosis.

Parameter	Total (n = 102)	Non-relapse (n = 81)	Relapse (n = 21)	p-Value
Age, median (range)	65 (33–91)	65 (35–91)	63 (33–83)	0.46
Male	61 (60)	48 (79)	13 (21)	0.83
Female	41 (21)	33 (81)	8 (20)	
Chronic obstructive pulmonary disease	26 (26)	21 (81)	5 (19)	0.38
Tuberculosis	21 (21)	19 (91)	2 (10)	
Non-tuberculous mycobacterial infection	9 (9)	6 (67)	3 (33)	
Allergic bronchopulmonary aspergillosis	8 (8)	7 (88)	1 (13)	
Pneumothorax	8 (8)	5 (63)	3 (38)	
Rheumatoid arthritis	7 (7)	7 (100)	0 (0)	
Lobectomy	7 (7)	5 (71)	2 (29)	
Asthma without ABPA or SAFS	5 (5)	3 (60)	2 (40)	
Sarcoidosis	3 (3)	2 (67)	1 (33)	
Sub-acute invasive pulmonary aspergillosis	2 (2)	2 (100)	0 (0)	
Asbestosis	2 (2)	0 (0)	2 (100)	
Severe asthma with fungal sensitisation	1 (1)	1 (100)	0 (0)	
Community acquired pneumonia	1 (1)	0 (0)	1 (100)	
No underlying pulmonary disorder	2 (2)	1 (1)	1 (5)	
Bilateral CPA disease	48 (51)	33 (69)	15 (31)	0.01**
Unilateral CPA disease	54 (49)	48 (89)	6 (11)	
No aspergilloma	26 (31)	24 (92)	2 (8)	0.06*
Aspergilloma	76 (69)	57 (75)	19 (25)	
Single aspergilloma	33 (43)	27 (82)	6 (18)	0.23
Multiple aspergilloma	43 (57)	30 (70)	13 (30)	
Duration of therapy before discontinuation, median (range) (months)	19 (1–106)	21.3 (1–106)	15.8 (2–90)	0.35
Therapy prior to discontinuation				
Itraconazole	8 (8)	8 (100)	0 (0)	0.28
Voriconazole	61 (60)	47 (77)	14 (23)	
Posaconazole	31 (30)	25 (81)	6 (19)	
Isavuconazole	2 (2)	1 (50)	1 (50)	
Reason for discontinuation of therapy				
Adverse events	71 (70)	53 (75)	18 (25)	0.48
Triazole resistance	20 (20)	18 (90)	2 (10)	
Adverse events and triazole resistance	5 (5)	4 (80)	1 (20)	
Clinical failure	5 (5)	5 (100)	0 (0)	
Clinical stability	1 (1)	1 (100)	0 (0)	

* Close to statistical significance

** Statistically significant.

groups are summarised in Table 2. Patients with bilateral disease and patients with one or more aspergillomas were more likely to relapse on univariate analysis. Age, sex, underlying pulmonary disorder, duration of previous triazole antifungal therapy, reasons for discontinuation of therapy and presence of a single or multiple aspergilloma were not associated with relapse.

In a multivariable logistic regression analysis including bilateral/unilateral CPA disease and presence of aspergilloma, bilateral CPA disease was the only independent risk factor for relapse (Odds ratio (OR): 3.0; 95% confidence interval (CI): 1.0–8.8; $p = .044$). Presence of an aspergilloma was not a significant risk factor for relapse (OR: 2.9; 95% CI: 0.6–14.0; $p = .189$) on multivariate analysis.

Overall, 8/21 (38%) patients had early relapse (relapses occurred before or at 6 months from the time of discontinuation of therapy). All 6 patients with unilateral CPA disease who relapsed, had late relapse. In contrast, 53% (8/15) of the patients with bilateral CPA disease had early relapse (Fig. 1).

There was no difference in the time to relapse for patients with or without intracavitary aspergilloma (Fig. 2).

For patients with unilateral disease, there was no difference in the median duration of continuous prior triazole therapy between relapse and non-relapse patient groups i.e. 16.7 (8–90) months vs. 20.0 (2–106) months respectively ($U = 141$, $p = 1.000$). For patients with bilateral disease, the median duration of therapy was longer for the non-relapse compared to the relapse patients i.e. 22.8 (1–92) months vs. 15.8 (2–79) months (Fig. 3). This difference was however not statistically significant ($U = 212.5$, $p = .53$).

The overall survival was 96% (98 of 102) among this cohort. Of the 4 deaths, 3 (75%) patients were male. All patients died within the first 2 months following discontinuation of therapy. Three patients had progressive respiratory symptoms (clinical failure) but did not meet relapse criteria. The 4th patient was an 80-year-old with bilateral CPA disease, COPD with progressive respiratory symptoms (clinical failure) and worsening radiological features (CPA relapse) who died 2 months after discontinuation of therapy.

4. Discussion

Recurrence is well known to occur in CPA, but little studied. For this reason, antifungal treatment tends to be prolonged and often long-term or indefinite. Knowing which patients are at low risk of relapse will

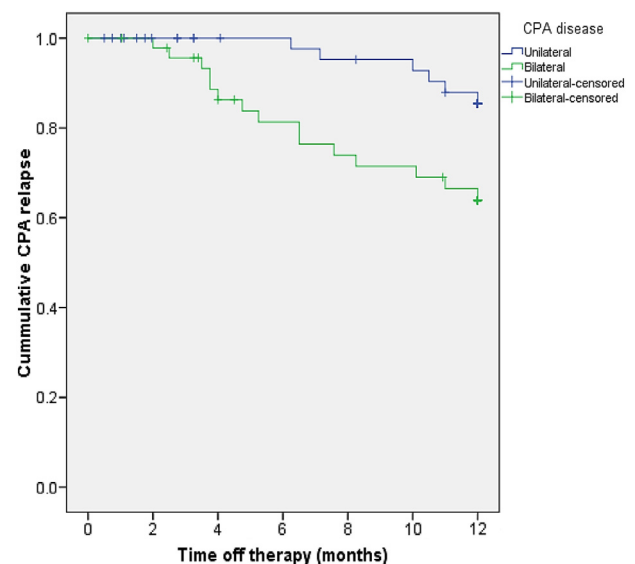


Fig. 1. Time to relapse of CPA in patients with unilateral and bilateral disease. Patients with bilateral disease were more likely to relapse than patients with unilateral disease; moreover, patients with bilateral disease appeared to relapse earlier (log rank $p = .014$).

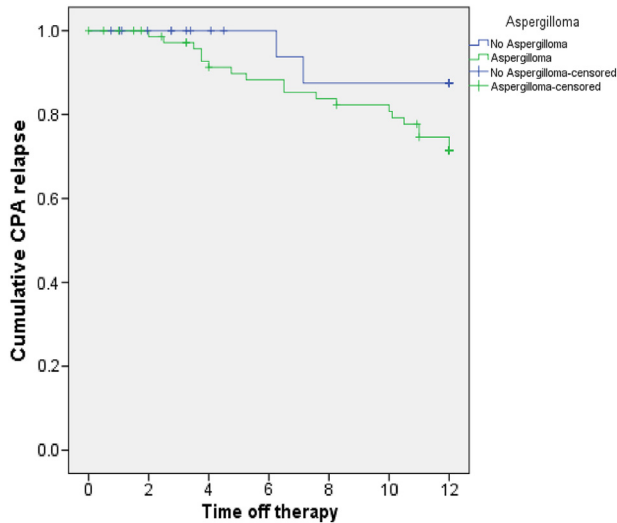


Fig. 2. Time to relapse of CPA in patients with or without intracavitary aspergilloma. There is no statistically significant difference in the time to relapse for patients with or without intracavitary aspergilloma (log rank $p = .180$).

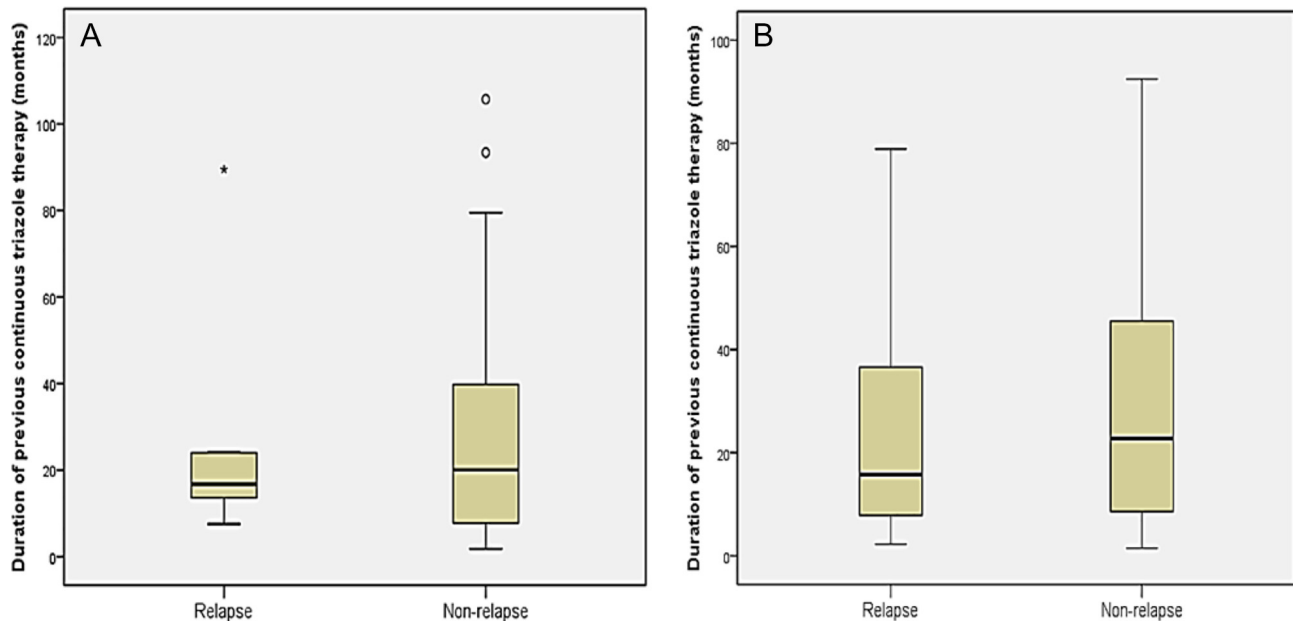
allow for earlier discontinuation of antifungal treatment, thereby limiting antifungal toxicity, cost and emergence of resistance. Our study showed that bilateral disease and, to a lesser extent, presence of an aspergilloma are the main risk factors for relapse.

Recurrence rates in CPA vary from 17% to 38% in various studies. In a prospective trial of itraconazole for 6 months vs. placebo, 5 of 13 (38%) patients who had initially responded had a relapse after a median of 11 months off treatment [12]. A prospective trial of voriconazole, in which the mean duration of treatment was 8.3 months, resulted in radiological or mycological relapse in 3/18 (17%) of patients. Finally, a retrospective study of patients who were mainly treated with itraconazole showed a 36% recurrence rate (14 out of 39), after a median duration of

treatment more than 2 years [5]. Relapse can even occur following surgical resection of CPA. In a retrospective survey 30 patients who underwent surgery for CPA in our centre, relapse was noted in 8 patients (26%) [14]. Relapse after surgery carries a poor prognosis [14].

There is no consensus definition for relapse in CPA. Different studies employ different criteria to define relapse. The difficulty arises from the frequent presence of comorbidities including bacterial superinfection and concomitant non-tuberculous mycobacterial infection to which these patients are susceptible. In addition, deterioration of the underlying pulmonary condition (e.g. COPD) often plays a role. A variety of criteria were used in the aforementioned studies. In real-life clinical practice, a combination of clinical, radiological and microbiological parameters often leads the clinician to suspect a recurrence. In our study, restarting antifungal therapy was most often associated with a clinical deterioration only, without evidence of radiological, microbiological or serological relapse. Using our definition of relapse, about half of the patients who were restarted on antifungal therapy did not fulfil this definition of relapse of CPA.

To date, only one study has focused on defining risk factors for recurrence in CPA [5]. In a retrospective study of patients with CPA who were mainly treated with itraconazole, presence of disease in more than one lobe on CT scan, younger age and longer duration of treatment to achieve remission were associated with a higher risk of relapse. Multilobar disease appeared to be the strongest risk factor. In our study, we used bilateral disease as a marker of extent of disease, as more than half of patients had disease involving both lungs. In addition, we found an association between the presence of aspergilloma and recurrence. Both bilateral disease and presence of aspergillomas are established markers of higher CPA burden. Regarding duration of treatment, patients with bilateral disease who did not relapse were treated for almost 2 years, whereas duration of treatment did not affect relapse rate in unilateral disease. Therefore, treatment duration of 2 years may be recommended for patients with bilateral CPA, whereas a shorter course, e.g. 6–18 months may be adequate for most patients with low-burden disease. Genetic polymorphisms [16–18] and subtle



Chronic pulmonary aspergillosis relapse status

Fig. 3. Duration of prior triazole therapy. Median duration of therapy in patients with CPA who relapsed vs. those who did not. Unilateral disease (A): 16.7 (8–90) months in the relapse group vs. 20.0 (2–106) months in the non-relapse group ($U = 141, p > .99$) and bilateral disease (B) 22.8 (1–92) months for non-relapse vs. 15.8 (2–79) months for relapse ($U = 212.5, p = .53$).

immunodeficiency states [19] have been associated with the development of CPA. Further research is required to determine if there is a link between these conditions and risk of relapse of CPA.

Our study has several limitations. First, our definition of relapse did not include radiological confirmation in every case, as in the study by Koyama and colleagues [5]. However, in patients with CPA, radiological deterioration may lag behind clinical relapse and early changes are challenging to interpret. Second, it was a retrospective study that was characterised by the typical methodological limitations. Third, our cohort had variable durations of treatment, and antifungals were stopped mainly because of side effects or resistance development, and not because of achieving remission of disease. Although the median duration of continuous triazole therapy before discontinuation of therapy was 19 months, some patients may have actually had persistent disease and not a recurrence. This could have led to an overestimate of the rate of relapse.

In conclusion, bilateral disease is a risk factor for relapse after treatment discontinuation in CPA. A longer duration of treatment, e.g. 24 months, may be associated with a lower rate of relapse in extensive CPA, whereas more limited disease may respond to shorter courses.

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Declaration of competing interest

Dr. Denning and family hold Founder shares in F2G Ltd., a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen, Quintiles, Pulmatrix, Pulmocide and Zambon. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and the British Society for Medical Mycology Standards of Care committee.

FB, AO, CH, FP and CK: None to declare.

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