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Research

Incidence of invasive aspergillosis following remission–induction chemotherapy for acute leukemia: a retrospective cohort study in a single Canadian tertiary care centre

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Abstract

Background: The decision to use universal primary antimould prophylaxis to prevent invasive aspergillosis in patients with acute leukemia depends on the incidence of infection at individual centres. We determined our institution's incidence of invasive aspergillosis among patients who received remission–induction chemotherapy for acute leukemia to evaluate the potential benefits of primary antimould prophylaxis.

Methods: We conducted this retrospective cohort study at a Canadian tertiary care centre. From the central pharmacy registries, we retrieved records for all adult patients for whom remission–induction chemotherapy for acute leukemia was prescribed between 2008 and 2010. We retrieved clinical, microbiologic, pathologic and radiologic data from the patients' medical charts. The primary outcome was a diagnosis of probable or proven invasive aspergillosis up to 180 days after resolution of aplasia.

Results: We retrieved records for 123 patients with acute leukemia. Twenty-two of these patients did not receive the prescribed chemotherapy and were excluded from the analysis. Of the 101 patients included, 77 (76.2%) had acute myeloid leukemia. Overall, 136 courses of chemotherapy were administered, with more than 1 course administered to 26 (25.7%) of the 101 patients. In 9 of the patients (8.9%; 95% confidence interval 4.2%–16.2%), invasive aspergillosis was diagnosed (3 proven and 6 probable cases) a median of 19 (range 11–34) days after initiation of chemotherapy. In 7 (78%) of these 9 patients, invasive aspergillosis occurred during the first course of chemotherapy. Three patients died within the first year after diagnosis of invasive aspergillosis.

Interpretation: We found a high incidence (8.9%) of invasive aspergillosis at our centre. This finding triggered the introduction of targeted antimould prophylaxis for patients with acute leukemia who were undergoing remission–induction chemotherapy.

Invasive fungal infections contribute substantially to illness and death among patients with hematologic malignancy.[1] The most commonly diagnosed type of invasive fungal infection has shifted over time from invasive candidiasis to invasive aspergillosis.[2] This shift has been attributed, in part, to the widespread use of fluconazole prophylaxis.[2] In fact, recent epidemiologic surveys reported that over 90% of cases of invasive mould diseases in patients with hematologic malignancy were caused by *Aspergillus* species.[1,3] Among hematologic cancers, acute myeloid leukemia carries the highest risk of invasive aspergillosis.[1,3–6] Moreover, despite the growing antifungal armamentarium and new diagnostic strategies, the aspergillosis-attributable mortality rate remains about 30%–40% in patients with hematologic cancer.[3,7] These findings emphasize the need to develop efficient strategies to avoid this complication.

In a previous randomized multicentre study, prophylaxis with posaconazole (an extended-spectrum triazole) prevented invasive aspergillosis in patients receiving remission–induction chemotherapy for acute myeloid leukemia or myelodysplastic syndrome.[8] That study also showed that the use of antifungal prophylaxis was associated with improved overall survival.[8] More recently, the results of a prospective cohort study showed that the incidence of invasive aspergillosis among patients undergoing their first course of remission–induction chemotherapy for acute myeloid leukemia decreased from 13.4% to 2.6% (p = 0.018) after introduction of universal

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posaconazole prophylaxis.[9] International guidelines now recommend posaconazole as the first-line prophylactic agent in patients with neutropenic acute myeloid leukemia or myelodysplastic syndrome.[10,11] Fluconazole remains the first-line agent for patients with neutropenia associated with other hematologic malignancies.

The incidence of invasive aspergillosis is influenced by many factors, such as underlying disease, age, type of antifungal prophylaxis used, access to recent diagnostic tools, geoclimatic influences, nosocomial outbreaks and construction activities in and around medical centres.[6,12–14] Accordingly, the incidence of probable or proven invasive aspergillosis among patients undergoing treatment for acute myeloid leukemia before the introduction of posaconazole prophylaxis was variable, ranging from 1.0% to 18%.[1,3,7,9,15–25] The effectiveness of such prophylaxis depends on the incidence of the targeted disease at individual centres.[26]

Our objective was to retrospectively establish the incidence of invasive aspergillosis at our centre among patients who received remission–induction chemotherapy for acute leukemia to evaluate the potential benefit of primary antimould prophylaxis in high-risk patients with profound neutropenia following intensive chemotherapy.

Methods

Study population and setting

The study was approved by the research ethics committee of the Hôpital Maisonneuve-Rosemont.

We conducted this single-centre retrospective cohort study between January 2008 and December 2010. All adult patients (≥ 18 years of age) with acute myeloid leukemia or acute lymphocytic leukemia who were admitted during the study period for remission–induction chemotherapy were eligible. Patients with a positive result on a galactomannan antigen-detection test at the beginning of chemotherapy were excluded. Our institution, a 588-bed tertiary care hospital built in 1953, is an important referral centre for hematology and hematopoietic stem cell transplantation. Remission–induction chemotherapy is conducted in protected rooms with positive-pressure, high-efficiency particulate air filtration. Fluconazole was the first-line antifungal prophylactic used during the study period. All patients were screened for serum-circulating galactomannan antigen (with Platelia *Aspergillus* enzyme immunoassay, Bio-Rad Laboratories, Montréal, Quebec) twice weekly from the start of chemotherapy until bone marrow recovery (defined as absolute neutrophil count > 0.5×10^9/L for 2 consecutive days). If a patient had a positive result on the galactomannan antigen-detection test and/or unexplained and persistent (≥ 4 days) febrile neutropenia refractory to broad-spectrum antibiotics, thoracic computed tomography (CT) was performed, followed by fibreoptic bronchoscopy with bronchoalveolar lavage when clinically indicated. In addition to the usual histopathologic analysis and bacterial, viral and fungal culture, bronchoalveolar lavage fluid was subjected to galactomannan antigen-detection testing.

Data collection

We retrieved records from the hospital's central pharmacy database registries for remission–induction chemotherapy regimens prescribed during the study period for patients with acute myeloid leukemia or acute lymphocytic leukemia. We performed a retrospective systematic review of patients' medical charts and computerized hospital databases up to 180 days after resolution of aplasia. We did not exclude patients who received posaconazole prophylaxis during remission–induction chemotherapy (as part of a clinical trial or for other reasons), because our aim was to determine the true incidence of invasive aspergillosis at our centre. We collected data on demographic characteristics, underlying disease, type of remission–induction chemotherapy, duration of neutropenia, administration of antifungals (for prophylaxis or therapy) and diagnostic procedures, along with any relevant microbiologic, pathologic and radiologic data. We included in our analysis any systemic antifungal therapy administered over the period from initiation of remission–induction chemotherapy to resolution of aplasia.

Definitions and data analysis

We based our definitions of invasive aspergillosis on the 2008 criteria of the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.27 Only patients with proven or probable invasive aspergillosis were included in the analysis. Briefly, proven cases of invasive aspergillosis required histopathologic or cytopathologic examination showing hyphae from a biopsy specimen, with evidence of associated tissue damage or a positive culture result for a sample obtained from a normally sterile site. Probable cases required an association of host factors, mycologic results (including but not limited to detection of galactomannan antigen and positive culture result for a sample from a nonsterile site) and clinical criteria. The results of serum galactomannan antigen-detection testing were considered positive if 2 consecutive serum samples had optical density of 0.5 or higher. For bronchoalveolar lavage fluids, optical density of 2.0 or higher (cut-off established in a local performance study28) was defined as positive. Data were analyzed with descriptive statistics. Categorical variables are expressed as frequencies and percentages, and non-normally distributed continuous variables are expressed as medians with interquartile ranges (IQRs).

Results

From the pharmacy registries, we retrieved remission–induction chemotherapy prescriptions for treatment of acute leukemia in 123 patients. Twenty-two of these patients did not undergo their chemotherapy course and were excluded from the analysis (Figure 1). We analyzed data for a total of 136 courses of remission–induction chemotherapy administered to 101 patients over the 3-year study period (Table 1). The annual number of regimens administered was 40 in both 2008 and 2009 and 56 in 2010. The majority of patients (75 [74.3%])

received only 1 course of chemotherapy; 19 (18.8%) received 2 courses, and 7 (6.9%) received more than 2 courses. Acute myeloid leukemia was the most common diagnosis (77 patients [76.2%]).

During the study period, posaconazole prophylaxis was administered in conjunction with 11 courses of chemotherapy (no courses in 2008, 3 courses in 2009 and 8 courses in 2010). Five patients received posaconazole prophylaxis during their

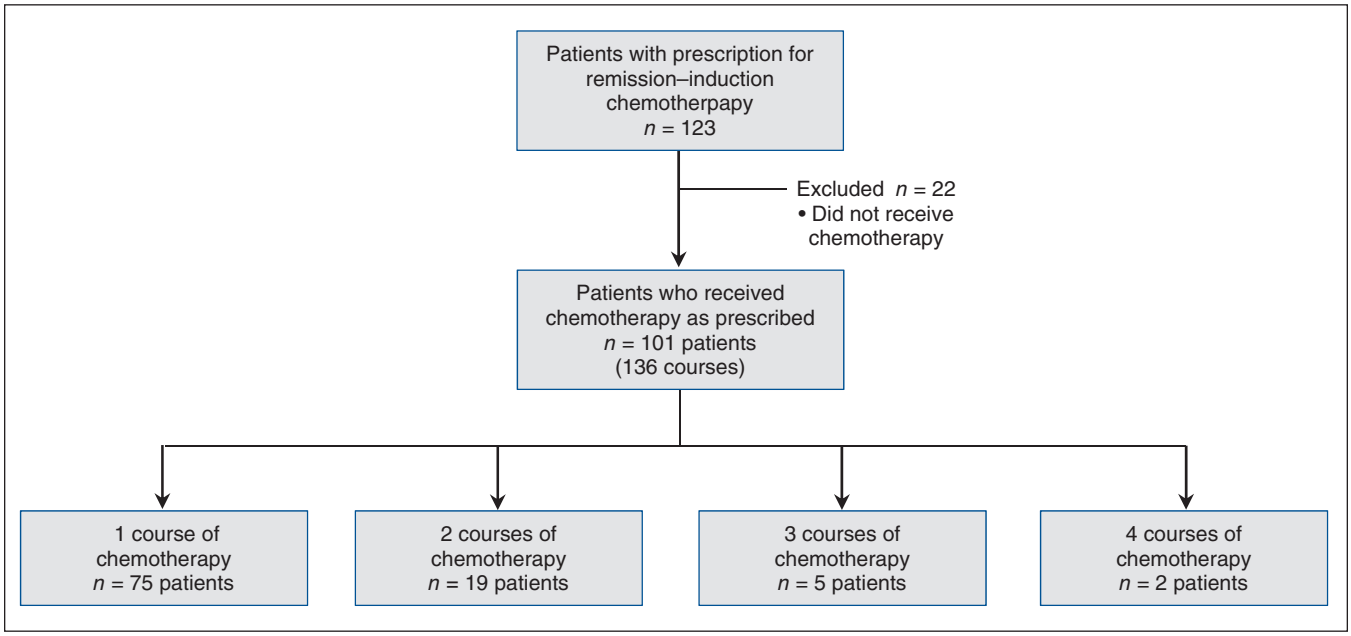

Figure 1: Selection of patients from the hospital's central pharmacy database registries, on the basis of prescriptions for remission–induction chemotherapy for acute leukemia.

Table 1: Clinical characteristics of patients and chemotherapy courses over time

Characteristic	Year; no. of patients*			
	2008	2009	2010	All years
No. of patients				
Eligible	43	37	43	123
Did not receive chemotherapy	8	11	3	22
With evaluable data	35	26	40	101
Age, yr, median (IQR)†	50 (38.5–59.5)	49 (39.0–58.3)	43.5 (36.0–60.3)	48 (37.0–60.0)
Sex, male, no. (%)†	20 (57)	18 (69)	21 (52)	59 (58)
Underlying disease†				
Acute myeloid leukemia	24	21	32	77
Acute lymphocytic leukemia	8	5	7	20
Biphenotypical acute leukemia	3	0	1	4
Total	35	26	40	101
Courses of remission–induction chemotherapy				
1 course	31	17	27	75
2 courses	3	6	10	19
3 courses	1	1	3	5
4 courses	0	2	0	2
Total no. of courses	40	40	56	136

Note: IQR = interquartile range.
*Except where otherwise indicated.
†For patients with evaluable data.

first course of remission–induction chemotherapy, usually as part of a clinical trial (4 patients). Fluconazole prophylaxis was prescribed in conjunction with a total of 109 courses (80.1%). Patients were exposed to a wide range of systemic antifungal agents during the period of aplasia, as detailed in Table 2.

A total of 9 cases of invasive aspergillosis (3 proven and 6 probable) were diagnosed over the 3-year study period, for a calculated cumulative incidence of 8.9% (95% confidence interval [CI] 4.2%–16.2%). The incidence increased to 10.0% (95% CI 4.7%–18.1%) when the 11 patients who received posaconazole prophylaxis were excluded from the analysis. Table 3 details the clinical characteristics of the 9 proven and probable cases of invasive aspergillosis. Pulmonary disease was observed in all 9 patients, 8 of whom underwent fibreoptic bronchoscopy with bronchoalveolar lavage. One patient, a 66-year-old woman (patient 1), experienced disseminated infection with positive histopathologic f indings and growth of *Aspergillus fumigatus* complex in skin lesions. The median age at diagnosis was 57 (IQR 53–58) years, and the ratio of men to women was 4:5. In 7 cases (78%), invasive aspergillosis occurred after the first course of remission–induction chemotherapy, and the remaining 2 cases (22%) were diagnosed during the second course of chemotherapy. Acute myeloid leukemia was the underlying hematologic malignancy in 7 patients (78%). Invasive aspergillosis was diagnosed at a median of 19 (range 11–34) days after initiation of chemotherapy. The lowest absolute neutrophil count was 0×10^9/L in all but 1 patient; the exception was a patient with acute lymphocytic leukemia who never

Table 2: Systemic antifungal treatment (prophylactic and therapeutic)

Antifungal agent	No. (%) of courses of chemotherapy *n* = 136
Monotherapy	
Fluconazole	37 (27.2)
Echinocandin*	9 (6.6)
Antifungal azole	5 (3.7)†
Amphotericin B	0 (0)
Combination therapy	
Fluconazole + echinocandin	46 (33.8)
Fluconazole + echinocandin + antifungal azole	17 (12.5)‡
Echinocandin + antifungal azole	10 (7.4)
Other combinations§	12 (8.8)

*Echinocandin consisted of caspofungin and/or micafungin.
†Posaconazole for 4 courses of chemotherapy and voriconazole for 1 course.
‡The antifungal azole was posaconazole for 8 courses of chemotherapy, voriconazole for 8 courses, and both posaconazole and voriconazole for 1 course (total 17 courses).
§Fluconazole + antifungal azoles (*n* = 3 courses), fluconazole + caspofungin + amphotericin B (*n* = 1 course), fluconazole + antifungal azole + amphotericin B (*n* = 2 courses), fluconazole + caspofungin + antifungal azole + amphotericin B (*n* = 3 courses), caspofungin + antifungal azole + amphotericin B (*n* = 2 courses), antifungal azole + amphotericin B (*n* = 1 course).

Table 3: Characteristics of patients with proven or probable invasive aspergillosis

Patient no.	Year	Sex	Age, yr	Diagnosis	Course of occurrence*	Interval to diagnosis, d†	Nadir ANC, $\times 10^9$/L	Biopsy site‡	Galactomannan antigen test, index value§	Organism cultured	PPx	Outcome
Proven												
1	2008	F	66	AML	1	19	0	Skin	Serum: > 6.4	*Aspergillus fumigatus*	Fl	Died
2	2009	M	53	AML	1	19	0	Lung	Serum: 3.0 Lavage: 3.0	*Aspergillus terreus*	Fl	Died
3	2010	F	57	ALL	2	11	1.4	Lung	Serum: < 0.5 Lavage: < 2.0	No growth	C	Survived
Probable												
4	2009	M	56	AML	1	11	0	NA	Serum: < 0.5 Lavage: 3.5	No growth	Fl	Died
5	2009	F	40	ALL	2	28	0	NA	Serum: < 0.5 Lavage: 6.9	*Aspergillus* sp.	C	Survived
6	2009	M	57	AML	1	24	0	NA	Serum: < 0.5 Lavage: 5.8	*Aspergillus nidulans*	C	Survived
7	2010	M	38	AML	1	19	0	NA	Serum: < 0.5 Lavage: 4.9	No growth	Fl	Survived
8	2010	F	65	AML	1	17	0	NA	Serum: 4.4 Lavage: < 2.0	No growth	Fl	Died
9	2010	F	58	AML	1	34	0	NA	Serum: 5.9 Lavage: 3.0	No growth	Fl	Survived

Note: ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, ANC = absolute neutrophil count, C = caspofungin, Fl = fluconazole, NA = not applicable, PPx = prophylaxis.
*Course of remission–induction chemotherapy during which invasive aspergillosis occurred.
†Number of days from initiation of chemotherapy until diagnosis of invasive aspergillosis.
‡Histopathology results compatible with invasive aspergillosis (hyphae-associated tissue damage).
§Index value refers to optical density. "Lavage" refers to fluid from bronchoalveolar lavage. Values < 0.5 for serum and < 2.0 for lavage fluid are considered negative.

experienced neutropenia. The median duration of neutropenia was 18 (IQR 13–22) days. Three patients received caspofungin prophylaxis, and the other 6 patients received fluconazole prophylaxis. *Aspergillus* species were cultured in samples from 4 of the 9 patients. The galactomannan antigen was detected in 8 patients: in bronchoalveolar lavage fluids only (n = 4), serum only (n = 2) or both (n = 2). Detection of galactomannan antigen was the only positive mycologic criterion identified in 4 of the 6 patients with probable invasive aspergillosis.

A total of 4 patients died, 2 with proven and 2 with probable invasive aspergillosis. Three of the patients died within 1 year of the diagnosis of invasive aspergillosis. Only 1 death was directly attributable to invasive aspergillosis (patient 1).

Interpretation

In this study, we sought to determine the incidence of invasive aspergillosis among adult patients who underwent remission–induction chemotherapy for acute leukemia in a Canadian tertiary care centre.

We identified 9 cases of proven or probable invasive aspergillosis following remission–induction chemotherapy during the 3-year study period. One case occurred in 2008, and the other 8 cases were divided evenly between 2009 and 2010, which suggests the absence of an outbreak. No seasonal variation or notable temporal trends were observed. There were no major construction activities around the institution during the study period, and none of the interior renovation projects that took place during these targeted years were located close to the hematology units. Moreover, courses of remission–induction chemotherapy for patients with acute leukemia were administered in individual rooms with positive-pressure high-efficiency particulate air filtration. However, even in this setting with low environmental risk, the cumulative incidence of invasive aspergillosis among patients with acute leukemia was 8.9% (95% CI 4.2%–16.2%), higher than some of the values reported in recent studies (Table 4). In fact, the incidence of invasive aspergillosis has been highly variable across studies, a reflection of the multiple risk factors that determine its occurrence.[2,6,12,13,31] For purposes of homogeneity, we excluded from Table 4 any studies that clearly described universal use of posaconazole as first-line prophylaxis. Important heterogeneity among studies dictates caution when generalizing results from one institution to another.

As expected, most cases of invasive aspergillosis in this study (7 of 9 patients [78%]) occurred during the first course of remission–induction chemotherapy, which is considered the highest-risk period for development of invasive fungal disease among patients with acute leukemia.[1,18,25,32] Our study included 10 patients with acute promyelocytic leukemia, all of whom were treated with an all-*trans*-retinoic acid regimen. All-*trans*-retinoic acid is metabolized by cytochrome P450 isoenzymes, including CYP2C9 and CYP3A4. Possible interactions between this agent and fluconazole (CYP2C9 inhibitor), voriconazole (CYP2C9/3A4 inhibitor) and posaconazole (CYP3A4 inhibitor) have been reported,[33–37] but we did not observe any interactions of this type in our patients. The aspergillosis-attributable mortality rate in our study was 11% (1 of 9 patients). Three other patients with acute myeloid leukemia died within 2 years after diagnosis of invasive aspergillosis, for a 2-year global mortality rate of 44% (4 of 9 patients). A recent study reported that the 2-year survival rate among patients with acute myeloid leukemia and invasive aspergillosis was significantly lower than among patients without invasive aspergillosis, even when the rate was adjusted for response to induction chemotherapy.[38]

The galactomannan antigen-detection test, in combination with CT of the lung, is an important tool for early recognition of pulmonary aspergillosis,[39] and the performance of galactomannan antigen-detection testing in serum has been studied extensively.[40,41] However, among the patients in our study, serum galactomannan antigen-detection testing had limited performance. If diagnosis had been based solely on the results of this test, 5 cases of invasive aspergillosis would have been missed. Interestingly, 3 of these 5 patients were receiving caspofungin therapy. Marr and others[42] reported a significant decrease in the sensitivity of galactomannan antigen-detection testing when patients were receiving mould-active antifungal treatment. In our study, bronchoalveolar lavage fluid was more useful than serum for diagnostic assay of galactomannan antigen.

Following the randomized controlled trial by Cornely and colleagues in 2007,[8] subsequent studies showed, in real-life settings, that the incidence of invasive aspergillosis among patients with acute myeloid and lymphocytic leukemia declined after introduction of posaconazole prophylaxis.[9,43–45] Cornely and colleagues[8] reported a 1% incidence of breakthrough invasive aspergillosis among patients with acute myeloid leukemia who received posaconazole prophylaxis, with a relative risk reduction of 0.9. Given the overall incidence of invasive aspergillosis at our centre (8.9%) and the theoretical relative risk reduction with posaconazole prophylaxis (0.9), the number needed to treat to prevent 1 case of invasive aspergillosis is 13 patients.

The burden of invasive aspergillosis, in terms of mortality, morbidity and cost, and the high incidence at our institution prompted us to consider using posaconazole prophylaxis in this high-risk population. Using data from the study by Cornely and colleagues,[8] subsequent researchers have conducted cost-effectiveness analyses of posaconazole prophylaxis.[46–48] Two of these studies, which were conducted from the perspective of provincial health care systems in Canada, showed that posaconazole prophylaxis was cost-effective.[47,48] Taking into account these cost-effectiveness analyses and our institution's high incidence of invasive aspergillosis, it appeared reasonable to initiate use of posaconazole prophylaxis as a standard of care for patients with acute myeloid leukemia undergoing remission–induction chemotherapy.

Limitations

Our study had several limitations. First, many of the patients were exposed to 1 or more mould-active antifungal therapies during the period of aplasia. However, because we sought to determine the incidence of invasive aspergillosis in a real-life setting, we did not exclude patients on the basis of exposure to these drugs. Interestingly, proven or probable invasive aspergillosis was not diagnosed in any of the patients who

received posaconazole prophylaxis. Second, because the data were collected retrospectively, it was difficult to establish, at least for some patients, the clinical indications for antifungal treatment (prophylactic v. empiric) and to confirm that the patients actually received the prescribed medication. Third, we did not determine risk factors for invasive aspergillosis in this population because the small sample size would have impaired the validity of the results. Finally, we conducted our study at a single tertiary care institution, a referral centre for hematology and hematopoietic stem cell transplantation. As such, and given that the incidence of invasive aspergillosis is influenced by many factors, generalizability may be limited.

Conclusion

We determined that the incidence of invasive aspergillosis among adult patients who underwent intensive remission–induction chemotherapy for acute leukemia at our institution was 8.9% (95% CI 4.2%–16.2%). The number needed to treat to prevent 1 case of invasive aspergillosis would be about 13 patients. These findings triggered the initiation, in 2011, of universal posaconazole prophylaxis for patients with acute myeloid leukemia undergoing remission–induction chemotherapy at our institution. However, many issues remain unresolved regarding this form of prophylaxis, including the performance of serum galactomannan antigen-detection testing and thoracic CT in low-prevalence populations, the impact of chemotherapy-induced gastrointestinal tract disturbances on bioavailability of posaconazole, the need to monitor serum concentration of posaconazole, the indication for empiric antifungal treatment in febrile neutropenia and the treatment of breakthrough invasive aspergillosis in patients who are receiving posaconazole prophylaxis. Prospective surveillance for invasive aspergillosis in patients with acute myeloid leukemia following introduction of universal posaconazole prophylaxis may shed light on some of these issues.

Table 4: Reported incidence of proven or probable invasive aspergillosis in adult patients with acute leukemia*

Reference	Surveillance period	Study design	Country	Hematologic malignancy	No. of patients	Incidence, %	Standardized definitions
Klimowski et al.[21]	1964–1983	Single centre	USA	AML ALL	716 546	6.7 3.3	NA
Pagano et al.[18]	1987–1998	Multicentre, retrospective	Italy	AL	4448	6.2†	MSG[29]
Nosari et al.[22]	1989–1999	Single centre, retrospective	Italy	AL	675	7.1	NA
Cornet et al.[20]	1994–1999	Multicentre, prospective	France	AML ALL	NA	8.0 6.3	2002 EORTC/MSG[30]
Mühlemann et al.[25]	1995–1999	Single centre, retrospective	Switzerland	AL MDS	101	12	2002 EORTC/MSG[30]
Caira et al.[3]	1999–2003	Multicentre, prospective	Italy	AML	1596	10.5	2002 EORTC/MSG[30]
Pagano et al.[1]	1999–2003	Multicentre, retrospective	Italy	AL AML ALL	4185 3012 1173	6.1 7.1 3.8	2002 EORTC/MSG[30]
Slobbe et al.[15]	2002–2007	Single centre, prospective	Netherlands	AML MDS	269	18	2008 EORTC/MSG[27]
Vehreschild et al.[9]	2003–2005	Multicentre, prospective	Germany	AML	82	13.4	2002 EORTC/MSG[30]
Nicolle et al.[23]‡	2004–2009	Single centre, prospective	France	AL AML ALL	2928 2078 850	3.8 4.4 2.2	2008 EORTC/MSG[27]
Montagna et al.[17]	2007–2008	Multicentre, prospective	Italy	AL AML ALL	243 195 48	1.2 1.0 2.1	2008 EORTC/MSG[27]
Pagano et al.[19]	2007–2009	Multicentre, prospective	Italy	AML	747	4.2	NA
Nucci et al.[24]	2007–2009	Multicentre, prospective	Brazil	AML MDS	202	5.9	2008 EORTC/MSG[27]
Barkati et al. (present study)	2008–2010	Single centre, retrospective	Canada	AL	101	8.9	2008 EORTC/MSG[27]

Note: AL = acute leukemia, ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, EORTC/MSG = European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases, MDS = myelodysplastic syndrome, MSG = Mycoses Study Group of the National Institute of Allergy and Infectious Diseases, NA = not available.
*Patients with invasive aspergillosis following hematopoietic stem cell transplant for acute leukemia were excluded from this review.
†Incidence for all cases of filamentous fungal infection (76% of which were invasive aspergillosis).
‡Posaconazole prophylaxis was introduced in remission–induction chemotherapy for patients with AML during the year 2007.

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