Incidence of Nosocomial Aspergillosis in Patients with Leukemia Over a Twenty-Year Period

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ABSTRACT
The incidence of invasive nosocomial aspergillosis was studied in leukemia patients at an oncology center from 1964 to 1985. A total of 97 cases of aspergillosis occurred in 1,886 patients, yielding an overall case rate of 5.2 cases per 100 patients and an incidence rate of 9.1 per 10,000 patient days. The highest incidence rate was in patients with chronic myelogenous leukemia (13.7 cases per 10,000 patient days), followed by patients with acute myelogenous leukemia (10.6 cases per 10,000 patient days). Subdividing patients after 1978 into those receiving bone marrow transplantation and those who did not demonstrated the predisposition of transplant recipients to aspergillosis. The rates of aspergillosis among those patients who did not receive a bone marrow transplant were highest for patients with acute myelogenous leukemia. Increases in the annual rates of aspergillosis over time coincided with the level of internal renovation activity and major construction projects upwind of patient care facilities. [Infect Control Hosp Epidemiol 1989; 10(7):299-305.]

INTRODUCTION
Invasive aspergillosis is an important infection and increasingly more common in patients whose host defenses have been altered by severe primary disease or immunosuppressive therapy. The commonly affected patient populations include those with leukemia, lymphoma, and other types of malignancies, bone marrow, renal, and cardiac transplant recipients, and burn patients. Nosocomial outbreaks of aspergillosis have been attributed to environmental factors such as ongoing construction, renovation, and fireproofing. Also, nosocomial aspergillosis has been associated with certain host factors.

Because patients with leukemia are the most commonly affected group among cancer patients, specific host factors predisposing this population to aspergillosis have been studied. These factors include the type of leukemia, granulocytopenia, age, sex, smoking history, other infections, cytotoxic chemotherapy, antimicrobial therapy, antifungal prophylaxis, corticosteroid therapy, nasopharyngeal colonization with Aspergillus, history of lung or sinus disease, days of hospitalization in preceding six months, and duration of fever.

Although many investigators have reported that aspergillosis is increasing in frequency, no study to date has been published that shows the incidence of the disease over an extended period of time. The present study was undertaken to provide estimates of the incidence of aspergillosis for a 20-year period in patients with leukemia at Roswell Park Memorial Institute (RPMI). This investigation also evaluated variation in the incidence of aspergillosis by type of leukemia.

PATIENTS AND METHODS
The study population included patients with leukemia admitted to RPMI, a comprehensive cancer center with a 273-bed inpatient hospital located in Buffalo, New York, from 1964 to 1983. Medical records of all patients with leukemia seen at RPMI dur-
ing the 20-year period were reviewed. Information collected from these records included the patient’s name, chart number, type of leukemia, dates of admission and discharge, status as of last discharge and evidence of invasive aspergillosis. Computerized medical files for the aforementioned information were available for the years 1964 to 1976, and 1978 to 1983. For the years 1976 to 1978, manual inspection of the medical records was performed by one of the authors (LLK) based on the discharge diagnosis of “leukemia.”

A patient was considered at risk for the development of nosocomial aspergillosis and included in the study if he or she spent at least three consecutive nights in the hospital sometime during the 20-year study period. Outpatients and hospitalized patients who spent fewer than three consecutive nights in the hospital were excluded from the investigation. In addition, patients in whom aspergillosis was diagnosed but the infection was present or considered to be incubating on admission to the hospital also were excluded. All medical records were reviewed. Each patient was placed on a list according to type of leukemia: acute lymphocytic leukemia (ALL); chronic lymphocytic leukemia (CLL); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML), which included patients in chronic, accelerated and blastic phases; and other types of leukemia (other). Admission and discharge dates were analyzed, and the number of hospitalized days was calculated. The number of hospitalized days per year was recorded for each patient. For each type of leukemia, the number of patients at risk per year and the total number of days per year were tallied.

All cases diagnosed as invasive aspergillosis from 1964 to 1983 were identified. Listings were obtained from the pathology department, a computerized medical roster or the actual medical records. Cases of aspergillosis were categorized according to patient’s name, chart number, date of diagnosis and underlying disease. Data from each source were cross-checked for accuracy of information. A case was defined as a patient who had histologically-confirmed evidence of invasive aspergillosis that was not incubating or present on admission. Such evidence consisted of tissue invasion with the fungus in autopsy material or open lung biopsy specimens. Autopsy and postmortem culture evidence of Aspergillus was available for 25% of the cases. No cases were included on the basis of clinical criteria alone. Only aspergillosis cases identified in patients with the underlying diagnosis of leukemia were used in this investigation.

From the data collected, the annual case rate of aspergillosis per 100 patients and the yearly incidence of aspergillosis per 10,000 patient days (PD) were calculated for each of the five types of leukemia and for all types of leukemia combined.

Because allogeneic bone marrow transplant (BMT) patients are at increased risk for the development of aspergillosis,7,8,10,11 all BMT recipients at RPMI were identified according to name, chart number, date of transplantation, underlying disease and presence or absence of aspergillosis. The yearly incidence of Aspergillus infection among leukemia patients who had BMTs was calculated. The yearly incidence of aspergillosis in non-BMT (NBMT) leukemia patients also was calculated. Rates among the groups were compared.

Since increased rates of infection due to Aspergillus have been attributed to ongoing construction and excavation,6,13,14,19 the engineering and maintenance department at RPMI was contacted for a listing of such projects on or near the RPMI complex during the study period. Also, a listing of all internal renovation projects underway in the patient care facilities during the study period was obtained.

A Wilcoxon rank sum test was employed to evaluate the difference in the incidence of aspergillosis between the years in which construction was being performed to the west of the patient care facilities versus those years in which it was not. A Spearman rank correlation was used to test the relationship between the level of internal renovation activity and the annual incidence of aspergillosis.

RESULTS

All Leukemia Patients

Medical records of approximately 2,200 leukemia patients were screened, but only 1,866 patients had at least one hospital admission of three or more consecutive nights at RPMI. The distribution of patients was: AML 716; ALL 546; CLL 258; CML 247; and other types of leukemia 99 (including erythro-leukemia and hairy cell leukemia).

The total number of patient days at risk contributed by the 1,866 leukemia patients was 106,697 days. Some patients were admitted once and only contributed days for one year. Other patients were admitted several times over a period of years, and thus contributed days for two or more years and were at risk for the development of aspergillosis for more than one year.

A total of 97 cases of invasive aspergillosis occurred in leukemia patients during this 20-year period. Almost half of the cases were seen in AML patients (48 cases). Twenty-one percent of the cases were seen in patients with CML (20 cases). Fourteen of the 20 cases were evenly distributed between patients with CML in accelerated or blastic phase; the disease status of the remainder was unknown. The remaining cases occurred in patients with ALL (18 cases), CLL (7 cases) and other types of leukemia (4 cases). The distribution of the cases during the 20-year period is found in Table 1.

The overall case rate of aspergillosis in leukemia patients during 1964 to 1983 was 5.2 cases per 100 patients (97 cases/1,866 patients). The highest rate occurred in patients with CML (8.1), followed by AML (6.7), other types of leukemia (4.0), ALL (3.3) and CLL (2.7). The yearly variation in the individual case rate for each type of leukemia is shown in Table 1. A chi-square analysis for linear trend to assess the
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Table 1: Incidence of Aplastic Anemia in Leukemia Patients at Roswell Park Memorial Institute (APM) from 1962 to 1974.
increasing case rate over time for all the types of leukemia demonstrated statistical significance ($p<0.01$). Also, the annual case rate rose significantly over time for patients with CML and AML, respectively ($p<0.01$ and $p=0.03$), but not for patients with other types of leukemia.

The overall incidence of aspergillosis in those patients admitted to RPMI with leukemia over the study period was 9.1 cases per 10,000 PD (97 cases/106,697 PD). Table 1 demonstrates the yearly incidence of aspergillosis during 1964-1983 for all types of leukemia combined. The highest incidence occurred in 1983 (35.8 cases/10,000 PD) and 1982 (21.9 cases/10,000 PD). The incidence for all other years was less than or equal to 12.5 cases per 10,000 PD. The incidence of aspergillosis per 10,000 PD in the 20-year period was highest in CML (13.7), followed by AML (10.6), other types of leukemia (7.2), ALL (6.4) and CLL (5.4). The rank order of the incidence of aspergillosis per 10,000 PD according to type of leukemia was the same rank order as the case rate. The variation in the incidence of aspergillosis by four-year intervals for each type of leukemia is depicted in Figure 1. The category of other types of leukemia was omitted from the graph, as only four cases of aspergillosis occurred in this group over the 20-year period.

### BMT Recipients Versus NBMT Patients

A bone marrow transplant program for leukemia patients initiated at RPMI in March 1978. Between 1978 and July 1983, 624 leukemic patients were admitted. Of these, 53 BMTs were performed on 52 patients with leukemia. Most BMTs were performed...
on patients with AML (21 cases), followed by those with ALL (18 cases), CML (10 cases) and other types of leukemia (3 cases). No BMTs were performed on CLL patients. The greatest number of BMTs in leukemia patients took place in 1981 (18 patients), followed by 1982 (13 patients), 1983 (9 patients), 1978 (5 patients), 1979 (4 patients) and 1980 (4 patients).

A total of seven cases of invasive aspergillosis occurred in BMT recipients with leukemia. Six cases were seen in patients with CML, and one case developed in a patient in the other types of leukemia category. No aspergillosis cases occurred in BMT recipients with ALL or AML. Most Aspergillus infections in BMT recipients with leukemia developed in 1983 (four cases). Two cases occurred in 1982 and one case in 1978.

As shown in Table 2, the overall case rate for aspergillosis in BMT recipients with leukemia from 1978 to 1983 was 13.5 cases per 100 patients (7 cases/52 patients). In contrast, among the 572 NBMT leukemia patients treated at RPMI between 1978 and 1983, 39 aspergillosis cases were diagnosed, yielding an overall case rate of 6.8 cases per 100 patients (39 cases/572 patients). The highest rate among NBMT patients occurred in patients with AML (10.6 cases per 100 patients), followed by CML (7.2 cases per 100 patients), ALL (5.0 cases per 100 patients), CLL (2.7 cases per 100 patients) and other types of leukemia (2.1 cases per 100 patients). The incidence of aspergillosis was highest in BMT recipients and NBMT patients in 1983.

**Construction at RPMI**

During the 20-year study period, 13 construction sites were identified in the RPMI area. As illustrated in Figure 2, 11 construction sites were located on the RPMI campus. Four structures were built between 1964 and 1966, six between 1970 and 1976 and one in 1979. Construction of a rapid transit system, which involved considerable earth movement, was underway from 1980 to 1982. Excavation for a 17-story building for another hospital adjacent to RPMI started in 1982.

The temporal relationship between construction and the annual incidence of aspergillosis is depicted in Figure 3. When all construction sites are considered, no direct relationship appears to exist. Taking into account that the prevailing winds in western New York are from the southwest, the rates for aspergillosis appear to be increased for years in which construction took place to the west of the patient care facilities (1974-1976 and 1980-1983). A satellite building (#2), directly west of the main hospital complex (#1), and a research studies center (#3), southwest of

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*Figure 1.* Incidence of aspergillosis in leukemia patients at RPMI from 1964 to 1983. This figure depicts the incidence of aspergillosis by type of leukemia per 10,000 patient days in four-year intervals.

*Figure 2.* Location of construction projects during the study period 1964 to 1983.
the main hospital, were under construction from June 1975 to July 1976, and July 1973 to August 1975, respectively, as indicated in Figure 1. A rapid transit system was under construction directly west of the RPMI campus from 1980 to 1982. The rates of aspergillosis in 1981, 1982 and 1983 rose steadily (11.4, 21.9, and 35.8 per 10,000 PD, respectively). However, the differences in incidence rates based on a Wilcoxon two-sample test were not statistically significant ($p=0.24$).

A total of 93 sundry interior renovation projects were underway in the RPMI patient care facilities during the study period. A significant correlation was demonstrated between the number of renovation projects performed each year and the annual incidence of aspergillosis ($p<0.05$ Spearman rank correlation). As environmental air sampling was not carried out longitudinally over the 20-year period, these data could not be used in the analysis.

**DISCUSSION**

Because of the paucity of data available on the actual incidence of invasive nosocomial aspergillosis among patients with leukemia, we endeavored to determine the incidence of aspergillosis among patients with different types of leukemia at RPMI over a 20-year period. Results showed that the incidence of aspergillosis increased over time. This upward trend coincided with the increasing number of internal renovation projects and major construction upwind of the patient care facilities, although the latter association was not significant. Other investigators have attributed nosocomial outbreaks of aspergillosis to ongoing construction and renovation.5,10,14,15,20,21 Unfortunately, during our study period, longitudinal fungal air cultures for *Aspergillus* were not obtained.

In our study, patients with CML and AML had the highest attack rates of invasive aspergillosis. A study by Fisher et al. found that at Memorial Sloan-Kettering Cancer Center, patients with AML and CML had the highest attack rates of aspergillosis among all patients admitted to that facility from 1971 to 1976.5 The incidence of aspergillosis for patients with AML (12.0 per 100 new patients with AML) and CML (9.80 cases per 100 new cases with CML) is similar to rates observed at RPMI. Reasons for the observed high rates seen in CML and AML patients may be related to such host factors as cytotoxic chemotherapy,7,20,24 antimicrobial therapy7,8,20,24 and prolonged granulocytopenia5,7,9,22 which have prolonged survival but rendered patients more susceptible to opportunistic pathogens.

We also found that when leukemia patients were subdivided further into those who were BMT recipients and those who were NBMT patients for the years 1978 to 1983, BMT recipients emerged as the highest risk group for the development of aspergillosis. In particular, as we previously reported, aspergillosis was found predominantly in patients with CML who received transplants.7 Other investigators have corroborated this predisposition to aspergillosis of both BMT recipients8 and those recipients who had CML.12 Our results also revealed that for this six-year period, the incidence of aspergillosis among NBMT patients increased notably, as did the incidence for all leukemic patients.

Clearly, patients undergoing BMT and those with CML and AML are more susceptible to nosocomially-acquired aspergillosis. Efforts to curb the increasing
Aspergillus approach. Aspergillosis has developing losis has high risk of developing aspergillosis. Reducing prolonged periods of granulocytopenia by employing granulocyte-macrophage colony-stimulating factor may reduce the likelihood of infection. In addition, further concerted investigations to evaluate prophylactic antifungal regimens are needed.

Once aspergillosis is suspected or diagnosed, early initiation of therapy is advocated.

REFERENCES