

ORIGINAL ARTICLE

An evaluation of nebulised amphotericin B deoxycholate (Fungizone®) for treatment of pulmonary aspergillosis in the UK National Aspergillosis Centre

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Summary

Antifungal treatment options for allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) are largely limited to itraconazole based on the outcome of randomised controlled trials. It is unclear if nebulised amphotericin B deoxycholate (Fungizone®) is a viable therapeutic option. We evaluated the safety and efficacy of nebulised Fungizone® in the long-term treatment of various forms of pulmonary aspergillosis. We assessed the records of 177 patients with various forms of pulmonary aspergillosis attending the National Aspergillosis Centre in Manchester who had received Fungizone®. Patients first received a challenge test with nebulised Fungizone® in hospital with spirometry pre/post-Fungizone® and nebulised salbutamol given pre-Fungizone®. Tolerability and changes in Aspergillus IgE, Aspergillus IgG and total IgE were evaluated. Sixty-six per cent (117/177) were able to tolerate the test dose of Fungizone® and in all cases, the reason for discontinuation of the first test dose was worsening breathlessness. Twenty six (21%) stopped therapy within 4–6 weeks, and the commonest reason cited for discontinuation of therapy was increased breathlessness, hoarseness and cough. Eighteen (10.2%) patients continued the Fungizone® for >3 months of which 5 (27.8%) recorded an improvement in total IgE, Aspergillus-specific IgE and Aspergillus IgG. Eleven had ABPA, four had SAFS, two had Aspergillus bronchitis and one had Aspergillus sensitisation with cavitating nodules. Among these 18 patients, sputum fungal culture results went from positive to negative in five patients, became positive in one patient, remained positive in three patients, and remained negative in seven patients. Nebulised Fungizone® appears to be a poorly tolerated treatment for pulmonary Aspergillosis with high dropout rates. There appears to be both clinical and serological benefits following sustained treatment with nebulised Fungizone® in some patients.

KEYWORDS

allergic bronchopulmonary aspergillosis, amphotericin B, challenge test, Fungizone®, severe asthma with fungal sensitisation, tolerability

1 | INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) are immunologically driven pulmonary disorders characterised by hypersensitivity to *Aspergillus* species. These eosinophilic lung diseases are characterised by T-helper lymphocyte activation with the recruitment of inflammatory mediators and elaboration of IgE.¹ ABPA is the most significant manifestation of allergic aspergillosis² and is estimated to affect over 3.5 million persons in 43 countries with the highest prevalence rates being recorded in India.³ Asthma and cystic fibrosis are the commonest conditions which predispose to the development of ABPA, occasional patients have no underlying disease.⁴ The features of ABPA are a positive immediate skin test or elevated serum total or *Aspergillus* IgE antibody and an exacerbation of the underlying pulmonary disease manifesting with cough, wheezing, expectoration of mucus plugs, haemoptysis and fever.⁵ SAFS occurs in patients with severe (poorly controlled) asthma with either a positive skin prick test result for fungi or elevated antifungal IgE of at least 0.4 kU/L and/or total serum IgE concentration <1000 kU/L.⁶ Mucoid impaction and bronchiectasis which characterise ABPA are not found in those with SAFS.⁷ The diagnosis of SAFS is limited to those with severe asthma while ABPA can occur in those with mild or moderate asthma. *Aspergillus* bronchitis is a discrete clinical entity that describes patients with structural lung disease and repeated isolation of *Aspergillus* from sputum or positive PCR.⁸ Patients may have elevated *Aspergillus* IgG and a history of recurrent chest infections.⁹

Early diagnosis and treatment of *Aspergillus* pulmonary disease reduces morbidity and probably limits parenchymal damage as well as disease progression. Immune suppression with corticosteroids is the mainstay of therapy in ABPA and SAFS,¹⁰ which increases the *Aspergillus* load in the airways.¹¹ Antifungals are thought to act as steroid-sparing agents by limiting mycelium proliferation thus decreasing the antigen burden and subsequent immune response.⁵ Patients with *Aspergillus* bronchitis have been shown to have a major response to antifungal therapy.⁹

At the National Aspergillosis Centre in Manchester UK, itraconazole is used as the first-line antifungal for management of ABPA

in line with results of two randomised controlled trials.^{12,13} The general strategy is to limit steroid therapy for ABPA in view of the immunosuppressive and metabolic adverse effects associated with chronic use. When there is intolerance to itraconazole, antifungal resistance or progression of disease despite treatment, nebulised amphotericin B deoxycholate (Fungizone®) is utilised as a second-line treatment option for patients who were able to tolerate the initial administration. In our centre, itraconazole is the only triazole antifungal which is approved for treatment of ABPA or SAFS. We reported some benefit in 21 patients in 2015,¹⁴ and there have been a few case reports of prompt clinical and physiological response following the administration of nebulised amphotericin B in patients with ABPA⁸⁻¹⁰ but larger studies are lacking. Some of the proposed benefits of nebulised amphotericin include its potential to achieve higher lung tissue concentrations with minimal systemic distribution and treat azole-resistant strains of *Aspergillus*.⁹ Liposomal amphotericin B also contains phospholipids and cholesterol which may play a role in improving pulmonary compliance as seen in natural surfactant.¹⁰

We carried out a review of the database of patients with ABPA who received nebulised Fungizone® at the National Aspergillosis Centre in Manchester, United Kingdom.

2 | MATERIALS AND METHODS

This was a retrospective service evaluation of 177 patients with various forms of pulmonary aspergillosis attending the ABPA clinic in the National Aspergillosis Centre Manchester between June 2014 and December 2018. The ABPA clinic is run with the assistance of respiratory physiotherapists who facilitate the provision of Fungizone® treatment to ABPA patients as second-line therapy. Our general approach to safely administering any nebuliser to our patients was described in detail previously.¹⁵

Due to risk of intolerance/bronchospasm, patients first receive a challenge test with nebulised Fungizone in the hospital setting with spirometry pre/post-Fungizone®. To improve tolerability, a nebulised short acting beta agonist is given prior to

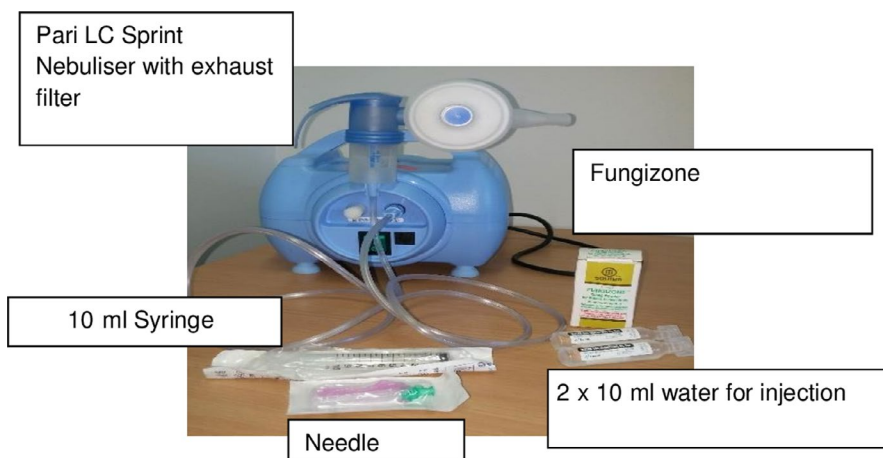
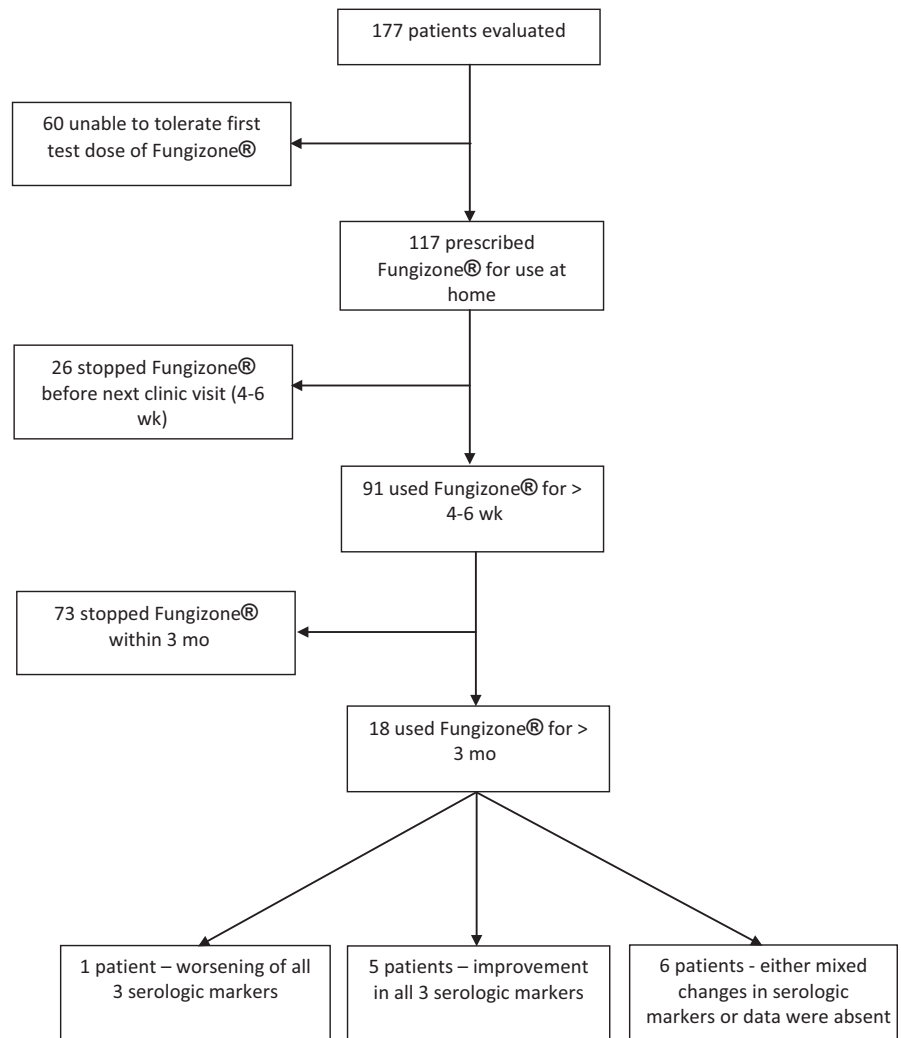


FIGURE 1 Pari LC Sprint nebuliser with supplies needed to administer Fungizone®

FIGURE 2 Patient flowchart showing Fungizone tolerability, discontinuation and outcomes



administration of Fungizone® (10 mg in 4 mL water for injection) by simple jet nebuliser (Figure 1). Fungizone® is administered via a breath-enhanced jet nebuliser (Pari LC Sprint). To further reduce environmental contamination/ collateral exposure, the nebuliser is fitted with an exhaust filter attachment and patients are advised to nebulise in isolation in a room with the window open. Nebulisation time is approximately 7 minutes but depends on patient factors, for example minute volume. Fungizone® must be refrigerated and used needles require specialised disposal. Typically patients add 10 mL water for injection to 50 mg Fungizone® powder, draw back 2 mL/10 mg to which they add a further 2 mL of water for injection to achieve a fill volume of 4 mL for the 10 mg dose. Following successful completion of the challenge test, a prescription of Fungizone® at a dose of 10 mg twice a day is provided to the patients and a follow-up appointment is arranged in 4-6 weeks' time.

We assessed the patients' baseline spirometry in addition to tolerability of the first test dose and rate/reasons for discontinuation of Fungizone®. Changes in their serologic markers (Aspergillus IgE, Aspergillus IgG as well as total IgE) as well as sputum conversion rates were evaluated.

3 | RESULTS

The results of 177 patients were extracted and analysed. There were 80 (45.2%) males with mean age of 63.9 ± 13 and age range of 23-88. Their baseline FEV1 and FVC ranged from 0.94 to 2.97 L and 1.33 to 5.15 L, respectively. Sixty-six per cent (117) were able to tolerate their first test dose, of whom 26 (21%) stopped using the nebulised therapy before their next clinic visit (usually 4-6 weeks later). Among the patients who did not tolerate the first test dose, the duration of Fungizone® they actually received varied greatly with median time being 2 minutes. In all cases, the reason for discontinuation of the first test dose was worsening breathlessness. Among those who stopped using the nebulised therapy before their next clinic visit, reasons cited included increased breathlessness (8), wheeze (7), bronchospasm (6), sore throat/voice (4), coughing (4), chest tightness (3), light-headedness/dizziness (2), diarrhoea (2), fatigue (2), mouth blisters/ulcers (2), headaches (2) and nausea/vomiting (2). There were singular mentions of an admission to hospital with wheeze, poor saturations, reduced exercise capacity, worsening sinus/eye pain, haemoptysis, back pain, dry mouth, abdominal pain, tinnitus, blurred vision, muscle aches,

TABLE 1 Characteristics of the patients who were able to tolerate Fungizone® therapy for >3 mo

Sex	Age (years)	Aspergillosis diagnosis	Fungizone course time	Challenge spirometry FEV1 pre- and post-Fungizone (L)		Change in value		
						Aspergillus IgE (kAU/L)	Aspergillus IgG (mg/L)	Total IgE (kU/L)
Male	67	SAFS	4 y ongoing	1.58	1.59	-1.5	3	30
Female	72	ABPA	>3 y ongoing	0.95	0.95	-19.3	-26	-400
Male	48	Aspergillus bronchitis	3 y	1.94	1.61		7	1
Male	55	SAFS	2 y ongoing	2.9	2.95	-4.2	0	-66.7
Female	60	SAFS	>2 y	2.3	2.23	0.1		3.6
Male	55	ABPA	1 y	0.93	0.9	-5.5	8	-357
Female	58	ABPA	8 mo	2.12	2.04			
Female	26	ABPA	9 mo ongoing	2.13	2.3	-10.8	-9	-326
Male	62	Aspergillus bronchitis	3 mo then stopped. Restarted, now 6 mo ongoing	0.94	0.78	-2.19	-25	-252
Male	58	ABPA	4 y	2.42	2.28	-40.9	11	-440
Female	57	SAFS	6 y	1.71		0		-3.2
Male	50	ABPA	18 mo	1.7	1.47			140
Female	61	SAFS	18 mo	1.76	1.71	0.4		100
Female	57	ABPA	12 mo ongoing	2.39	2.33	-0.31		-210
Female	34	Aspergillus bronchitis	7 mo	2.97	2.8	0.04	21	4.7
Female	50	ABPA	1 y	1.66	1.6	-1	-149	-239
Male	73	ABPA	6 mo	1.31	1.12	-2.4	-6	-884
Female	46	ABPA	4 mo	1.84	1.82	3.8		-7925
							Better	
							Worse	
							Absent data	

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; MBL, Mannose-binding lectin deficiency; SAFS, severe asthma with fungal sensitisation.

skin wheals, burning sensation, palpitations, generalised tremors and the inconvenience of the equipment. The patient who got admitted into hospital passed the Fungizone® challenge in clinic but developed increasing wheeziness subsequent to this and was managed with steroids, nebulised short-acting beta agonists and anticholinergic agents. We were unable to obtain specific details of why three patients were unable to tolerate Fungizone®.

Eighteen (10.2%) patients continued nebulisation of Fungizone® 10 mg twice a day for >3 months (Figure 2). Eleven had ABPA, five had SAFS and two had *Aspergillus* bronchitis (Table 1). Treatment courses ranged from 4 months to 4 years. At their first clinic follow-up, there were reported benefits with less sputum production (7), fewer sinus symptoms (2), reduced dyspnoea (2), improved exercise tolerance (2) and reduction in prednisolone maintenance dose (1) and one (with nodules) demonstrated radiological improvement. The improvement in exercise tolerance was subjective and based solely on patient reports.

Of the 18 patients, three had interruptions to the Fungizone® therapy which was restarted following clinical deterioration off

therapy (two of whom had a dose reduction to 12.5 mg once daily). The interruptions in therapy ranged from 1 to 4 months.

Four patients discontinued therapy as there was no perceived clinical benefit, and eight patients have remained on treatment. Fungizone® was discontinued for two patients with the aim of monitoring their progress off therapy. Subsequently, one of the two patients was reviewed and deemed to be stable off therapy and so Fungizone® was not restarted. The other patient will be reviewed at a future date. One patient never returned and was lost to follow-up.

Of 11 patients with baseline *Aspergillus* IgG, all had follow-up results and of these five showed a decline (signifying improvement), five showed an increase (signifying deterioration) and the *Aspergillus* IgG remained unchanged in one patient. Of 13 patients with baseline *Aspergillus* IgE, all had follow-up results and of these 11 showed a decline, three showed an increase and the *Aspergillus* IgE remained unchanged in one patient. Of 17 patients with baseline total IgE, all had follow-up results and of these 11 showed a decline and six showed an increase. A decline in all three parameters, that is total IgE, *Aspergillus*-specific IgE and *Aspergillus* IgG, was recorded

in 5 (27.8%) of the patients who received >3 months of Fungizone®. In 1 patient, all three serologic markers increased. In six patients, there were either mixed changes in all three serologic markers or data were absent (Figure 2). In all patients, *Aspergillus fumigatus* was the only species recovered from fungal culture over time. Among the patients who received Fungizone® for >3 months, sputum fungal culture results went from positive to negative in five patients, became positive in one patient, remained positive in three patients and remained negative in seven patients. One of the patients who had a positive sputum test result did not produce any further sputum samples. No sputum test results were found for one non-productive patient.

4 | DISCUSSION

We found high intolerance rates among this cohort who received nebulised Fungizone® primarily for the treatment of ABPA. For those who received Fungizone® for up to 3 months, improvement in serologic markers were seen in almost a third with reported improvements in symptoms in addition to a reduction in prednisolone maintenance dose and radiological improvement in one person. Nebulised medications have the inherent advantage of achieving topical delivery while avoiding systemic toxicity issues such as nephrotoxicity that is traditionally associated with parenteral use of amphotericin B. The utility of nebulised amphotericin in dramatically reducing invasive fungal infections has been previously demonstrated in a randomised controlled trial among neutropenic patients.¹⁶ This trial involved the use of liposomal amphotericin B (LAmB) which contains cholesterol and phospholipids that confer on it properties similar to natural surfactant.¹⁷ Research into the pharmacokinetics of LAmB suggest that its concentrations within the proximal airway following once a week nebulisation remain high enough to inhibit the growth of *Aspergillus* spp. (>2 µg/mL) for up to 14 days with no significant systemic absorption detected.¹⁸

A previous assessment of Fungizone® use in our centre involving 21 adult asthmatics with SAFS (11) and ABPA (10) showed clinical benefit in three (14.3%) with improvements recorded in overall mean Juniper Asthma Quality of Life Questionnaire (AQLQ-J) scores, mean FEV1 and overall asthma control.¹⁴ Seven (33%) of the patients failed the initial challenge with Fungizone® due to bronchospasm with 11 (52.4%) discontinuing therapy within 12 months due to delayed bronchospasm, lack of clinical benefit and equipment issues.¹⁴

There has been sustained interest in defining the role of nebulised amphotericin in the treatment of ABPA. A pilot randomised controlled trial involving twenty one subjects with ABPA who were randomised to receive either nebulised amphotericin B plus nebulised budesonide or nebulised budesonide alone reported significantly lower exacerbations in the amphotericin B arm after 1 year.¹⁹ Interestingly, three patients developed bronchospasm after the first dose of nebulised amphotericin B; however, subsequent doses were well tolerated and none of the study drugs were discontinued in all 21 patients.¹⁹ There have been a few case reports describing the use

of amphotericin B in the setting of ABPA.²⁰ Laoudi and colleagues reported good clinical, biological and functional response following a combination of nebulised amphotericin B (at 5 mg twice a day) with nebulised budesonide for treatment of ABPA in three patients with cystic fibrosis aged 7, 12 and 13 years of age.¹⁷ Another case report described the efficacy of nebulised LAmB (25 mg twice weekly) as maintenance therapy following the discontinuation of glucocorticoid therapy in a 67-year old man with prednisolone-dependent ABPA.²¹ Treatment with either nebulised Fungizone® (25 mg 3× a week) or amphotericin deoxycholate LAmB (50 mg twice weekly) was reported to be successful in achieving steroid withdrawal without ABPA relapse within 12 months in six of seven cystic fibrosis patients.²²

Amphotericin B is a polyene antifungal that is derived from the fermentation of *Streptomyces nodosus*, an actinomycetes found in the soil. The action of amphotericin B could be either fungistatic or fungicidal depending on the concentration of the drug, the pH and the fungus involved.²³ The value of nebulised amphotericin B is likely to be related its direct activity on fungi thus reducing the antigen burden arising from fungal colonisation of the airways. There are few data on the efficacy of nebulised amphotericin B in SAFS.¹⁴ Aside from amphotericin and itraconazole, benefits have been demonstrated in the use of other antifungals among patients with moderate to severe asthma who many have failed standard therapy. An evaluation of 41 patients with asthma and culture proven airway mycosis treated with either terbinafine, fluconazole, itraconazole, voriconazole or posaconazole for 4->12 weeks together with standard bronchodilator and anti-inflammatory agents showed improved asthma control and significantly reduced serum IgE levels and blood eosinophil counts when compared to those who had standard therapy with no antifungals.²⁴ Interestingly, a reduction in medication use and symptoms as well as relapse rates was demonstrated among this cohort as duration of therapy increased. There have been studies comparing triazole antifungals to steroids for treatment of ABPA. A randomised controlled trial comparing itraconazole to prednisolone for treatment of acute-stage ABPA revealed that although prednisolone was more effective in inducing response than itraconazole, itraconazole had a better side effect profile and was efficacious in a considerable number.²⁵ In another randomised controlled trial by the same group, voriconazole monotherapy was found to be effective and safer than glucocorticoids for treatment of ABPA.²⁶ This trial revealed similar rates of exacerbations among subjects after 1 and 2 years with similar percentage decline in IgE and change in lung function in the two groups after 6 weeks of treatment.

A significant proportion of the patients in our cohort did not pass the initial challenge test with Fungizone® and this is likely to be due to bronchospasm. Bronchospasm is mediated by anaphylatoxins that stimulate the degranulation of mast cell or basophils resulting in bronchial constriction. Nebulised medications are less likely to be tolerated by persons with low baseline pulmonary function.²⁷ Our earlier service evaluation found bronchospasm to be the main reason for poor efficacy of Fungizone® therapy among 21 adult asthmatic patients with ABPA and SAFS.¹⁴ Nebulisers are effective in producing respirable aerosols of drugs such as amphotericin B which are

smaller than 5 µm and can get deep into the lungs. To mitigate the bronchospasm that can arise from nebulised amphotericin B, our patients received nebulised salbutamol prior to the Fungizone® challenge test. They were also instructed to use nebulised salbutamol prior to the administration of Fungizone® at home. However, the rate of intolerance of Fungizone® was high despite this measure. It is not clear if LAmB causes less bronchoconstriction than Fungizone® as no direct comparisons have been made between these two medications.

The serologic markers of ABPA include total serum IgE >1000 IU/mL, elevated specific IgE to *A. fumigatus* and/or IgG to *A. fumigatus*.^{28–30} To diagnose SAFS, patients need to have severe asthma and with serologic markers which do not meet the criteria for ABPA in addition to a positive immediate skin test or in vitro specific IgE to ≥1 filamentous fungus.^{28,31,32} Monitoring of the total IgE is vital as it has been shown to decline and increase with response and exacerbation.³³ However, the trend of *Aspergillus*-specific IgE is unpredictable and has limited utility as a monitoring index.³³ Our study showed an improvement in almost a third of the patients who were able to tolerate Fungizone® for >3 months which is reflective of response to this therapy. This suggests that Fungizone® may hold benefits for patients with ABPA and SAFS whose respiratory function is not compromised by bronchospasm resulting from its use. However, the high drop off rate is likely to limit widespread use of this medication among these groups of patients. Prospective studies may be able to delineate patient groups that are less likely to experience bronchospasm and promote Fungizone® as a plausible treatment option for ABPA and SAFS. Further research is required to establish the optimal amphotericin formulation, dose and delivery system. Alternatively, development of other antifungal agents for these indications would be valuable and two companies have compounds in phase 2 development with hand-held metered dose inhalers.^{34,35}

This study has several limitations. First, this was a retrospective study that had the methodological disadvantages of this particular study design. Second, radiological imaging and spirometry was not routinely carried out on patients who tolerated Fungizone treatment so we are unable to comment on this. Third, only a relatively small number of patients were eventually able to tolerate Fungizone therapy for more than 3 months.

In conclusion, nebulised Fungizone® appears to be a poorly tolerated treatment for pulmonary Aspergillosis with high dropout rates. There appears to be both clinical and serological benefits following sustained treatment with nebulised Fungizone® in some patients.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

Denning and family hold Founder shares in F2G Ltd., a University of Manchester spin-out antifungal discovery company, in Novocyt

which markets the Myconostica real-time molecular assays. He acts or has recently acted as a consultant to Scynexis, Cidara, Biosergen, Quintilles, Pulmatrix and Pulmocide. 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. All other authors: none to declare.

AUTHOR CONTRIBUTIONS

PL and AAO conceived the ideas; PL collected the data; PL, AAO and DWD analysed the data; AAO and PL led the writing. DWD reviewed the manuscript for intellectual content.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this was a service evaluation audit.

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