Invasive aspergillosis in patients with chronic obstructive pulmonary diseases

Aziz Muquim MD[1], Sandra Dial MD Msc[1,2], Dick Menzies MD Msc[1]

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OBJECTIVES: To determine the outcomes, and clinical and therapeutic factors associated with the development of invasive pulmonary aspergillosis (IPA) in patients with obstructive pulmonary diseases.
DESIGN: A case control study examining patients who developed IPA while hospitalized, and controls who were matched by year of hospitalization and type of obstructive lung disease.
SETTING: A tertiary care university-affiliated respiratory hospital.
PATIENTS: Twelve patients were identified who had developed nosocomial IPA. Each case was compared with four control patients: two with and two without *Aspergillus* colonization.
RESULTS: Patients and control patients had similar demographic characteristics, comorbid illnesses and severity of underlying pulmonary disease. All cases required admission to the intensive care unit and eight patients (67%) died, whereas only 17% of control patients required admission to the intensive care unit and 7% died. The patients with IPA received significantly higher daily doses of corticosteroids (median 106 mg of prednisone or equivalent for 18 days) and more broad-spectrum antibiotics (median three antibiotics for 13 days) in hospital before the development of aspergillosis compared with the control patients (median 44 mg for 14 days, and 1.5 antibiotics for nine days, respectively). Among the control patients, those with *Aspergillus* colonization were more likely to have received corticosteroid therapy and broad-spectrum antibiotics during and in the month preceding the index hospitalization, although the hospital course was not different.
CONCLUSIONS: IPA, although rare in patients with chronic obstructive lung diseases, was associated with high doses of corticosteroids and multiple broad-spectrum antibiotics. More judicious use of antibiotics and avoidance of prolonged high-dose corticosteroids may help prevent occurrences of IPA with its attendant serious morbidity and high mortality.

Key Words: Aspergillus *colonization; COPD; Corticosteroids; Fungal pneumonia; Invasive Aspergillosis; Nosocomial complications*

Aspergillose invasive chez des patients atteints d'une maladie pulmonaire obstructive chronique

OBJECTIF : Déterminer les résultats ainsi que les facteurs cliniques et thérapeutiques associés à l'aspergillose pulmonaire invasive (API) chez des patients atteints d'une maladie pulmonaire obstructive chronique (MPOC).
TYPE D'ÉTUDE : Il s'agit d'une étude cas/témoins dans laquelle des patients ayant contracté une API pendant leur séjour à l'hôpital ont été comparés à des témoins appariés selon l'année d'hospitalisation et le type de pneumopathie obstructive.
LIEU : Centre hospitalier universitaire de soins tertiaires, spécialisé en pneumologie.
PATIENTS : Douze cas d'API nosocomiale ont été relevés et chaque cas a été comparé à quatre cas témoins : deux avec colonisation à *Aspergillus*, et deux sans colonisation.
RÉSULTATS : Les malades et les témoins présentaient des caractéristiques démographiques similaires, à peu près les mêmes maladies concomitantes et un degré comparable de gravité de pneumopathie sous-jacente. Tous les malades ont dû être admis au service de soins intensifs et 8 d'entre eux (67 %) sont morts, tandis que 17 % seulement des témoins ont été admis au service de soins intensifs et 7 % sont morts. Les patients atteints d'API ont reçu des doses quotidiennes sensiblement plus fortes de corticostéroïdes (médiane : 106 mg de prednisone ou l'équivalent pendant 18 jours) et plus d'antibiotiques à large spectre (médiane : 3 antibiotiques pendant 13 jours) à l'hôpital, avant l'apparition de l'aspergillose, que les témoins (médiane : 44 mg pendant 14 jours et 1,5 antibiotique pendant 9 jours, respectivement). Ceux parmi les témoins qui présentaient une colonisation à *Aspergillus* étaient plus susceptibles d'avoir reçu des corticostéroïdes et des antibiotiques à large spectre au cours de l'hospitalisation de référence ou du mois précédent, même si leur évolution à l'hôpital n'a pas été différente de celle des autres témoins.
CONCLUSIONS : L'API, rare chez les patients atteints d'une MPOC, a été associée à des doses plus fortes de corticostéroïdes et à l'administration de plusieurs antibiotiques à large spectre. Un emploi plus judicieux des antibiotiques et le fait d'éviter l'administration prolongée de corticostéroïdes à forte dose pourraient prévenir l'apparition de l'API, source d'une grave morbidité et d'une mortalité élevée.

Aspergillus species can cause a wide spectrum of pulmonary illnesses ranging from the saprophytic colonization of airways to a necrotizing form with vascular invasion, termed invasive pulmonary aspergillosis (IPA). Because the incidence of IPA has increased over the past 40 years, it is now one of the most common mycoses (1,2). For example, a European study (3) reported a 14-fold increase in its detection at autopsy between 1978 and 1992, and another study (4) reported that *Aspergillus* was found in 6.9% of all patients admitted to a medical intensive care unit (ICU). This condition has an important economic impact – ICU length of stay is almost doubled with invasive *Aspergillus* (5), and in the United States, each case has been estimated to cost US$65,000 (1). Because mortality is 50% to 100% even with appropriate therapy (1,2,4-9), the identification of risk factors to prevent its occurrence would be highly beneficial.

IPA is a well-recognized complication of immunosuppressive therapy following organ transplantation (1,2), chemotherapy for cancer (particularly for leukemias and lymphomas) (1,2) and corticosteroid therapy (10). Although case reports

[1]*Respiratory Epidemiology and Clinical Research Unit of the Montreal Chest Institute;* [2]*The Jewish General Hospital, McGill University, Montreal, Quebec*
Correspondence: Dr Dick Menzies, Montreal Chest Institute, room K1.24, 3650 Street Urbain, Montreal, Quebec H2X 2P4.
Telephone 514-934-1934, fax 514-483-2083, e-mail dick.menzies@mcgill.ca

and case series have been published (6,9,11-13), chronic obstructive pulmonary disease (COPD) was not included as a high-risk condition for the development of IPA in recent published authoritative reviews (1,2) or guidelines (14). In a recent study (4), COPD was the underlying disease in 49% of proven or probable IPA in patients without malignancy (4). This suggests that IPA may be under-recognized in patients with COPD, and the factors contributing to its development in these patients have not been defined.

At the Montreal Chest Institute in Montreal, Quebec, IPA developed in 12 patients who were hospitalized for the management of acute respiratory failure from COPD. We hypothesized that treatment of these patients with high-dose corticosteroids and/or broad-spectrum antibiotics was contributing to the occurrence of IPA; therefore, we conducted a case control study to investigate this hypothesis.

METHODS

Definition of cases

Cases were defined as patients with COPD who developed IPA while hospitalized between January 1994, and January 2001 (considered the 'index' hospitalization). IPA was defined following the guidelines of an international consensus committee (15):

- confirmed IPA: histopathological evidence from biopsy or autopsy and a positive culture for *Aspergillus* species from sputum, tracheal aspirate or bronchoalveolar lavage (BAL).

- probable IPA: positive culture for *Aspergillus* species from sputum, tracheal aspirate or BAL and all of the following: new respiratory symptoms (cough, dyspnea, hemoptysis or pleuritic chest pain) and/or pleural rub; new undiagnosed radiographic infiltrate; and no clinical response to broad-spectrum antibiotics and/or did respond to therapy with amphotericin B.

Definitions of control subjects

Control subjects were selected from patients with the same underlying pulmonary disease who were hospitalized within a year of the case's index hospitalization and who did not develop IPA. Records of consecutive patients admitted during a single month, selected randomly from the 12 months before or after the case's index hospitalization, were reviewed to identify control subjects. Months were selected randomly to assess seasonal differences in occurrence, but within a year to reduce potential confounding from changes in therapy over time. Control subjects with cystic fibrosis (CF) were identified from our institutional registry of all CF patients. Two 'colonized' control subjects/case had a positive sputum or BAL culture for *Aspergillus* species during their hospitalization. Control subjects without colonization had no positive culture (out of at least one sputum culture performed) for *Aspergillus* during their hospitalization or the preceding year.

Data gathering

Demographic, clinical and therapeutic information were gathered from hospital records. The diagnoses of COPD and bronchiolitis (as the major underlying obstructive respiratory disease) were taken from the primary discharge diagnosis made by the treating respirologist, and were based on chest x-rays, pulmonary function testing and clinical course. Diagnosis of CF was based on genetic testing. For all patients, a series of three chest radiographs, from admission, the approximate time of onset of IPA and two to seven days later were reviewed by two board certified chest specialists (SD and DM), without knowledge of case status or the dates of the radiographs. When there was a discrepancy between the two readings for a particular patient, a consensus reading was organized (by AM). Microbiological data on *Aspergillus* and therapy with antibiotics and corticosteroids (in milligram doses equivalent to prednisone) were reviewed in detail for period during the index hospitalization, one month and one to 12 months preceding the index hospitalization. For the patients with COPD who developed IPA, therapy was counted until the date when clinical deterioration related to the occurrence of IPA was first noted. Outcomes recorded included ICU admission, invasive or noninvasive mechanical ventilation, death and length of stay in the ICU and acute care service.

Data analysis

The patients with COPD who developed IPA (cases) were compared with all controls and with each set of controls separately; in addition, the two groups of controls were compared. Differences were tested for statistical significance using Wilcoxon rank sum tests for non-normally distributed variables, including all variables relating to corticosteroid and antibiotic therapy. For normally distributed continuous variables, which included the clinical and demographic characteristics of patients, Student's *t* tests were used, while χ^2 tests were used to test differences for categorical variables (16). Multivariate logistic regression provided adjusted estimates of the association of IPA and *Aspergillus* colonization with clinical characteristics and therapy (17). Due to the very small number of cases, stepwise backward regression was performed. Initial models included all factors significantly associated in univariate or bivariate analysis. Final models included only those variables that were significantly associated. All analyses were conducted using SAS, Version 8.02 for Windows (SAS Institute, USA).

RESULTS

Between January 1994 and January 2001, 14 possible cases and 56 matched controls were identified. However, on further review, one patient was reclassified as a control with *Aspergillus* colonization and a second patient had possible invasive *Candidiasis*, but no *Aspergillus* was ever identified. This left 12 cases with IPA, four of whom were confirmed at autopsy (three with COPD and one with CF), and eight probable cases that met the international diagnostic criteria outlined. Four of these probable cases died and the other four manifested slow improvement with therapy with intravenous amphotericin B. *Aspergillus flavus* was isolated in one case and *Aspergillus fumigatus* was isolated in the remainder of the cases.

Of the 10 cases with underlying COPD and one with bronchiolitis, no patient had documented bronchiectasis. The case with underlying CF was diagnosed to have extensive IPA at autopsy. Based on discharge diagnoses during the study period, 3267 patients with COPD, 195 with CF and 40 with bronchiolitis were hospitalized, resulting in estimated case rates of invasive aspergillosis of 3.1/1000, 5.0/1000 and 25.0/1000 admissions, respectively. There were no significant differences between the cases and all controls, nor between colonized and noncolonized controls in terms of the season of admission, room on the acute care ward or the day hospital where the patients received care. During the study period, there were no major construction or renovation projects in the hospital buildings. Limited environmental sampling was performed to assess mold

TABLE 1
Personal and clinical characteristics, and hospital course for the three patient groups

	Cases (n=12)	Controls with *Aspergillus* (n=29)	Controls without *Aspergillus* (n=28)	P* 1	P* 2	P* 3
Personal characteristics						
Age, Mean (SD)	60 (14.7)	67 (15.1)	67 (12.6)	NS	NS	NS
Sex, n (%)						
Male	7 (58)	21 (72)	17 (61)	NS	NS	NS
Female	5 (42)	8 (28)	11 (39)			
Smoker, n (%)						
Current	3 (25)	6 (21)	4 (14)	NS	NS	NS
Former	7 (58)	19 (66)	20 (71)			
Never	2 (17)	4 (14)	4 (14)			
Pack years, mean (SD)	42 (31)	36 (16)	41 (23)	NS	NS	NS
Clinical characteristics						
FEV_1, % predicted (SD)†	34 (21)	40 (15)	36 (17)	NS	NS	NS
FEV_1:FVC ratio (SD)†	46 (21)	49 (12)	48 (12)	NS	NS	NS
On home oxygen, n (%)	2 (17)	5 (17)	10 (36)	NS	NS	NS
Major comorbid disease(s), n (%)	5 (42)	16 (55)	14 (50)	NS	NS	NS
Hospital course						
Length of stay (median [IQR])	51 (56)	12 (18)	9 (10)	0.001	0.001	NS
Reason for admission, n (%)						
Exacerbation	8 (67)	20 (69)	19 (68)		NS	NS NS
Other (pneumonia, CHF, pneumothorax)	4 (33)	9 (31)	9 (32)			
Admitted to intensive care unit, n (%)	12 (100)	5 (17)	5 (18)	<0.0001	<0.0001	NS
Developed respiratory failure, n (%)	12 (100)	5 (17)	2 (7)	0.0001	0.0001	NS
Intubated, n (%)	10 (83)	2 (7)	0 (–)	0.0001	0.0001	NS
Died, n (%)	8 (67)	3 (10)	1 (4)	0.001	0.0001	NS
Autopsy, n (%)	4 (33)	0 (–)	0 (–)	0.01	0.01	NS

**P for comparison between groups, from χ^2 tests for categorical variables or Student's* t *tests for continuous variables: 1 – Comparison of patients with COPD (cases) who developed invasive pulmonary aspergillosis with controls with* Aspergillus*, 2 – Comparison of patients with COPD who developed invasive pulmonary aspergillosis with controls without* Aspergillus*, and 3 – Comparison of controls with* Aspergillus *to controls without* Aspergillus*; †Best result in one year preceding index hospitalization. CHF Congestive heart failure; FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity; IQR Interquartile range; NS Not significant*

contamination in the rooms and ventilation systems of the hospitals in 2001. No *Aspergillus* contamination was found.

As shown in Table 1, there were no significant differences in the clinical characteristics among the three patient groups, including cause and severity of illness at the time of the initial hospitalization. Onset of IPA occurred after five to 37 days in hospital (median 13 days, interquartile range 10 to 18 days). All four patients who developed IPA within 10 days of hospitalization had received oral prednisone (or equivalent) in the preceding month for an average of 18 days and an average total dose of 800 mg (of prednisone or equivalent). When admitted to hospital, eight patients with IPA had normal chest x-rays (considered to have exacerbation) and four had evidence of airspace infiltrates (pneumonia) which improved in the first few days. After a period of relative stability, the patients with IPA manifested sudden clinical deterioration, with the development of new, rapidly progressive radiographic infiltrates, accompanied by acute respiratory failure requiring ICU admission. Eight of the cases had multifocal airspace patterned opacification, two had lobar airspace disease and one had multinodular disease. Only one patient had cavitary infiltrates, which were multiple and small.

The most significant difference between the cases and either group of controls was the average daily corticosteroid dose (expressed as prednisone equivalent in milligrams) during the index hospitalization before the onset of IPA (Table 2). As seen in Figure 1, no cases occurred among patients who received an average of less than 80 mg per day. A total of 15 patients studied had received an average daily dose of more than 80 mg; 12 (80%) of these patients developed IPA after a median of 12 days; three controls received this dose for two to 28 days. The cases also received a significantly higher total dose of corticosteroids in the month before the index hospitalization, as well as more broad-spectrum antibiotics during hospitalization and in the preceding month. Compared with noncolonized controls, *Aspergillus* colonized controls received significantly higher total corticosteroid doses and more broad-spectrum antibiotics in the month preceding, as well as during the index hospitalization (Table 2).

In multivariate analysis, IPA was not associated with clinical characteristics but was associated with more antibiotics and higher dose corticosteroid therapy during the index hospitalization. *Aspergillus* colonization was also not associated with clinical characteristics but was associated with antibiotic therapy during the index hospitalization and corticosteroid therapy in the preceding month (Table 3).

DISCUSSION

In the present study, 12 cases of IPA occurred among hospitalized patients with COPD. When compared with 29 similar patients colonized with *Aspergillus* and 28 others with no *Aspergillus*, IPA was associated with very high doses of corticosteroid therapy and multiple broad-spectrum antibiotics. *Aspergillus* colonization was also associated with treatment of higher doses of corticosteroids and more broad-spectrum antibiotics, albeit to a lesser extent than for the patients with IPA.

TABLE 2
Comparison of corticosteroid and antibiotic treatment given to the three patient groups

	Cases (n=12)	Controls with *Aspergillus* (n=29)	Controls without *Aspergillus* (n=28)	P* 1	P* 2	P* 3
Corticosteroids (prednisone equivalent)						
Current hospitalization						
Days of therapy	18 (15.5)	15 (8)	13 (8.5)	NS	NS	NS
Median daily dose (mg)	106 (28.5)	45 (35)	44 (26)	<0.0001	<0.0001	NS
Total dose (mg)	1974 (2220)	775 (715)	597 (673)	<0.001	<0.001	NS
0 to 1 month preadmission						
Days of therapy	11.5 (7.5)	10.0 (26.0)	0 (11.0)	NS	0.05	NS
Median daily dose (mg)	29 (58)	21 (37)	0 (16)	NS	0.002	0.02
Total dose (mg)	378 (442)	220 (432)	0 (268)	NS	0.005	0.04
1 to 12 months preadmission						
Days of therapy	40 (56)	24 (28)	0 (38)	NS	NS	NS
Median daily dose (mg)	22.5 (14.6)	27.0 (17.0)	21.0 (19.0)	NS	NS	NS
Total dose (mg)	1050 (2156)	720 (785)	0 (1030)	NS	NS	NS
Total (full year)						
Days on steroids	58.5 (81)	50 (35)	32 (44)	NS	NS	NS
Total dose (mg)	3648 (3465)	2084 (7643)	1640 (1375)	0.004	0.002	NS
Broad-spectrum antibiotics†						
Current hospitalization						
Number given	3.0 (2.5)	2.0 (1.0)	1.0 (2.0)	0.004	0.001	NS
Days of therapy	13.0 (8.0)	11.0 (7.0)	7.0 (14.0)	NS	0.03	0.09
0 to 1 month preadmission						
Number given	1.0 (2.0)	0 (1.0)	0 (1.0)	NS	0.006	0.05
Days of therapy	10.0 (8.0)	0 (14.0)	0 (5.0)	NS	0.002	0.05
1 to 12 months preadmission						
Number given	3.5 (4.0)	1.0 (3.0)	2.0 (3.0)	NS	NS	NS
Days of therapy	13.5 (9.0)	14.0 (17.0)	10.0 (14.0)	NS	NS	NS
Total						
Number given	8.0 (7.0)	4.0 (4.0)	3.5 (4.5)	0.05	0.01	NS
Days of therapy	34.5 (25.5)	30.0 (31.0)	23.0 (30.0)	NS	0.04	0.04

*All results are median (interquartile range); *P for comparison between groups, from nonparametric Wilcoxon rank sum tests (not significant at P>0.1): 1 – Comparison of patients with COPD who developed invasive pulmonary aspergillosis (cases) with controls with* Aspergillus*, 2 – Comparison of patients with COPD who developed invasive pulmonary aspergillosis with controls without* Aspergillus*, and 3 – Comparison of controls with* Aspergillus *with controls without* Aspergillus*; †90% of all antibiotics given were of broad spectrum category (consistently in all patient groups and time periods). Antibiotics classified as broad spectrum included imipenim, fluoroquinolones, second- and third-generation cephalosporins, aminoglycosides and synthetic penicillins (eg, piperacillin)*

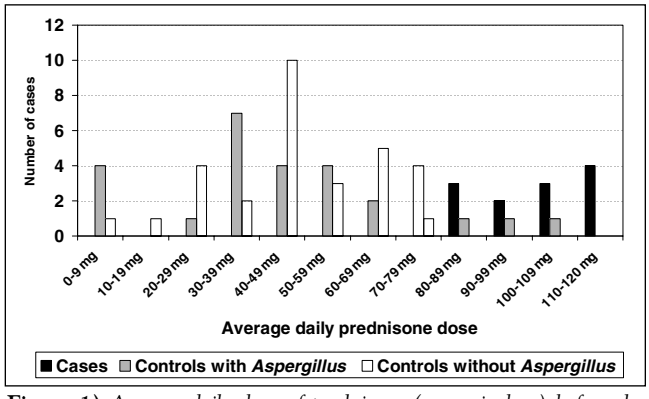

Figure 1) *Average daily dose of prednisone (or equivalent) before the development of invasive aspergillosis for patients with invasive pulmonary aspergillosis (cases) and during index hospitalization for controls*

In animal studies, the development of fungal pneumonia has been related to the dose and duration of corticosteroids (17). In a recent study of patients without malignancy who developed proven or probable IPA (4), 94% had received corticosteroids but at unspecified doses. In two uncontrolled case series of IPA complicating prednisone therapy, 16 patients with COPD had received an average of 73 mg/day (8) and 39 patients "without major immune suppression" received 140 mg/day for an unspecified duration (9). Of the 24 COPD patients with IPA reported until 1998 (9), 10 (42%) had taken more than 80 mg per day, eight (33%) had taken prednisone for at least two months and only two had not taken any corticosteroids. In a more recent report, Agusti et al (18) described nosocomial fungal pneumonia in nine patients (six patients with *Aspergillus*) who had received at least 30 mg/day of corticosteroids for at least 30 days. With very prolonged corticosteroid therapy following bone marrow transplantation, IPA was uncommon in patients who received less than 0.25 mg/kg/day and increasingly common at doses above 0.5 mg/kg/day (2,10).

In the present study, all of the patients with IPA received an average daily dose of corticosteroids of 80 mg or more compared with 4% of all controls, resulting in a crude incidence of 4.3/100 patients who received similar doses. (The incidence by dose could be estimated because the controls were selected randomly from all patients with similar obstructive lung diseases). IPA was not observed in patients who received less than 80 mg/day. This is in contrast to earlier studies (2,10,18), where IPA was associated with a lower dose but longer therapy duration. From this, it seems likely that IPA is rare in patients with COPD, simply because they usually receive much shorter

TABLE 3
Adjusted odds of therapeutic factors with development of invasive pulmonary aspergillosis (IPA) or *Aspergillus* colonization (from multivariate logistic regression)

	Adjusted for selected aspects of therapy*		Adjusted for therapy and age, sex and pack-years smoking†	
	OR	95% CI	OR	95% CI
IPA‡				
Index hospitalization				
Daily prednisone dose (per 10 mg increase)	11**	1.1 to 113**	9.8	0.95 to 100
Broad-spectrum antibiotics (per each)	2.9	0.8 to 10.0	4.3	0.4 to 44
Month prehospitalization				
Daily prednisone dose (per 10 mg increase)	1.2	0.8 to 1.8	1.4	0.7 to 2.7
Broad spectrum antibiotics (per each)	1	0.1 to 8.0	§	§
Aspergillus colonization¶				
Index hospitalization				
Daily prednisone dose (per 10 mg increase)	0.95	0.7 to 1.2	1.1	0.8 to 1.4
Broad-spectrum antibiotics (per each)	4.6**	1.2 to 17.2**	4.3**	1.0 to 19.4**
Month prehospitalization				
Prednisone (any received)	3.7**	1.1 to 11.8**	5.7**	1.5 to 21.6**
Broad-spectrum antibiotics (any received)	1.4	0.6 to 3.3	1.5	0.5 to 4.2

**The best models included only the therapeutic parameters. Estimates for these parameters were adjusted only for the four items shown: daily prednisone dose and broad-spectrum antibiotic therapy during the index hospitalization, as well as any broad-spectrum antibiotics or corticosteroid therapy in the month prehospitalization; †The same models were used, but age, sex and pack-years of cigarette smoked were added to all; ‡12 patients with IPA compared with all 57 controls. §Too few numbers in certain categories, estimates in this model were unstable; ¶29 patients with* Aspergillus *colonization were compared with 28 patients without* Aspergillus *colonization; **Statistically significant results*

courses of high-dose corticosteroids. Current guidelines (19) recommend the use of much lower doses of corticosteroids than received by some of the patients with COPD who developed IPA, and practice in our institution has since changed to use much lower doses. These changes may help prevent IPA.

Antibiotic therapy before or during the index hospitalization was also an important risk factor, as has been observed in earlier case series (6,8,9,20). The risk for IPA increased according to the number of antibiotics used. Because many broad spectrum antibiotics were used and because the small number of cases limited the power to detect significant associations, no single agent could be identified that was associated with IPA.

Although colonization with *Aspergillus* was first described in patients with COPD over 40 years ago (21), the incidence, risk factors (besides cigarette smoking [13]) and clinical significance remain undefined. Our observation that corticosteroid and antibiotic therapy of patients with *Aspergillus* colonization was between that of patients with IPA and patients without any *Aspergillus*, suggests that *Aspergillus* colonization may be a marker of moderate but potentially important immune suppression. In patients with obstructive lung diseases, *Aspergillus* colonization may be a precursor of IPA, as has been reported in patients receiving cancer or transplant therapy (22).

The occurrence of IPA in hospitalized patients has been linked with *Aspergillus* species contamination of hospital air handling systems (23), mechanical ventilator filters (12) or nearby construction projects (1). However, no environmental contamination or source has been identified in most series of IPA. In the current study, patients with IPA or colonized controls were unlikely to have acquired *Aspergillus* as a result of a nosocomial source. This is because there was no seasonal, temporal or spatial clustering of the cases or colonized controls. In the years reviewed, there were one to two cases of IPA each year.

There were a number of limitations in the present study. First, only four cases were histologically confirmed (all at autopsy). No patients had lung biopsies because they were judged to be too unstable at the time. However, the four patients who recovered had a well-documented clinical response to amphotericin B therapy after failure to respond to multiple broad spectrum antibiotics. Some diagnostic uncertainty is inevitable regarding the four patients who died without autopsy, although they did meet the criteria of the international consensus guidelines (3). The difficulties of antemortem diagnosis are well-known (6,9), related in part to the low sensitivity of sputum cultures (2). In an autopsy series of 22 patients with IPA (24), while still alive, only two patients (9%) had confirmed IPA, six patients (27%) met the criteria for probable IPA and the remainder were considered possible or unclassifiable (24). The small number of cases with IPA limited the statistical power, which was another weakness. However, despite the small number, highly significant differences in the corticosteroid and antibiotic therapy between cases and controls were detected in univariate and multivariate analyses, which is consistent with a very strong effect.

The strengths of the study included the use of a case-control design and matching of each case to four controls (25) to maximize the efficiency of the study. The inclusion of controls randomly selected from all other patients with similar obstructive lung diseases allowed the estimation of the overall incidence and by dose of corticosteroid therapy, plus the assessment of clinical and therapeutic risk factors. By including controls with *Aspergillus* colonization, the factors associated with invasive disease could be distinguished from factors simply associated with colonization. The requirement that controls had been hospitalized and had the same underlying pulmonary disease should have ensured reasonable matching of the severity of underlying, as well as acute, illnesses (26).

CONCLUSIONS

Therapy with high-dose corticosteroids with or without broad-spectrum antibiotics for as little as one to two weeks can result in *Aspergillus* colonization or IPA in patients with COPD. If a hospitalized patient with COPD develops severe

nosocomial pneumonia, IPA should be excluded, corticosteroid therapy re-evaluated and the institution of systemic antifungal therapy considered.

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