Survey of aspergillosis in non-neutropenic patients in Swiss teaching hospitals

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Abstract

Invasive aspergillosis (IA) is a live-threatening opportunistic infection that is best described in haematological patients with prolonged neutropenia or graft-versus-host disease. Data on IA in non-neutropenic patients are limited. The aim of this study was to establish the incidence, disease manifestations and outcome of IA in non-neutropenic patients diagnosed in five Swiss university hospitals during a 2-year period. Case identification was based on a comprehensive screening of hospital records. All cases of proven and probable IA were retrospectively analysed. Sixty-seven patients were analysed (median age 60 years; 76% male). Sixty-three per cent of cases were invasive pulmonary aspergillosis (IPA), and 17% of these were disseminated aspergillosis. The incidence of IPA was 1.2/10 000 admissions. Six of ten cases of extrapulmonary IA affected the brain. There were six cases of invasive rhinosinusitis, six cases of chronic pulmonary aspergillosis, and cases three of subacute pulmonary aspergillosis. The most frequent underlying condition of IA was corticosteroid treatment (57%), followed by chronic lung disease (48%), and intensive-care unit stays (43%). In 38% of patients with IPA, the diagnosis was established at autopsy. Old age was the only risk factor for post-mortem diagnosis, whereas previous solid organ transplantation and chronic lung disease were associated with lower odds of post-mortem diagnosis. The mortality rate was 57%.

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Introduction

Invasive aspergillosis (IA) is an opportunistic infection that occurs mainly among patients with haematological malignancies, most notably during prolonged periods of neutropenia [1–4]. In recent years, however, IA has increasingly been recognized as an emerging disease of non-neutropenic patients [5–10]. Underlying conditions have included obstructive pulmonary disease or connective tissue diseases requiring corticosteroid therapy, liver cirrhosis, and solid cancer with and without treatment. Many of the affected patients needed intensive care. IA was often not suspected, and diagnosed late or at autopsy [6,11,12]. Mortality rates >80% have been reported. A high level of suspicion is needed to allow for early diagnosis and timely therapeutic intervention. A better understanding of the population at risk and the spectrum of diseases caused by IA in non-haematological patients may contribute to improving the outcome of this potentially treatable disease. Therefore, we conducted a nationwide study to analyse documented cases of aspergillosis in non-neutropenic patients at five Swiss university hospitals.

Methods

Patient population and data collection

We conducted a retrospective observational analysis of all aspergillosis cases in non-neutropenic patients diagnosed at the five Swiss university hospitals collaborating in the fungal network of Switzerland (FUNGINOS) between 1 January 2004 and 31 December 2005.

Patient identification was based on comprehensive screening of hospital records, infectious diseases consultants' notes, all types of microbiology laboratory results, radiology reports, and pharmacy records on antifungal drugs with activity against *Aspergillus* spp.

We excluded patients with current or past neutropenia (defined as neutrophil counts <500/μL for >10 days), haematopoietic stem cell transplantation (HSCT), and leukaemia.

Data were extracted from patient's charts as well as microbiology, pathology and radiology reports. Case report forms were subjected to the scrutiny of a data review committee before being entered into a database.

Hospital statistics for the years 2004 and 2005 (number of patient beds, admissions, and patient-days) were collected at all five university hospitals.

Case definition

Diagnosis of invasive disease was based on the case definition by the European Organization for Research and Treatment of Cancer/Mycoses Study Group [13], with the following modifications: the restriction to patients with cancer and recipients of HSCT was lifted to include all patient groups (allowing for inclusion of patients with no recognized predisposing host factors); and galactomannan in serum, bronchoalveolar lavage fluid, and cerebrospinal fluid, as well as detection of *Aspergillus* spp. in clinical specimens by PCR. Patients with histological evidence of mould infection and negative cultures were only included when *Aspergillus* was confirmed as the causative pathogen by PCR [14].

Only proven/probable cases of IA were enrolled in the study.

The diagnosis of disseminated IA required the demonstration of *Aspergillus* sp. at two or more non-contiguous sites [15,16].

Diagnosis of subacute and chronic pulmonary aspergillosis was based on definitions proposed by Segal *et al.* [17] and Denning *et al.* [18], respectively.

Invasive *Aspergillus* rhinosinusitis was diagnosed in symptomatic patients with opacified sinuses and tissue invasion outside the eroded bony walls of the sinuses on imaging studies and/or by histological demonstration of tissue invasion by moulds confirmed as *Aspergillus* spp. by either culture or PCR [15,16].

Corticosteroid treatment was defined as exposure to ≥10 mg/day prednisone equivalent for ≥30 days. Immunosuppression refers to exposure to other immunosuppressive drugs (e.g. azathioprine, mycophenolate, tacrolimus, and infliximab) that did not induce neutropenia for ≥9 days.

Statistical analysis

Basic demographic characteristics, comorbidities, laboratory parameters and treatment modality of IA were compared with the chi-square test and Fisher's exact test for categorical variables, and the Mann–Whitney test for continuous variables. Logistic regression was used to estimate the ORs of post-mortem diagnosis of pulmonary IA. We built the final multivariate model with a forward stepwise approach, adding in the model, one by one, each factor significant at the level of 0.1 in the univariate analysis and other factors defined in the literature as prognostic. A p-value of 0.05 for two-tailed tests was set as the cut-off for significance. All analyses were performed with STATA software version 9.2 for Windows (StataCorp, College Station, TX, USA).

Results

A total of 76 patients were enrolled during the 2-year study period.

Nine patients were excluded from the analysis. The reasons for exclusion by the data review committee were lack of evidence of invasive disease in eight cases of sinus aspergilloma and disease occurrence outside of the study time frame in one patient. Thus, the analysed study population comprised 67 cases with proven/probable IA. In 2004–2005, 353 741 patients were admitted to the 4079 patient beds (medical, surgical, paediatric wards, and intensive-care unit (ICU)) at the five university hospitals (430 ICU beds with 65 152 admissions).

Invasive pulmonary aspergillosis (IPA) was diagnosed in 42 of 67 (63%) of patients: 30 of 42 (72%) cases were proven, and 12 (28%) were probable cases (Table 1). In seven of 42 patients (17%), aspergillosis had spread from the lungs to at least one other organ (brain, kidney, heart, eye, peritoneum, bone, and skin); in the others, only pulmonary disease was diagnosed. Invasive extrapulmonary aspergillosis without a detectable pulmonary focus was found in ten of 67 (15%) patients. In two patients, direct inoculation into the skin and bone was the most likely route of infection. Interestingly, in six patients with central nervous system aspergillosis, neither the lungs nor the sinuses, the most likely portals of entry, showed any signs of disease. Invasive rhinosinusitis did not give rise to disseminated disease in any patient. Subacute and

TABLE 1. Manifestations of invasive aspergillosis in non-neutropenic hosts

Invasive pulmonary aspergillosis	42
Localized disease	35
Disseminated disease	7
Invasive extrapulmonary aspergillosis[a]	10
Invasive rhinosinusitis	6
Subacute pulmonary aspergillosis	3
Chronic pulmonary aspergillosis	6
Total	67

[a]Central nervous system (n = 7), bone (n = 2), skin (n = 1).
In addition, there were 21 patients with pulmonary aspergilloma and 40 patients with sinus aspergilloma.

TABLE 2. General characteristics of patients with invasive pulmonary aspergillosis (*n* = 42)

Characteristic	*n*	%
Age (median, IQR)	60	51–66
Male gender	32	76.2
Cancer	13	31.0
Transplantation	13	31.0
Chronic lung disease	20	47.6
Chemotherapy	3	7.1
ICU stay	18	42.9
Mechanical ventilation	14	33.3
Prednisone	24	57.1
Immunosuppression	11	26.2
CRP (mg/mL) (median, IQR)	61.5	5–183
Post-mortem IA diagnosis	16	38.1
Outcome: treatment failure	29	60.0
Death	24	57.1
Time to death (if ante-mortem diagnosis), days (median, IQR)	40	12–91

CRP, C-reactive protein; IA, invasive aspergillosis; ICU, intensive-care unit; IQR, interquartile range.

chronic pulmonary aspergillosis was diagnosed in nine of 67 (13%) patients.

Further analysis was focused on the patients with IPA. Their median age was 60 years (interquartile range 51–66) and 32 (76%) were male. Their underlying diseases and risk factors for IA are shown in Table. 2. Chronic lung disease, cancer and solid organ transplantation were the most common underlying diseases. The majority of patients had received prednisone or another immunosuppressive regimen. The median level of C-reactive protein was 61 UI (interquartile range 5–183). Twenty-five patients were given antifungal treatment, which was combined with surgery in ten. Three patients were treated with surgery alone; none of them died. The mortality rate among patients who received antifungal treatment was 35% (eight of 23 died) The median time to death was 40 days (interquartile range 12–91). In 16 of 42 (38%) patients, the diagnosis of IPA was only established after death; 15 of them (94%) did not receive antifungal treatment with activity against *Aspergillus*. Overall, the mortality rate reached 57.1%.

Among non-neutropenic patients admitted to a university hospital in Switzerland, we found an incidence of IPA of 1.2 per 10 000 admissions. The incidence rate for patients admitted to the ICU was 2.8 (18 per 65 152).

To elucidate why the diagnosis of IPA is often missed during the patient's life, a risk factor analysis was performed. In univariate analysis, only higher age was significantly associated with post-mortem diagnosis (OR 2.1; 95% CI 1.1–4.2;, p 0.034). The results of the multivariate analysis are shown in Table 3. After adjustment for age, history of chronic lung disease, solid organ transplantation or previous corticosteroid treatment, and C-reactive protein, older age remained a significant risk factor for post-mortem diagnosis of IA. In contrast, solid organ transplantation and chronic lung disease were independently associated with lower odds of post-mortem diagnosis (Table 4).

Diagnostic tools and imaging

The pathology report was the diagnostic tool that permitted identification of the largest number of patients: 48 of 67 (72%). It was based on biopsies in 29 (43.3%) cases and on autopsy in 19 (28.4%). Sixteen of the autopsy cases had IPA.

A chest X-ray was available for 48 of 51 (94%) patients with IPA, and abnormal findings were present in 42 (87.5%). A chest computed tomography (CT) scan was available for 37 of 51 (72.5%) of the patients with IPA, and was considered to be abnormal in 35 (94.6%).

Discussion

A number of recent reports of case series and single-centre cohorts document the expansion of the at-risk population

TABLE 3. Risk factors and univariate ORs of post-mortem diagnosis of pulmonary invasive aspergillosis (IA) in 42 non-neutropenic patients

	IA diagnosis post-mortem *N* = 16		IA diagnosis ante-mortem *N* = 26				
Variable	*n*	%	*n*	%	OR	95% CI	p-value
Age (median, IQR)	65	57–71	58	48–63	2.1[a]	1.1–4.2	0.034
Male gender	13	81.3	19	73.1	0.6	0.1–2.9	0.548
Cancer	7	43.8	6	23.1	2.6	0.7–9.9	0.165
Transplantation	3	18.8	10	38.5	0.4	0.1–1.6	0.188
Chronic lung disease	5	31.3	15	57.7	0.3	0.1–1.2	0.101
ICU stay	6	37.5	12	46.2	0.7	0.2–2.5	0.583
Mechanical ventilation	6	37.5	8	30.8	1.4	0.4–5.0	0.654
Prednisone	12	75.0	12	46.2	3.5	0.9–13.8	0.073
Immunosuppression	4	25.0	7	26.9	0.9	0.2–3.8	0.891
CRP (mg/μL) (median, IQR)	74	22–187	20	0–183	1.0[b]	0.9–1.1	0.340

CRP, C-reactive protein; ICU, intensive-care unit; IQR, interquartile range.
[a]Per 10 years older
[b]Per 10 mg/mL increase in CRP.

TABLE 4. Multivariate ORs of post-mortem diagnosis of pulmonary invasive aspergillosis in 42 non-neutropenic patients

Variable	OR[a]	95% CI	p-value
Age, per 10 years older	3.16	1.08–9.21	0.035
Transplantation	0.02	0.01–0.37	0.009
Chronic lung disease	0.05	0.01–0.69	0.025
Prednisone	8.04	0.79–81.5	0.078
CRP, per 10 mg/mL increase	1.00	0.93–1.07	0.961

CRP, C-reactive protein.
[a]Adjusted for all variables listed in the table.

for IA beyond the traditionally recognized risk groups to include patients with chronic obstructive pulmonary disease (COPD) (commonly receiving corticosteroid treatment and often admitted to the ICU), critically ill patients with prolonged corticosteroid treatment for reasons other than obstructive lung disease, and patients with decompensated hepatic cirrhosis [6,10,19–26]. Indeed, IA among patients with non-haematological diseases may be more common in certain centres than among those with haematological diseases known to be risk factors. Exacerbated COPD was the underlying disease in more than one-half of 53 patients with IPA seen at a single institution [10]. In addition, patients with haematological diseases accounted for minorities of 41%, 36% and 34% of three cohorts with proven/probable IA admitted to the ICU [6,12,22]. Corticosteroid treatment, mostly for exacerbated COPD, was the dominant underlying factor in these three cohorts.

Most reports of the past few years have focused on IA in particular risk groups, i.e. patients with COPD or critically ill patients admitted to the ICU, and were commonly conducted at a single centre. The present study, in contrast, was conducted countrywide at all five teaching hospitals, and enrolled all non-neutropenic patients irrespective of the nature of their risk. Over the 2-year study period, we identified 67 patients with proven or probable IA.

The lungs and sinuses, the portals of entry of airborne *Aspergillus* conidia, were the sites of infection of 85% of cases. IPA, the most common disease manifestation, was found in 63%. Disseminated disease was detected in 17% of patients with documented pulmonary foci of disease. In addition, in the absence of evidence of infection of the paranasal sinuses, the six cases of apparently isolated cerebral aspergillosis must also represent disseminated disease. Primary pulmonary or, much more rarely, gastrointestinal foci may have been missed in imaging studies or at autopsy. Among 36 autopsied patients with COPD and IA, dissemination from the lungs was described in 20% [23].

IA not involving the respiratory tract was rare. No patient with primary gastrointestinal aspergillosis was identified. Most of the cases with skin and bone disease were caused by direct traumatic inoculation of fungal conidia. The incidence of IPA in non-neutropenic patients of 1.2 per 10 000 hospital admissions found in Switzerland is similar to the rate reported for a large Spanish teaching hospital (1.1 per 10 000 admissions) [10]. The incidence among patients admitted to the ICU of 2.8 cases per 10 000 ICU admissions, however, is ten-fold inferior to the rate reported for non-neutropenic patients from a single centre in Belgium (28.5 per 10 000 ICU admissions) [22]. The entry criterion of a respiratory specimen positive for *Aspergillus* spp. in the Belgian study may account for this difference.

The most prevalent underlying conditions for IPA in non-neutropenic patients identified in this study were corticosteroid treatment (≥10 mg/day prednisone for ≥30 days) and chronic lung disease. The European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria list corticosteroid administration for more than 3 weeks as a predisposing host factor for IA, and, indeed, steroids have been documented as risk factors for the development of IA in the majority of critically ill patients as well as those with COPD. Forty-three of 56 (77%) COPD patients with IA reported in the literature up to 2005 were receiving steroids at admission [23]. Among critically ill patients without haematological malignancy, 87% of those with proven IA and all of those with probable IA had been given steroids [6]. In patients with underlying lung disease, even low doses (≤15 mg/day prednisone) of continuously administered steroids are sufficient for the development of IA [19]. Although most patients with COPD, particularly those with exacerbations severe enough to be treated by mechanical ventilation, are given steroids, COPD alone, without concomitant use of steroids, can be a risk factor for IA, as documented by Cornillet *et al.* [8].

Steroid use may also explain the absence of fever observed in as many as two-thirds of patients [10,23]. Together with the milder symptoms of IA in non-neutropenic patients, particularly with respect to cough and pleuritic chest pain, this may explain why the correct diagnosis is often made late or at autopsy, with grave consequences for outcome [8]. Indeed, mortality rates exceeding 80% are consistently reported for non-haematological patients [6,19,20]. A higher survival rate of 28.3% has been recently been reported in COPD patients with lower respiratory tract specimens positive for *Aspergillus* spp. [10], which may have increased the clinicians' awareness of the possibility of IA. The mortality rate in this study reached 57.1%; only 62% of patients, however, received treatment active against *Aspergillus* spp. In a worrisome 38% of our patients who were not given antifungal drugs the diagnosis

was only made at autopsy. In a multivariate analysis, older age was significantly associated with the diagnosis of IA missed during the patient's lifetime. Solid organ transplantation and chronic lung diseases, in contrast, lowered the odds of a post-mortem diagnosis. These findings possibly reflect more aggressive diagnosis and prompt commencement of antifungal therapy in younger patients, who are known to be at higher risk of invasive fungal disease.

If the diagnosis of IPA is considered at all, it is difficult to establish in a patient population in whom histopathological examinations can often not be performed, where imaging studies are of limited value, culture and microscopy of respiratory samples have a sensitivity and specificity of approximately 50%, and the galactomannan assay in serum has a substantially lower sensitivity than in neutropenic patients [23,25]. Galactomannan detection in bronchoalveolar lavage fluid has recently been ascribed a sensitivity and specificity for IA in critically ill patients approaching 90% [6]. If confirmed, this approach could substantially enhance our diagnostic capacity in these patients.

In addition, surveillance in the non-neutropenic population must be emphasized, particularly in the presence of factors associated with IA: corticosteroid therapy (even at low doses), chronic respiratory diseases, and ICU admission, with or without mechanical ventilation.

An important limitation of the study results from its retrospective design and the rarity of some disease manifestations of IA except for IPA. We were unable to perform a comparative analysis of the clinical presentation and risk profiles associated with individual manifestations of IA. This might have been helpful to establish improved diagnostic approaches. Considering the large proportion of cases diagnosed at autopsy and the declining autopsy rate at all the participating clinics, it is conceivable that some cases may have been missed and that the true incidence of IA in this patient population may be higher. Nevertheless, by combining a wide range of search strategies, a remarkable number of cases of IA in non-neutropenic patients were identified. Inclusion of all forms of IA, careful review of cases by an experienced data review committee and collaboration between all university hospitals providing a countrywide survey are the strengths of the present study.

In conclusion, IA remains a major life-threatening infection. This 2-year survey at all five Swiss teaching hospitals emphasizes the high frequency of IA in non-neutropenic patients, its high mortality rate, and the high proportion of post-mortem diagnosis. Clinical signs are frequently lacking in mildly immunosuppressed patients, but recent major advances in the diagnosis of IPA may aid in identifying affected patients. Conditions that should increase the level of suspicion of IPA include corticosteroid therapy, chronic lung disease, and ICU stay with or without mechanical ventilation.

Transparency Declaration

The authors have no conflicts of interest to declare.

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