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Invasive Aspergillosis in Renal Transplant Recipients: Correlation with Corticosteroid Therapy

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During a 31-month period in 1979–1981, nine patients at a renal transplant center in Tennessee developed invasive infections with *Aspergillus* species. Despite an extensive search, no common environmental source of contamination was found. A matched case-control study of host risk factors showed that leukopenia, prior administration of antibiotics, and treatment with azathioprine and antilymphocyte serum were not significantly related to the development of aspergillosis. In contrast, the administration of high-dose corticosteroids posed a significant risk. An average daily dose of ≥1.25 mg of prednisone/kg per day for the entire interval studied was the best predictor of subsequent invasive infection with *Aspergillus*.

Invasive infections with *Aspergillus* species remain an important cause of morbidity and mortality among renal transplant recipients. Although aspergillosis is usually a sporadic disease, small outbreaks have been reported among patients with leukemia or lymphoma and patients who have received cardiac or renal transplants [1–7]. These infections have been attributed to foci of environmental fungal contamination in or near the hospital. Because the reports on the outbreaks have focused on environmental sources, the host factors predisposing to infection with *Aspergillus* have received less attention. In particular, individual variations in immunosuppression have rarely been considered. Thus, it is not clear which components of therapy contribute most to a patient's susceptibility to aspergillosis [8–10].

We investigated a cluster of invasive infections with *Aspergillus* at a renal transplant center. An extensive search for a common environmental source was unrevealing. A matched case–control study of host characteristics demonstrated a significant relation between the total dose of corticosteroids administered and the subsequent development of invasive aspergillosis. In contrast, the use of other immunosuppressive drugs, the administration of antibiotics, and leukopenia were not important risk factors for aspergillosis.

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Patients and Methods

The renal transplant center in Nashville treats patients at both Vanderbilt University Hospital and the affiliated Veterans Administration Hospital. One surgical team performs ~100 renal transplantations per year at the two hospitals. On September 23, 1980, patients at Vanderbilt University Hospital were moved into a new building that had a central filtered air-conditioning system. During the 10 months after the move, five transplant recipients developed invasive aspergillosis. Only four patients had developed this infection during the previous 21 months in the old window-ventilated building. Therefore, the physicians on the transplant team strongly suspected a source of environmental contamination in the new hospital.

Since 1979, no major changes had been made in terms of the selection of patients, the proportion of patients receiving kidneys from cadavers, or the protocols for treatment of rejection or infection. Laboratory methods for the isolation of fungi had not changed. Indeed, the microbiology laboratory remained in the same location in the old building. All patients in whom a fungal infection was suspected underwent bronchoscopy or open-lung biopsy. Empiric therapy for suspected fungal infection was not employed.

All renal transplant recipients with one or more cultures positive for *Aspergillus* between January 1, 1979, and July 31, 1981, were identified by a search of laboratory records. A patient was considered to have had invasive disease if he or she had had a compatible clinical illness and *Aspergillus* had been cultured from a bronchial washing (one patient), tissue biopsy specimen (four patients), or autopsy specimen (four patients). A patient with a positive nasopharyngeal or nasal-sinus culture alone was not considered to have had invasive disease.

Environmental cultures were performed in August 1981; 15-cm, 24-hr settle plates of Sabouraud's agar were used. A total of 53 sites were sampled in the old and new hospital buildings. Plates were placed on shelves in every room on the transplant ward as well as in various rooms in other wards in the new building. Rooms in the old building that had previously been occupied by transplant recipients were also cultured, as was the transplant ward of the affiliated hospital. The total number of fungal colonies was counted, and isolates of *Aspergillus* were identified by their characteristic microscopic morphology [11].

A multiple matched case–control study was performed in order to examine the contribution of host characteristics and treatment modalities to the risk of aspergillosis. According to the following criteria, two to four control patients were matched with each transplant recipient who had developed aspergillosis. The absolute criteria were: (*1*) same number of previous renal transplants as the patient with aspergillosis; (*2*) transplanted kidney obtained from the same kind of donor (cadaver or living relative); and (*3*) survival of the control patient and transplanted kidney for at least as long as that of the infected patient and transplanted kidney. The relative criteria were: (*1*) same underlying renal disease as the infected patient; (*2*) age within 10 years of the infected patient's age; and (*3*) transplant received within six months of the date of the infected patient's surgery.

Data on the characteristics of transplant recipients were obtained by review of hospital, clinic, and transplant service records. Each patient with aspergillosis and the matched controls for that patient were considered for the same number of days after transplantation. The study interval for each infected patient was defined as the number of days between the date of transplantation and the date when he or she developed symptoms leading to the diagnosis of aspergillosis.

Modes of immunosuppressive therapy included the administration of azathioprine, rabbit antiserum to human lymphocytes (ALS), and/or corticosteroids and local graft irradiation. A few patients also underwent thoracic duct drainage. Azathioprine was initially given in doses of 200 mg per day and was tapered to 100 mg per day within one month after transplantation. Doses were reduced more rapidly if the peripheral white blood cell (WBC) count fell below 2,000/mm^3. ALS (15 ml) was given daily after transplantation for six doses, then every other day for seven doses, every third day for two doses, and once a week for four doses (total, 19 doses). Prednisone was administered in doses of 60 mg per day for the first month and then gradually tapered. Methylprednisolone was administered in doses of 250–500 mg per day for three to five days for the treatment of rejection episodes. Local graft irradiation and various doses of ALS were also used for the treatment of rejection crises.

For purposes of comparison, we calculated the average dose of immunosuppressive drug(s) administered to each patient during the study interval by dividing the total dose by the patient's weight and the number of days he or she was studied (average mg/kg per day). We expressed the combined corticosteroid dose as milligrams of prednisone; the dose of methylprednisolone was thus multiplied by 1.25. The dose of local graft irradiation was expressed as the total number of rads administered.

Frozen serum specimens obtained just prior to transplantation were available from all subsequently infected patients and from controls. Serologic testing was done at the Centers for Disease Control (Atlanta). Antibody to cytomegalovirus was detected by the CF and IHA tests [12]. Antibody to *Aspergillus* was detected by the immunodiffusion technique [13]. For statistical analysis of the matched case-control study, we used the Mantel-Haenszel χ^2 test with variable matching ratio [14].

Results

Epidemiology of aspergillosis. Nine cases of invasive aspergillosis occurred among 228 renal transplant recipients at Vanderbilt University Hospital between January 1, 1979, and July 31,

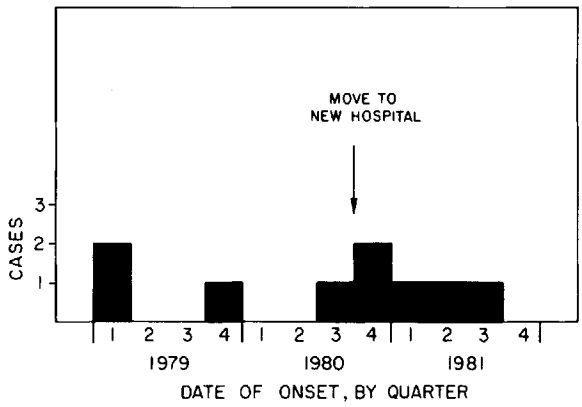

Figure 1. Cases of invasive aspergillosis in renal transplant recipients, Tennessee, 1979–1981.

1981 (figure 1). No cases occurred among the 33 transplant recipients at the Veterans Administration Hospital during this period; thus, these patients were excluded from subsequent analysis. No increase in the incidence of aspergillosis was noted among patients with leukemia at Vanderbilt University Hospital during the same period. Because these patients received amphotericin B for empiric treatment of illnesses unresponsive to conventional antibiotics [15], they were not a satisfactory control group.

The mean interval between transplantation and clinically recognized infection was 71 days (range, 31–152 days). The diagnoses were pneumonia due to *Aspergillus* (three patients), pneumonia with dissemination (five patients), and epidural abscess without pneumonia (one patient). Fungal isolates were speciated by the hospital laboratory in three cases; all were *Aspergillus fumigatus*. Seven of the nine patients died. One patient with a fatal infection was found to have coincident disseminated infections with *Candida albicans* and cytomegalovirus at autopsy. In the other six fatal cases, death was attributed to infection with *Aspergillus* alone.

The environmental investigation did not implicate a common source of infection in either the old or the new hospital building. Of the nine infected patients, seven had gone home after transplantation with no evidence of infection. No more than two patients had occupied the same hospital room, and there was little overlap of the dates of the patients' hospitalization. Before transplantation, all nine patients lived in different cities and attended different dialysis centers. After transplantation, they had no regular exposure to the hospital environment because the outpatient clinic was located in a separate facility two miles from the hospital. The transplanted kidneys themselves were unlikely sources of infection. Cultures of perfusates obtained from all nine kidneys before transplantation were negative for *Aspergillus*.

The total number of colonies of *Aspergillus* species recovered by environmental sampling was much lower than in previously reported outbreaks [2, 4, 16]. The mean number of colonies recovered in the 24-hr settle plates in the old hospital building was 8.5, in the new building was 4.1, and on the transplant ward at the Veterans Administration Hospital was 3.1.

Matched case-control study. The nine patients with aspergillosis were closely compared with a total of 24 control patients (table 1). The opportunity for exposure of the two groups to an environmental source of *Aspergillus* was assessed by comparison of the number of days spent in the new hospital building during the study interval. Among infected patients and controls in the new building, the average number of days of hospitalization was similar (27.8 days vs 25.5 days). Similarly, the average number of clinic visits was comparable for infected patients (8.8 days) and controls (6.4 days). Two patients with aspergillosis

Table 1. Characteristics of patients with invasive aspergillosis and of control patients in a matched case-control study of renal transplant recipients.

Characteristic	Patients	
	Infected (n = 9)	Control (n = 24)
Male	7 (78)	19 (79)
White	6 (67)	19 (79)
Cadaveric donor	9 (100)	24 (100)
No. of prior transplants		
0	7 (78)	17 (71)
1	1 (11)	4 (17)
2	1 (11)	3 (13)
Underlying disease		
Glomerulonephritis	3 (33)	10 (42)
Nephrotic syndrome	2 (22)	3 (13)
Pyelonephritis	0	2 (8)
Congenital disorder	1 (11)	4 (17)
Diabetes mellitus	1 (11)	1 (4)
Hypertension	1 (11)	2 (8)
Lupus erythematosus	1 (11)	1 (4)
Unknown	0	1 (4)
Transplantation performed in new building	5 (56)	11 (46)

NOTE. Data are no. (%) of patients. The mean age of infected patients was 36.3 years; that of controls was 35.6 years.

never visited the outpatient clinic after transplantation.

Other variables not related to the acquisition of aspergillosis included splenectomy, recent transfusions, and histocompatibility leukocyte antigen match (table 2). Antibody to cytomegalovirus was present in sera of the majority of infected patients and controls before transplantation. Convalescent-phase serum samples obtained one to six months after transplantation were available from four patients with aspergillosis and 19 controls; a fourfold rise in the titer of CF antibody to cytomegalovirus occurred in 25% of these infected patients and 58% of the controls (difference not significant). No infected patient had detectable immunodiffusion antibody to *Aspergillus* before transplantation. Both patients from whom a second specimen of serum was obtained after the onset of invasive infection developed antibody to *Aspergillus*.

Table 2. Characteristics of renal transplant recipients that were not related to the acquisition of invasive aspergillosis.

Time, characteristic	Patients	
	Infected	Control
Before or during transplantation		
Splenectomy	2 (22)	5 (21)
Transfusion*	8 (89)	20 (83)
Histocompatibility leukocyte antigen match		
3- or 4-antigen match	7 (78)	17 (71)
1- or 2-antigen match	2 (22)	7 (29)
Cytomegalovirus antibody	8 (89)	19 (79)
Aspergillus antibody	0	0
After transplantation		
Prophylactic amphotericin mouthwash	4 (44)	16 (67)
Prophylactic nystatin mouthwash	7 (78)	14 (58)
Prophylactic urinary antibiotic for ≥14 days†	7 (78)	22 (92)
Combination antibiotic therapy for ≥7 days‡	5 (56)	9 (38)
WBC count of <4,000 during follow-up	4 (44)	12 (50)

NOTE. Data are no. (%) of patients. *P* values were determined in the Mantel-Haenszel χ^2 test with variable matching ratio. No significant differences between the two groups were found.

* Transfusions during the 10 days before transplantation were considered.

† Prophylactic urinary antibiotics included sulfisoxazole, trimethoprim, and trimethoprim-sulfamethoxazole.

‡ Combination therapy included a penicillin or a cephalosporin given concurrently with a urinary antibiotic or an aminoglycoside.

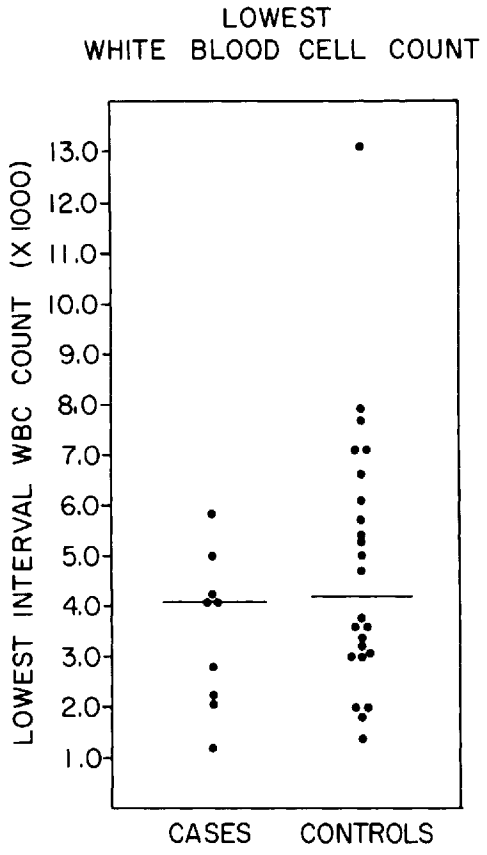

Figure 2. Lowest recorded WBC counts in transplant recipients with aspergillosis and in controls during the study interval. Median values are indicated by solid lines.

Several prophylactic antibiotics were routinely administered to transplant recipients. Isoniazid (200 mg per day) was prescribed for all patients. Amphotericin B (2% solution) and/or nystatin (100,000 units/ml) mouthwashes were employed daily in the hospital and at home, but neither provided protection against infection with *Aspergillus* (table 2). Antibiotics for prophylaxis of urinary tract infections (including sulfisoxazole, trimethoprim, and trimethoprim-sulfamethoxazole) were administered for prolonged periods. Their use was not related to subsequent aspergillosis. Combinations of broad-spectrum antibiotics were infrequently administered to transplant recipients. Combination antibiotic therapy (defined as the concurrent use of a penicillin or a cephalosporin and a urinary antibiotic or an aminoglycoside) for seven or more days during the study interval was not related to infection with *Aspergillus* (table 2).

One reason prolonged broad-spectrum anti-

biotic therapy was rarely necessary was that severe leukopenia was uncommon in transplant recipients. The lowest recorded peripheral WBC count was <4,000/mm³ in only 44% of infected patients and in 50% of controls (table 2). The distributions of the lowest recorded WBC counts among infected patients and controls were also comparable (figure 2).

All nine cases of aspergillosis occurred among the 148 patients who had received cadaveric kidneys. No cases of aspergillosis occurred among the 80 patients who had received kidneys from living, related donors ($P = 0.019$, Fisher's exact test). Recipients of cadaveric transplants generally experience more rejection crises than do recipients of transplants from living relatives. Indeed, in this study, patients who experienced one or more rejection episodes (as defined by the attending physician) ran a significantly greater risk of developing invasive infection with *Aspergillus* than patients who did not experience such episodes ($P = 0.03$, Mantel-Haenszel χ^2 test with variable matching ratio) (table 3). Local graft irradiation was an almost constant feature of therapy for rejection. Eight of nine infected patients and 11 of 24 controls underwent graft irradiation ($P = 0.03$, Mantel-Haenszel χ^2 test with variable matching ratio). The median dose of graft irradiation administered to patients with aspergillosis (600 rads; range, 0–900 rads) was larger than that administered to controls (0 rad; range, 0–1,050 rads) ($P = 0.004$, two-tailed Mann-Whitney test).

Because rejection episodes were related to infection with *Aspergillus*, we examined the average daily doses of immunosuppressive therapies administered to infected patients and controls (figure 3). Thoracic duct drainage could not be evaluated because it was employed in the case of only one infected patient and in no controls. The doses of azathioprine and ALS administered to patients who developed aspergillosis were not significantly different from those administered to controls. However, the median corticosteroid dose administered to patients who became infected (1.72 mg of prednisone/kg per day) was significantly larger than that administered to controls (0.97 mg/kg per day) ($P = 0.037$, two-tailed Mann-Whitney test). A matched analysis revealed that an average dose of ≥0.90 mg of prednisone/kg per day for the entire study interval was significantly associated with the development of invasive infection with *Aspergillus* ($P = 0.04$, Mantel-Haenszel χ^2 test with variable matching ratio). A significant association held for any dose up to 1.45 mg/kg per day ($P = 0.03$). The average corticosteroid dose that best discriminated subsequently infected patients from controls was 1.25 mg/kg per day (table 4). The only patient with aspergillosis who received a corticosteroid dose of <1.25 mg/kg per day was additionally immunosuppressed as a result of thoracic duct drainage. This patient presented with an epidural abscess and without prior pulmonary disease. Unlike a previously described patient [17], our patient had not received epidural anesthesia.

Because of the small number of infected patients and controls, matched analysis could not be used for separate evaluation of the effects of rejection episodes, graft irradiation, and corticosteroid administration. However, unmatched analysis suggested that high-dose corticosteroids are independently associated with aspergillosis. All of eight infected patients who experienced rejection episodes received an average corticosteroid dose of ≥1.25 mg/kg per day; in contrast, only six (55%) of 11 controls who experienced rejection episodes received such doses ($P = 0.04$, Fisher's exact test). All of seven infected patients who received local graft irradiation in doses of >400 rads received an average corticosteroid dose of ≥1.25 mg/kg per day, while only three (50%) of six controls given these doses of irradiation received ≥1.25 mg of prednisone/kg per day ($P = 0.07$, Fisher's exact test).

Table 3. Relation of rejection episodes to acquisition of invasive aspergillosis in renal transplant patients.

One or more rejection episodes	Patients	
	Infected	Control
Yes	8 (89)	11 (46)
No	1 (11)	13 (54)

NOTE. Data are no. (%) of patients. The difference between the incidence of aspergillosis among patients who experienced rejection episodes and that among those who did not was statistically significant ($P = 0.03$, Mantel-Haenszel χ^2 test with variable matching ratio).

Discussion

Aspergillus species are ubiquitous fungi with seasonal variations in the production of conidia [18]. Small nosocomial outbreaks of invasive aspergillosis have been attributed to the growth of

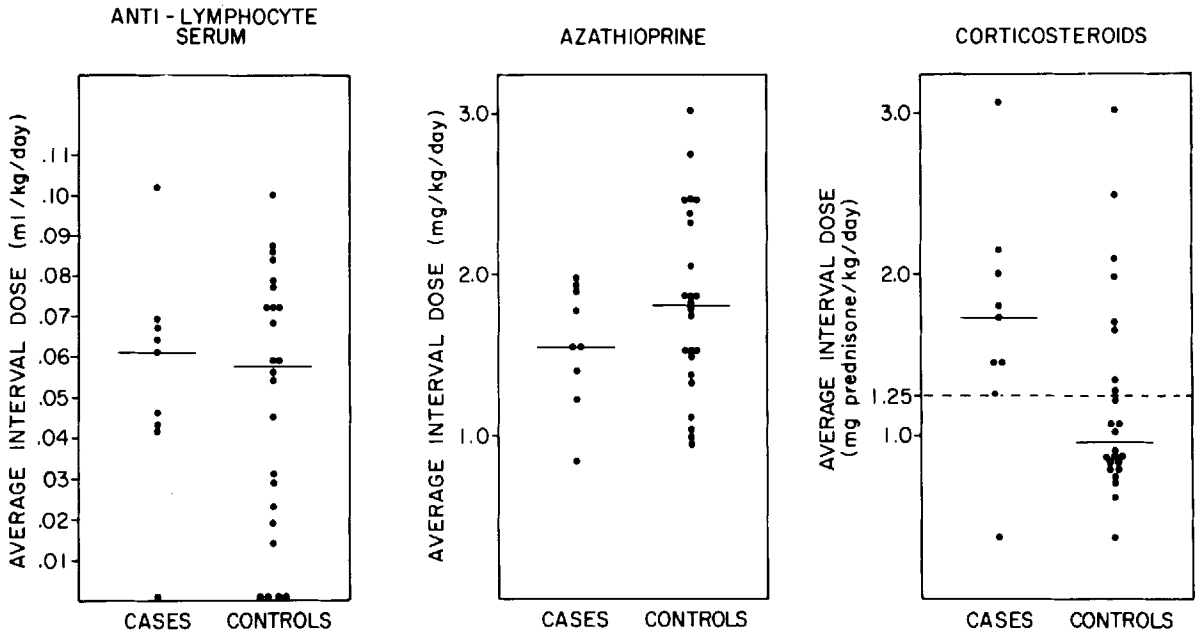

Figure 3. Average doses of immunosuppressive drugs administered to transplant recipients with aspergillosis and to controls during the study interval. Median values are indicated by solid lines. Corticosteroid doses of ≥1.25 mg/kg per day (on or above the dotted line) were strongly associated with subsequent aspergillosis.

the fungus in insulation, fireproofing materials, and air-conditioning vents [1–7]. However, studies of these outbreaks have provided only circumstantial evidence that patients acquired their infections from nosocomial sources. Little evidence has been offered, for example, that patients were more likely to inhale aspergillus spores in the hospital than at home. Indeed, given the magnitude and locations of the hazards described, it is surprising how few cases of aspergillosis have occurred in these outbreaks.

It is well recognized that invasive aspergillosis occurs almost exclusively in immunocompromised patients, including those with chronic granulomatous disease, leukemia, and lymphoma [19, 20]. Aspergillosis in renal transplant recipients, although unusual, is nonetheless an important cause of death [9, 21]. Although only 4% of the transplant recipients we studied developed this infection, *Aspergillus* caused 23% of all deaths among the entire population of transplant recipients.

Renal transplant recipients are at highest risk for invasive infection with *Aspergillus* during the period between one month and six months after transplantation [22]. All nine of our cases occurred during this high-risk interval. The lack of infections with *Aspergillus* during the first month after transplantation may suggest that the incubation period is longer than one month. It is also possible that the effects of immunosuppressive therapies are delayed or cumulative. The latter explanation is attractive because infections with cytomegalovirus, *Pneumocystis, Nocardia,* and *Toxoplasma* also occur predominantly during the same high-risk period [22].

Several recent studies have indicated that cytomegaloviral infection, especially primary infection, can predispose renal transplant recipients to other serious complicating infections [23, 24]. Some evidence suggests that cytomegaloviral infection itself has immunosuppressive effects [25, 26]. In the population studied here, however, pri-

Table 4. Relation of corticosteroid dose to acquisition of invasive aspergillosis.

Average daily dose of corticosteroid*	Patients	
	Infected	Control
≥1.25 mg/kg	8 (89)	8 (33)
<1.25 mg/kg	1 (11)	16 (67)

NOTE. Data are no. (%) of patients. The difference between the incidence of aspergillosis among patients given ≥1.25 mg of prednisone/kg per day and that among those given <1.25 mg/kg per day was statistically significant ($P = 0.006$, Mantel-Haenszel χ^2 test with variable matching ratio).

* Dose is expressed as milligrams of prednisone; thus, doses of methylprednisolone were multiplied by 1.25.

mary infection with cytomegalovirus was not identified. The limited data obtained in serologic studies and at autopsy further suggest that reactivation of latent cytomegaloviral infection was not associated with aspergillosis.

The immunosuppressive drugs administered to transplant recipients clearly predispose them to infection, but the doses and even the specific drugs that contribute most to susceptibility are unknown. Multiple immunosuppressive therapies and broad-spectrum antibiotics are frequently used together, and previous studies implicating these modes of treatment have not distinguished among the effects of individual components. Broad-spectrum antibiotics were not used frequently in the transplant recipients studied here. Neither prophylactic urinary-tract antibiotics nor combined antibiotic therapy enhanced the risk of invasive aspergillosis. Although local graft irradiation was associated with subsequent aspergillosis, it did not appear to be a biologically plausible risk factor for this systemic infection.

We found no relation between the average dose of ALS or azathioprine administered and the development of invasive aspergillosis. In prospective studies, the combination of azathioprine, corticosteroids, and antithymocyte globulin has not been associated with a greater number of infections or deaths than azathioprine and corticosteroids alone [27, 28]. Azathioprine doses are adjusted frequently by monitoring of the total peripheral and absolute granulocyte counts. Patients with WBC counts of $<2{,}000/mm^3$ or with granulocyte counts of $<500/mm^3$ are clearly at increased risk of developing bacterial sepsis [29]. Less well defined, however, is the importance of neutropenia and lymphopenia as risk factors for invasive fungal disease [30, 31]. Low leukocyte counts were not related to the occurrence of aspergillosis in the patients studied here. Only one of nine patients with aspergillosis had a WBC count of $<2{,}000/mm^3$ at any time between transplantation and the onset of illness.

We found a striking relation between the average daily dose of corticosteroids and invasive aspergillosis. Administration of average doses of $\geq$1.25 mg of prednisone/kg per day for a period of at least one month placed patients at high risk of developing this infection. In a 70-kg patient, this dose is equivalent to 45 mg of prednisone per day plus a total of 1,000 mg of methylprednisolone in a single month. The administration of large steroid doses did not necessarily immediately precede the onset of aspergillosis. Only five patients received $\geq$1.25 mg of prednisone/kg per day during the 30 days before the onset of illness. The largest doses of corticosteroids and other immunosuppressive agents usually are administered during the first month after transplantation. Because opportunistic infections, including aspergillosis, are rare during the first month, some physicians may have inferred that large doses of these agents can be given with relative safety at that time. Our results contradict this view and suggest that, in the case of corticosteroids, all doses have delayed or cumulative effects. It was the average daily dose for the entire study interval, not the dose administered in any single month after transplantation, that correlated most closely with the development of invasive aspergillosis.

Several interrelated factors, including rejection crises, corticosteroid therapy, and graft irradiation, were associated with aspergillosis. Studies in patients with leukemia and in animal models and experience at other renal transplant centers support the conclusion that the dose of corticosteroids is the most important of these risk factors. An autopsy study of patients with leukemia found an association between infections with *Candida* and *Aspergillus* and high-dose corticosteroid therapy but not between these infections and other modes of therapy for leukemia [30]. In another study, patients with leukemia and disseminated aspergillosis received corticosteroids in larger doses and for longer periods than did leukemia patients with aspergillosis limited to the lungs [32].

Studies in mice and rabbits have suggested that corticosteroids predispose these animals to the development of invasive aspergillosis by interfering with the function of alveolar macrophages [33, 34]. Elegant studies in animals have shown that normal mice, athymic mice, and mice made neutropenic with nitrogen mustard are resistant to infection by inhaled conidia of *A fumigatus*. In contrast, mice given prior treatment with cortisone (20–50 mg/kg per day for six days) invariably succumb to infection [35]. In these mice, alveolar macrophages ingest the conidia but are unable to prevent them from germinating. Similarly, in vitro experiments have shown that cortisone impairs the ability of human macrophages to prevent germination of ingested conidia [35]. A dose-related response has been demonstrated in rabbits given two inocula of 10^6 *A fumigatus* conidia by intra-

tracheal instillation. Rabbits given 1.14 mg of methylprednisolone/kg per day for three months do not develop invasive disease, whereas rabbits given 2.28 mg/kg per day invariably suffer fatal infections within three months [36]. These studies may explain why corticosteroids, but not other immunosuppressive agents, are associated with invasive infection with *Aspergillus*. The results in animal models also suggest that the effect of steroids is delayed or cumulative.

In renal transplant recipients, huge doses of corticosteroids (30 mg of prednisone/kg per day) were once used for treatment of rejection crises [37]. Such large doses were associated with many infectious complications. Anderson et al reported that prednisone in a large dose (>1 mg/kg per day for 14 days), hyperglycemia, and renal failure (rejection) were the best predictors of subsequent fatal infections [38]. Large doses of azathioprine (>2 mg/kg per day for 14 days) were not related to infections in that study. Bach et al reported a high rate (22%) of invasive aspergillosis when rejection episodes were treated with methylprednisolone (1 g per day for seven days) [10].

Current steroid dosage schedules vary widely among transplant centers. The schedule that provides the greatest benefit—that is, that most increases the rate of transplant survival at the least cost in terms of infectious complications—is not known. The frequency of fungal infections decreased at several centers when the total dose of corticosteroids administered was reduced [38–41]. Researchers at one center reported a marked reduction in the frequency of infectious complications (and a corresponding increase in the rate of survival of transplant recipients) after rejection therapy was changed from methylprednisolone (1 g per day for three to seven days) to prednisone (3 mg/kg per day for two to three days, with rapid tapering) [42]. Investigators at another center reduced the total dosage of steroids administered by decreasing the dose of routine oral prednisolone while leaving rejection therapy unchanged [43]. In a randomized trial this approach also was effective in reducing the incidence of infectious complications.

In summary, our investigation of invasive aspergillosis in renal transplant recipients suggested that the average daily dose of corticosteroids administered over the entire study interval was the single most important risk factor for this disease. An average dose of ≥1.25 mg of prednisone/kg per day was the best predictor of subsequent invasive infection with *Aspergillus*.

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