

# Period Prevalence of Allergic Bronchopulmonary Mycosis in a Regional Hospital Outpatient Population in Ireland 1985-88\*

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## Summary

The period of prevalence, 1988 inclusive, of Allergic Bronchopulmonary Aspergillosis (ABPA) and Allergic Bronchopulmonary Candidiasis (ABPC), the two most frequently reported forms of allergic Bronchopulmonary Mycosis (ABPM), was investigated in an Irish regional hospital respiratory medicine outpatients, catchment area population 536,000. ABPM was defined by the presence of a majority of seven criteria: asthma, eosinophilia, elevated IgE, antibodies to *Aspergillus Fumigatus* or *Candida Albicans*, immediate skin test reaction to either fungus, culture of either fungus in sputum, and otherwise unexplained transient or permanent lung field x-ray abnormalities. New referrals were investigated for ABPM if they had asthma and eosinophilia, or asthma and lung field x-ray abnormalities. Fourteen patients with ABPM were identified from a total of 1390 new referrals, a period prevalence of just over one per cent. It is concluded that (1) ABPM is a relatively common disorder in an Irish regional hospital respiratory medicine outpatient population and (2) ABPC constitutes a higher proportion of this disorder than previously considered.

## Introduction

Allergic Bronchopulmonary Aspergillosis (ABPA) is an allergic complication of chronic asthma characterised by serum antibodies to the fungus *Aspergillus Fumigatus* (AF), eosinophilia and transient or permanent lung field chest x-ray changes. It was originally described<sup>1</sup> in the United Kingdom in 1952. Its distribution is now considered to be worldwide<sup>2,3,4,5</sup>. Other fungi, most frequently *Candida Albicans* have also been reported as causing this syndrome<sup>6,7,8</sup> in chronic asthmatics i.e. serum antibodies to the particular fungus, eosinophilia, and transient or permanent lung field chest x-ray changes. Accordingly the name of the syndrome has been broadened to the more inclusive term Allergic Bronchopulmonary Mycosis (ABPM). Few epidemiological studies of ABPA or ABPM have been done. Henderson and colleagues<sup>9</sup> reported a prevalence of ABPA of 11% in a series of 46 asthmatics seen over a one year period (1965-66) in a Bristol hospital. In Delhi, India 8.1% of 407 patients with chronic respiratory disorders seen at either a research centre or a tuberculosis hospital were found to have ABPM<sup>10</sup>. The objective of our investigation was to ascertain how common ABPM is in a hospital outpatient population. Thus we investigated the period of prevalence of the most frequently reported forms of ABPM - Allergic Bronchopulmonary Aspergillosis and Allergic Bronchopulmonary Candidiasis in a regional hospital respiratory medicine outpatient clinic during the years 1985-88 inclusive.

## Patients and Methods

Patients were studied prospectively from general practitioner referrals seen at the Respiratory Medicine outpatient clinic, at the Regional Hospital, Cork, catchment area population 536,000 over the period 1985-88 inclusive. The definition of ABPM was based on the original report of ABPA by Hinson *et al*<sup>1</sup>. The criteria used were asthma, blood eosinophilia, elevated total serum IgE, serum antibodies to *Aspergillus Fumigatus* (AF) or *Candida Albicans* (C. Alb.), immediate skin test reaction to culture of either fungus in sputum, and otherwise unexplained transient or permanent lung field x-ray abnormalities. A diagnosis of ABPA or ABPC was made if 4 or more of the 7 criteria were present: asthma and serum antibodies were regarded as essential criteria for the diagnosis.

From the referred patients those with asthma and eosinophilia, or those with asthma and lung field x-ray changes (transient or permanent) were selected for further study. Over the period of investigation (1985-88) new referrals with chronic asthma were followed at the clinic at 3-6 monthly intervals. If eosinophilia or otherwise unexplained chest x-ray changes not present at first visit developed during follow-up these patients were also included in the study. (Patients with chronic asthma had at least 2 eosinophil counts and chest x-rays on average per year).

Further investigations done were total serum IgE, *Aspergillus* and *Candida* antibodies, sputum culture for fungi and immediate skin tests for AF and C.Alb. Total serum IgE was measured by the double radioimmunoassay (RIA) technique of Gleich *et al*<sup>10</sup>. Antibody to AF and C.Alb. was measured by the enzyme linked immunoassay (ELISA) technique. Antigens were obtained commercially (somatic and culture filtrate antigens of AF and somatic antigens of C.Alb.) (Mercia Diagnostics). Alkaline phosphatase conjugated anti-human IgG (Boehringer) and P-Nitrophenylphosphate (Sigma) were used in the secondary reaction. Tests were performed using a microtitre reader (Dynatech Minireader MR 590). Internal

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TABLE I  
Allergic Bronchopulmonary Fungal Disease : Clinical Data

Patient	Sex	Age	Asthma	Skin tests*		Chest x-ray changes*
				AF	C.Alb.	
ML	F	60	Yes	5mm	0	PERM
JD	F	29	Yes	3mm	0	NONE
CC	F	12	Yes	5mm	0	TR
SF	F	74	Yes	0	0	PERM
SP	F	47	Yes	0	3mm	NONE
JD	M	62	yes	3mm	0	TR
MN	F	55	Yes	8mm	0	PERM
CM	F	42	Yes	0	0	PERM
NL	F	70	Yes	3mm	3mm	PERM
DC	M	53	Yes	0	0	PERM
FH	M	53	Yes	5mm	0	PERM
ME	F	42	Yes	3mm	0	TR
MF	F	65	Yes	8mm	0	PERM
TD	F	49	Yes	5mm	0	PERM

\* Skin tests: positive reaction  $\geq$  3mm\* Chest x-ray changes: PERM = permanent  
TR = transient

positive controls (positively reacting sera) for both tests were standardised against commercially obtained positive controls (Mercia). Samples giving a positive result 1:2500 dilution or greater were deemed to be positive for antibodies to C.Alb. Results for antibodies to AF were expressed as an index or ratio – positively reacting sera gave readings that were twice or more the value of negative controls

### Results

The results are outlined in Tables I and II. Fourteen patients with Allergic Bronchopulmonary Mycosis were identified, a

period prevalence of just over 1% (14/1390) of respiratory medicine outpatients from 1985 to 1988 inclusive. Of these 14, nine had the diagnostic criteria for ABPA, three for ABPC and two had criteria of both ABPA and ABPC, a type of 'overlap syndrome'. All 14 patients had a history of asthma. Eleven (79%) had a raised index to AF, range 2.5 to 13.1. Five had elevated C.Alb titres of 1/2500 including the two 'overlap' cases. Radiological changes in the lung parenchyma were observed in twelve patients (86%) of which three were transient (21%) and eight (57%) were permanent. The transient changes were areas of consolidation or collapse/consolida-

TABLE II  
Allergic Bronchopulmonary Fungal Disease : Blood and sputum result

Patient	Antibodies* <sup>1</sup> AF (Index)	C.Alb (Titre)	IgE* <sup>2</sup> iu/ml	Blood Eosinophils* <sup>3</sup> cells/ $\mu$ litre	Sputum Culture
ML	10.7	0	1200	1500	C.Alb
JD	0	1/2500	125	490	C.Alb
CC	3.4	0	1300	485	H. Influenza
SF	0	1/2500	1200	340	C.Alb
SP	0	1/2500	450	459	C.Alb & Staph. aureus
JD	3.2	0	2000	660	Neg.
MN	10.3	0	1000	1170	AF
CM	13.1	0	650	1880	Neg.
NL	11.4	0	800	53	Staph. aureus
DC	11.0	0	375	645	C.Alb
FH	5.9	0	684	140	Neg.
ME	12.2	0	274	560	Neg.
MF	6.6	1/2500	1240	459	C.Alb
TD	2.5	1/2500	1500	1500	C.Alb

\*<sup>1</sup> Positive antibody tests: AF Index  $\geq$  2; C.Alb titre  $\geq$  1/2500\*<sup>2</sup> Normal IgE : 12-100 iu/ml\*<sup>3</sup> Normal blood Eosinophils: 40-450 cells/ $\mu$  litre

tion. The permanent changes were consistent with residual areas of pulmonary fibrosis following acute episodes of Allergic Bronchopulmonary Mycosis<sup>12,13</sup>. Total serum IgE were raised in 12 subjects (86%), range 125 to 2000 iu/ml (normal 20-100).

Sputum culture isolated AF in one case (7%); C.Alb was cultured in all three cases of ABPC, four of nine (44%) of ABPA, and in the two cases of overlap syndrome. Two patients (C.C. and N.L.) had cultures of *Staphylococcus aureus* and *Haemophilus Influenzae* respectively. One patient (S.P.) grew *Staphylococcus aureus* and C.Alb. All sputa were negative for *M. Tuberculosis*. All 14 had blood eosinophil counts above normal (normal 40-450 cells/microlitre). Skin tests showed nine patients (64%) with an immediate positive to AF, one patient (7%) with a positive reaction to C.Alb. Four (28%) had negative skin tests.

### Discussion

As mentioned above the period prevalence over four years of Allergic Bronchopulmonary Mycosis in the outpatient population studied was just in excess of one per cent. This suggests that ABPM is a relatively common disorder in such a population. One per cent is probably an underestimate in view of the fact that eosinophilia in this syndrome is variable: some patients with asthma who were not eosinophilic at the time of first or follow-up outpatient visits and whose chest x-ray remained normal would not have been investigated further for ABPM.

The relatively high percentage (35%) of cases of ABPC (including the 2 overlap cases) suggests that ABPC may be more common in this type of population than previously reported, for instance in the Indian series ABPC was found in 22 per cent of patients<sup>10</sup>.

The combination of ABPA and ABPC documented here in two cases was considered by Lee *et al*<sup>6</sup> to be a hypothetical possibility only as recently as 1987. However Pepys and colleagues suggested its occurrence in 1968<sup>6</sup> and a case is recorded in 1979 in the Indian series just mentioned<sup>10</sup>.

As noted earlier patient C.C. grew *H. Influenzae* in sputum (Table II) and 2 patients N.L. and S.P. grew *Staphylococcus aureus*. These sputum cultures indicate intercurrent respiratory tract infection. Patient C.C. had a transient abnormality on chest x-ray consistent with bacterial pneumonia or pulmonary opacification secondary to ABPA. Even excluding the abnormal chest x-ray this patient had sufficient other criteria to meet the diagnostic requirements for ABPM. Patient N.L. had permanent chest x-ray changes more in keeping with the radiological signs of chronic ABPA. Patient S.P. had a normal chest x-ray.

Because of the potentially irreversible sequelae of untreated ABPM<sup>12,13</sup> early diagnosis is important. Accordingly we suggest that all patients with chronic asthma and eosinophilia, or chronic asthma with otherwise unexplained transient or permanent pulmonary shadowing on chest x-ray have antibody activity to AF and C.Alb assessed. Organisms other than AF and C.Alb have been identified as causing ABPM syndrome e.g. *Torulopsis*<sup>14</sup>, *Helminthosporium*<sup>15</sup>, *Curvularia*<sup>16</sup>, *Drechslera*<sup>17</sup>, *Stemphylium*<sup>18</sup>, *Rhizopus*<sup>19</sup> and *Pseudoallescheria boydii*<sup>20</sup>. Some of those fungi have been implicated

together in an overlap syndrome similar to that caused by AF and C.Alb e.g. *Curvularia* and *Drechslera*<sup>17</sup>, e.g.g. AF and *Pseudoallescheria boydii*<sup>20</sup>. The prevalence of ABPM caused by these fungi in isolation or in combination is unknown but deserves further investigation.

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