Nosocomial Pneumonia in Adult Patients Undergoing Bone Marrow Transplantation: A 9-Year Study

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Two hundred seventy-five consecutive patients treated with bone marrow transplantation (BMT) during a 9-year interval were analyzed for the incidence and etiology of nosocomial pneumonia. Cases included adults who acquired pneumonia during the first hospitalization period within 100 days of the transplant. Fifty-five (20%) of the 275 patients developed nosocomial pneumonia, and the crude mortality during the hospitalization period was 74.5%. An etiology was established in 67.3% (37 of 55) of episodes. Thirty-six percent (20 of 55) of the cases were caused by Aspergillus species, either as the sole agent (15 patients) or in association with others. The crude mortality for patients with Aspergillus pneumonia was 95%. Elimination of 90% of Aspergillus cases in our unit would have the effect of reducing the overall attack rate of nosocomial pneumonia to 13.4% and the associated crude mortality to 43.4%.


PNEUMONIA remains a significant cause of morbidity and mortality in bone marrow transplantation (BMT) patients. Recent studies have reported rates of pneumonia ranging from 35 to 43 per 100 transplant patients and crude mortality figures varying from 58% to 84%.

In general, cytomegalovirus (CMV) has been found to be the most frequent etiologic agent, but most of the studies have restricted their analyses to the interstitial pneumonitis syndrome. The latter is characterized by the development of dyspnea, nonproductive cough, hypoxemia, and interstitial infiltrates on chest radiographs, which occur in the absence of documented bacterial or fungal infection. However, in recent years, certain fungal infections have been found to be major causes of pneumonia and fatality following BMT. Furthermore, results of studies of BMT-associated pneumonia could vary not only according to study design factors such as the criteria used for case definition, but also by the diagnostic approaches, age, primary diagnoses of the patients, the human leukocyte antigen matching between donor and recipient, and the length of the follow-up.

In order to achieve an accurate perspective of BMT-associated pneumonias, it is desirable to approach the problem from an unrestricted perspective. In this report, we define the incidence and etiology of nosocomial pneumonia occurring during the first hospitalization period for 275 consecutive BMT patients. Strict case definitions were used, and all patients were identified by prospective surveillance. All were adults who were treated at the University of Iowa Hospitals and Clinics (UIHC) Adult Bone Marrow Transplant Unit from January 1, 1980 to December 31, 1988.

MATERIALS AND METHODS

The UIHC is a 900-bed teaching hospital providing tertiary care for the state of Iowa and surrounding areas. In January 1980, a bone marrow transplant program was begun, and 373 procedures have been performed through December 1988 (98 on pediatric patients and 275 on patients 16 years of age or older). A prospective infection control surveillance program has been active at UIHC since 1976. Recent validation studies using standard methods showed that the sensitivity and specificity of hospital-wide reports were 81% and 97%, respectively. Since May 1980 the data have been stored in an on-line computer system.

Case Definitions

An infection was defined as nosocomial if it was neither present nor incubating at the time of the admission and did not become manifest until 72 hours following admission. An infection present at admission was classified as nosocomial.
only if it was directly related to a previous admission and occurred within 10 days of discharge.

Nosocomial pneumonia was defined in a patient who had a chest radiographic examination with a new or progressive infiltrate and at least one of the following criteria: (1) new onset of rales on physical examination; (2) new onset of sputum production or change in character of sputum; (3) isolation of a pathogenic agent from bronchoalveolar lavage (BAL) (> 100,000 colonies per milliliter mandatory for bacteria) or pulmonary tissue; (4) recovery of *Histoplasma, Cryptococcus, Aspergillus, or Mucor* species, *Pneumocystis carinii*, *Nocardia* or *Actinomyces* species, *Mycobacterium* species, or *Legionella* species from sputum, BAL or tissue biopsy; (5) recovery of a pathogenic agent from a blood culture that was the same species as that recovered from the sputum culture; (6) isolation of a virus or detection of viral antigens in respiratory secretions (except for CMV, herpes simplex virus (HSV), or Epstein-Barr virus; and (7) histopathologic evidence of pneumonia (mandatory for *Candida* species).

The diagnosis of CMV pneumonia required the isolation of CMV from BAL fluid or pulmonary tissue biopsy. We then attempted to stratify the infections into those that were primary and those that were secondary. Primary CMV infection was defined in patients who were seronegative before the transplant and demonstrated a fourfold or greater increase in immunoglobulin G (IgG)- and IgM-specific CMV antibodies and/or in whom a positive isolation of the virus from any site in the period posttransplant was obtained. For the definition of secondary infection the same criteria were used for patients who were seropositive before the transplant.

Almost all patients in this series received large amounts of blood products, including intravenous IgG in some cases. Since this could represent a source of passively acquired CMV antibodies, the patients who presented an increase of CMV-specific IgG antibodies without a concurrent IgM-positive titer or CMV isolation were considered as having an indeterminant CMV infection status.

**Exclusion Criteria**

For the purpose of this study, we excluded any patient with one of the following diagnoses: acute respiratory distress syndrome (ARDS), atelectasis, neoplastic pulmonary infiltration, pulmonary hemorrhage, pulmonary embolus with infarction, or fluid overload.

**Case Finding**

Cases were identified by screening the infection control surveillance data and identifying all patients who were 18 years of age or older who were subjected to a BMT and acquired nosocomial pneumonia during the first hospitalization period within 100 days of the transplant. When these patients were identified, additional clinical criteria were applied to meet our case definition, which is more rigorous than that used in routine epidemiologic surveillance.

**Patient Supportive Care**

Details of the transplant procedure at this institution have been reported elsewhere. All patients were housed in single rooms ventilated centrally with high-efficiency particulate air (HEPA)-filtered air at four exchanges per hour. During the time of neutropenia, patients were maintained in simple reverse isolation: individuals entering the room wore a clean hospital gown and observed thorough hand washing practices. Patients were allowed to leave their rooms only for diagnostic or therapeutic procedures and were required to wear surgical masks and clean gowns.

On admission to the transplant unit an indwelling double-lumen intravenous catheter was placed surgically. Trimethoprim-sulfamethoxazole in the form of a double-strength tablet was given orally twice daily from day -8 through day -1 and resumed from day 28 (or when the neutrophil count was > 500/mm³) through day 100. Acyclovir was given three times daily intravenously from day +1 at 500 mg/m² until the time of the engraftment and then switched to 400 mg orally three times daily until day 100. Daily showers are required with a chlorhexidine-containing soap.

Blood products were transfused for a hemoglobin less than 10 g/dL or a platelet count less than 20,000/mm³. Since the beginning of the bone marrow transplant program, patients whose serologic tests for CMV were negative were given CMV-negative blood products throughout the period of cytopenia.

Febrile, neutropenic patients were clinically evaluated, cultured at all important sites and immediately started on broad-spectrum antibiotics. Over the course of the study, the latter included vancomycin, tobramycin, and a beta-lactam antibiotic. If the patient remained febrile after 3 days, amphotericin B was begun and quickly escalated to a daily dose of 0.6 mg/kg. Broad-spectrum antibiotic coverage was continued until the neutrophils were greater than 500 cells per cubic millimeter for two consecutive days and the patient became afebrile.

**Surveillance Cultures**

Surveillance cultures for bacteria and fungi were obtained weekly from the skin, nose, throat, urine, and anus since 1985 for all BMT patients. In addition, weekly samples of sera were tested by latex bead agglutination method (Cand-Tec; Ramco, Houston, TX) for *Candida* antigen.

Environmental air cultures for fungi were introduced in September 1987. Air samples were performed using a surface air system (Pool Bioanalysis, Italy) portable air sampler (time of sampling of 1 minute, airflow of 180 L/min) and were obtained from the BMT unit and from various sites outside the unit, including the Radiology unit, Radiation Therapy unit, and some outdoor areas.

**RESULTS**

**Study Population and Incidence of Nosocomial Pneumonia**

During the 9-year study period, 76 cases of nosocomial pneumonia were identified by the infection control surveillance system. Of the 76 cases, 72 could be reviewed (four charts were not available). Although seventeen of the cases met
surveillance criteria, they did not meet all of the clinical criteria imposed for this study and were excluded for the following reasons: two acquired nosocomial pneumonia during the first hospitalization period but after 100 days of the BMT, four did not fulfill the clinical criteria of the study, and 11 were judged to have other diagnoses (six adult respiratory distress syndrome, three fluid overload, one atelectasis, and the other leukemic infiltrate of the lungs). Thus, 55 cases of pneumonia, occurring in 53 patients, were included in the present series (two patients had two distinct episodes). This constituted an incidence of 20% (55 of 275) during the study period. The inclusion of the four cases for which charts were not available would have increased the incidence to 21.4%. Thirteen of the 21 patients excluded from the study for any reason (62%) died during the hospitalization period immediately after the BMT.

Demographic Features

Fifty-six percent (31 of 55) of the patients were male, and the mean age was 31 (± 11) years. The most frequent primary diagnosis of the pneumonia patients was chronic myeloid leukemia (20 of 55, 36.4%), followed by acute leukemia and lymphoma (16 patients each). Another two patients had aplastic anemia, and the other had adenocarcinoma of the breast. Forty of the 55 patients (72.7%) received allogeneic transplants. Of those, 21 (38.2%) had an unrelated donor, and 19 (34.5%) received the bone marrow from a sibling. Fourteen transplants were autologous, and the remaining patient was syngeneic. Forty-eight percent (25 of 52) of the patients were serologically positive for CMV before the transplantation. In one case this information was not available.

Interval to Infection and Etiology

The median interval between BMT and identification of the pneumonia was 21 days, with a mean of 28 (± 25) days and a range from 2 to 85 days (Fig 1). Bronchoscopy with cytologic observation and viral culture of specimens obtained by BAL was performed in 69.1% of the patients, open lung biopsy or transthoracic needle aspiration in 12.7% (seven of 55), and autopsy studies in 14 of the 41 patients (34.2%) who died.

An etiology was established in 37 of the 55 episodes (67%) (Table 1). Fifteen of the 18 patients for whom no etiology was established underwent bronchoscopy with BAL, and another one had an open lung biopsy performed. Of the remaining two patients, one had positive cultures for Candida glabrata in multiple samples of blood and sputum. At the time of clinical presentation this agent was considered the cause of the pneumonia, and no further diagnostic procedures were done. However, since we required histopathologic evidence of pneumonia for Candida species, this patient was considered as having an unknown etiology. The last patient had HSV isolated from tracheal aspirate secretions but did not undergo BAL or lung biopsy. The mean interval from the BMT to the pneumonia in the subgroup without an etiologic diagnosis was 22.6 (± 17.1) days, with a median of 17 days and a range of 7 to 73 days.

Thirty-six percent (20 of 55) of the pneumonias were caused by Aspergillus species, either as the sole agent (15 patients) or in association with others (Candida albicans [two patients], CMV, P carinii, and Legionella pneumophila, [one patient each]). In most years, the attack rate for Aspergillus pneumonia was 3% to 10%. However, no cases were observed in 1980 and 1982, and an unusually high rate (21%) was observed in 1985 (Fig 2). The monthly distribution of Aspergillus pneumonia indicates that there was a strong late autumn peak for this infection that was not observed in the non-Aspergillus cases (Fig 3). The median interval between the BMT and the pneumonia in this subset of patients was 14 days, with a mean of 19 (± 15) days and a range from 2 to 65 days. Eight of the 20 isolates were identified as Aspergillus flavus, five as Aspergillus fumigatus, and one as Aspergillus niger. Another two patients had both A flavus and A fumigatus recovered from the cultures, and in the remaining four patients, the species of the Aspergillus was not determined. In three of those
patients the diagnosis of *Aspergillus* was based on histopathologic findings at autopsy or skin biopsy.

CMV, the second most frequent etiologic agent in the present series, caused pneumonia in seven of the 55 patients (12.7%). One of the patients had both CMV and respiratory syncytial virus (RSV) identified in respiratory secretion and lung tissue samples. Three of seven cases (42.8%) were classified as primary CMV infections and the remaining four as secondary. The interval between the BMT and the onset of the pneumonia ranged from 44 to 85 days, with a median of 55 and a mean of 58 days. Two patients presented with serologic evidence of CMV infection without pneumonia. Additionally, 10 other patients were considered as having an indeterminant CMV infection status, since they presented an increase of IgG-specific CMV antibodies without a concurrent IgM positivity or CMV isolation.

The crude mortality of the patients with nosocomial pneumonia during the hospitalization period was 74.5% (41 of 55 deaths), with most of the deaths occurring in the first 3 weeks after the diagnosis of pneumonia (Fig 4). During the same period, the mortality was 95.0% (19 of 20) for patients who had *Aspergillus* pneumonia, and 86% (six of seven) for CMV pneumonia cases. In the group of patients for whom no etiologic diagnosis was established, the overall mortality was 50% (nine of 18). The mean interval from the BMT to death was 60 (± 40) days for all patients, and 49 (± 25) for the *Aspergillus* patients. The mean length of stay was 69 (± 21) days for all patients. Only one patient with *Aspergillus* pneumonia survived and was discharged 110 days after the transplantation.

**Surveillance Cultures**

A total of 655 surveillance cultures for bacterial and fungal agents was obtained from 42 of the 55

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**Table 1. Etiologic Agents and Methods of Diagnosis in 55 Episodes of Nosocomial Pneumonia in Adult BMT Patients**

<table>
<thead>
<tr>
<th>Etiologic Agent</th>
<th>Number of Cases</th>
<th>Sputum</th>
<th>Sputum + Blood</th>
<th>BAL</th>
<th>OLB</th>
<th>Skin Biopsy</th>
<th>Nose Biopsy</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aspergillus</em> species</td>
<td>20 (36.4%)</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>3 (5.4%)</td>
<td></td>
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<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>1</td>
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<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>1</td>
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<tr>
<td><em>P. carinii</em></td>
<td>3 (5.4%)</td>
<td>1</td>
<td></td>
<td>2</td>
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<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>1</td>
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<tr>
<td><em>L. pneumophila</em></td>
<td>2</td>
<td></td>
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<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1</td>
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<tr>
<td><em>Xanthomonas maltophilia</em></td>
<td>1</td>
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<tr>
<td><em>Klebsiella pneumoniae</em></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>CMV</td>
<td>7 (12.7%)</td>
<td>4</td>
<td></td>
<td>1</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>3 (5.4%)</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Identified</td>
<td>18 (32.7%)</td>
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**NOTE.** Six patients had two agents isolated at the time of pneumonia.

Abbreviations: OLB, open lung.

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**Fig 2.** *Aspergillus* pneumonia in BMT patients: incidence by year of 20 cases.

**Fig 3.** Nosocomial *Aspergillus* pneumonia: monthly distribution, 1980 to 1988.
cases of pneumonia with a mean of 15.6 (± 8.6) samples per patient, a median of 13.5, and a range from 4 to 41. The mean number of cultures per patient was 3.3 (± 2.0) from the skin, 3.2 (± 2.0) from the stool, 2.2 (± 1.4) from the urine, 3.3 (± 1.9) from the nose, and 3.6 (± 2.1) from the oropharynx. Fifteen of the 20 patients with pulmonary aspergillosis had surveillance cultures performed at regular intervals before the diagnosis of pneumonia: no *Aspergillus* species was isolated from a total of 209 cultures from different sites, including 93 from the nose and oropharynx. On the other hand, none of the 199 nasal and/or oropharyngeal surveillance cultures of cases without the diagnosis of *Aspergillus* pneumonia was positive for this agent. In one patient, a culture of a swab taken from the skin grew *Aspergillus* species. No other etiologic agent was isolated from this patient. *Aspergillus* was not considered the cause of the pneumonia because this agent was not demonstrated in sputum, BAL, or tissue biopsy.

The surveillance cultures also did not correlate with the etiologic agents isolated from the other cases of pneumonia. The only exception might be *Candida albicans*, which was isolated from surveillance cultures from two of three cases of *Candida* pneumonia (from stools in one patient and from the oropharynx in the other). However, positive surveillance cultures for *Candida albicans* were also found in 41% (16 of 39) of the patients without *Candida albicans* pneumonia. Within this group, the proportion of patients with positive surveillance cultures for *Candida albicans* (any site, any time before the pneumonia) was 36% (eight of 22) in patients from whom an etiologic diagnosis for the pneumonia was established, and 47% (eight of 17) in the group with unknown etiology.

Eighty-seven of 257 (33.8%) environmental air samples were positive for different species of fungi, including *Alternaria* species, *Aspergillus versicolor*, *A. fumigatus*, *A. flavus*, and *Penicillium* species. Positive cultures were observed in all areas of the hospital, including the BMT unit, where 11.4% (11 of 96) of the cultures obtained from patients' rooms and the hallway were positive. Areas of the hospital where transplant patients are frequently taken were also monitored. Nineteen of 30 (63.3%) air samples taken from the Diagnostic Radiology and Radiation Therapy suites were positive for fungi. The outdoor cultures, collected from the eighth floor roof directly above the BMT unit (seventh floor) also presented a high proportion of positive cultures (eight of 14, 57.1%). Finally, a striking difference was observed between the proportions of positive cultures by season. In the BMT unit, 21.6% (eight of 37) of the cultures obtained in September, October, and November were positive for fungi, as compared to zero of 15 cultures obtained in January and February.

**DISCUSSION**

The 20% attack rate for pneumonia in BMT patients observed in the present study is lower than the 35% to 43% rates reported in recent series. Our prospective case-finding method and the exclusion of 17 cases that did not meet the more restrictive criteria used in the present study, are both factors that may have contributed to this figure. We also have restricted our cases to patients who presented with pneumonia during the first hospitalization period and within 100 days of the BMT. This is substantially different from the period of study of other series. CMV is stated to be the most frequent etiologic agent of pneumonitis after BMT, with an attack rate ranging from 36 to 61 per 100 patients. This contrasts with the rate of 12.7 per 100 found in the present series. Bronchoscopy with cytologic observation and viral culture of specimens obtained by BAL, a highly sensitive test for the detection of CMV infection of the lungs, was performed in 69% of the patients in the present study. Of the 17 patients without BAL, four had specimens submitted for lung biopsy and in six deaths, autopsy studies were performed. Thus, the low rate of CMV infections in the present study is not a result of inadequate diagnostic approach. The fact that 32% (88 of 275) of the patients in our study were treated with autologous transplantation could have
contributed to a lower incidence of CMV pneumonitis in this series.\textsuperscript{12} However, the most important factor is possibly related to the length of observation of the patients, since 34.5\% of the patients died or were discharged within 6 weeks of the BMT, and 45.4\% died or were discharged within 8 weeks. The mean interval between the BMT and CMV pneumonia in the present series was 58 days. In a study of 545 recipients of allogeneic BMT, the median onset of CMV pneumonia was 62 days after transplant.\textsuperscript{13} Furthermore, the use of CMV-negative blood products in all patients whose serologic tests for CMV were negative, and the use (since 1987) of intravenous IgG in the previously seropositive patients, may also have contributed to a lower incidence of CMV pneumonia.

BMT recipients have been found to have a 10-fold greater incidence of nosocomial Aspergillus infection than other immunocompromised patient populations,\textsuperscript{14} and this organism has emerged as a major cause of mortality in the transplant population.\textsuperscript{5,7} Host factors, such as corticosteroid therapy,\textsuperscript{15} prolonged neutropenia,\textsuperscript{16} chronic myelogenous leukemia, or aplastic anemia as primary diagnoses before allogeneic BMT\textsuperscript{17} have been shown to increase the risk of invasive aspergillosis in immunocompromised patients. Sixteen of the 20 (80\%) patients with aspergillosis were receiving steroids at the time of the pneumonia, 16 (80\%) were neutropenic, and eight (40\%) had a primary diagnosis of chronic myelogenous leukemia. In addition, 50\% (10 of 20) of the patients with Aspergillus were receiving amphotericin B for 7 days or more when the pneumonia was diagnosed.

Outbreaks of nosocomial aspergillosis have been traced to heavy contamination of the hospital air associated with dust and dirt raised during hospital renovation and construction.\textsuperscript{18-24} Aside from an unexplained peak in 1985 (incidence rate of 20.8\%) the annual incidence of pulmonary aspergillosis has been stable at 5\% to 10\%. The overall attack rate of 7.3\% (20 of 275) observed in this study is comparable to attack rates ranging from 4\% to 8.4\% found in other series.\textsuperscript{7,25,26} Inadequate filtration of outside air by the air-handling system is the most obvious source of Aspergillus spores in the hospital,\textsuperscript{19,27} and significant reductions of the incidence of nosocomial aspergillosis have been shown by improving the quality of the air in BMT units.\textsuperscript{15,39} The associated finding of positive cultures for fungi in 11.4\% of the air samples obtained from the BMT unit indicates that the four exchanges per hour of centrally HEPA-filtered air that has been routine in our BMT unit does not eliminate the risk of Aspergillus pneumonia. Furthermore, the higher rate of positive environmental cultures of air samples obtained in the BMT unit in the September to November interval supports a seasonal incidence. Reports of seasonal variation of Aspergillus spores in outdoor samples of air, with an increase of 2\% found in late winter to 3.5\% in late fall\textsuperscript{30} constitutes supportive evidence.

RSV infection, a leading cause of hospital-acquired lower respiratory tract infection in children aged 2 years or younger,\textsuperscript{29} has recently been reported as a cause of severe respiratory infections in immunocompromised adults.\textsuperscript{30} The three cases of the present series occurred in the winter, in a temporal cluster, and have been reported previously.\textsuperscript{31} Two of these three patients died. RSV infection should be considered in BMT recipients with pneumonia, especially during the winter months or if preceded by upper respiratory-tract symptoms.

One of the strategies that has been proposed to lower the mortality rate of pneumonia in immunocompromised patients is the use of aggressive diagnostic methods to establish an early diagnosis.\textsuperscript{32} A previous report has shown that weekly fungal surveillance cultures obtained from selected body sites from patients with malignancy or those submitted to BMT were useful in predicting systemic infection for specific Candida species (Candida tropicalis).\textsuperscript{33} Negative cultures for C albicans and C tropicalis also have been shown to aid in diagnostic and therapeutic decision making because of a high negative predictive value.\textsuperscript{34} Forty-one percent of the patients without Candida pneumonia had positive surveillance cultures for C albicans, which is very similar to the 43\% colonization rate found earlier in immunocompromised patients at the same institution.\textsuperscript{34} Our data confirm the low positive predictive value of this finding. The isolation of Aspergillus species from respiratory tract secretions (transtracheal aspirate, sputum and bronchial washing), on the other hand, has been shown to correlate significantly with invasive pulmonary aspergillosis in immunocompromised patients.\textsuperscript{32,34}
However, the finding of 15 cases of *Aspergillus* pneumonia in the present series of patients who had persistently negative oropharyngeal and nose swab surveillance cultures suggests that these procedures may be poorly predictive of the development of a pulmonary infection by this fungus.

The crude mortality of 74.5% for all pneumonia cases in the present study, as well as the mortality rate of 95.0% for *Aspergillus* and 86% for CMV support the high mortality rates of pneumonia observed in other series of patients undergoing BMT.\(^2,4,6,7,13,14,28\) In our BMT unit, elimination of 90% of *Aspergillus* cases, as might be expected to occur with HEPA filtration and unidirectional air flow in patients' rooms, would have the effect of reducing the overall pneumonia attack rate from 20% to 13.4% and the crude mortality from 74.5% to 43.4%.

### REFERENCES