GENERAL THORACIC SURGERY

PULMONARY RESECTION FOR INVASIVE *ASPERGILLUS* INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

Standard antifungal medical therapy of invasive pulmonary aspergillosis that occurs in immunocompromised patients with hematologic diseases with neutropenia or in liver transplant recipients results in less than a 5% survival. In view of these dismal mortality rates, we adopted an aggressive approach with resection of the involved area of lung along with systemic antifungal therapy when localized invasive pulmonary aspergillosis developed in these patients. Between January 1987 and December 1993, 14 patients with hematologic diseases and 2 liver transplant recipients underwent resection of acute localized pulmonary masses suggestive of invasive pulmonary aspergillosis a median of 7.5 days (range 1 to 45 days) after the diagnosis was clinically suggested and confirmed by chest computed tomographic scans. Operative procedures done included two pneumonectomies, one bilobectomy with limited thoracoplasty, nine lobectomies, and five wedge resections (one patient with hematologic disease had two procedures). All patients were treated before and after the operation with antifungal agents. Nine (64%) of 14 patients with hematologic disease and 2 (100%) of 2 liver transplant recipients survived the hospitalization with no evidence of recurrent *Aspergillus* infection after a median 8 months of follow-up (range 3 to 82 months). The five hospital deaths (all patients with hematologic diseases) occurred a median of 20 days after operation from diffuse alveolar hemorrhage in three, graft-versus-host disease in one, and multiple organ system failure with presumed disseminated *Aspergillus* infection in one. Four of the five deaths were in patients with allogeneic bone marrow transplants. Two of the three patients requiring resection of multiple foci of infection died, as did the only patient who was preoperatively ventilator dependent. In immunocompromised patients with hematologic diseases or liver transplantation with invasive pulmonary aspergillosis, early pulmonary resection should be strongly considered when the characteristic clinical and radiographic pictures appear. (J THORAC CARDIOVASC SURG 1995;109:1182-97)

Lary A. Robinson, MD,[a] Elizabeth C. Reed, MD[b] (by invitation), Timothy A. Galbraith, MD[a] (by invitation), Anselmo Alonso, MD[a] (by invitation), Anthony L. Moulton, MD,[a*] and William H. Fleming, MD,[a] *Omaha, Neb.*

Pulmonary infection is a major cause of morbidity and mortality in patients with compromised immune defenses from any cause.[1] Although bacterial infections are more frequent, invasive fungal infections occur commonly and carry higher risks in these immunocompromised hosts. One of the most serious opportunistic pathogens that may result in invasive pulmonary infections is *Aspergillus.* This fungus poses a significant threat to patients with cancer, especially when they have neutropenia, and to immunologically suppressed organ transplant recipients.

Invasive pulmonary aspergillosis (IPA) has been found at autopsy in 20% of patients who died with acute leukemia.[2] It may be diagnosed premortem in as many as 21% of patients with leukemia with a

From the Section of Cardiothoracic Surgery[a] and Section of Oncology and Hematology,[b] University of Nebraska Medical Center, Omaha, Neb.

Read at the Seventy-fourth Annual Meeting of The American Association for Thoracic Surgery, New York, N.Y., April 24-27, 1994.

Address for reprints: Lary A. Robinson, MD, Division of Cardiothoracic Surgery, University of South Florida, 12902 Magnolia Dr., Tampa, FL 33612-9497.

*Present address: Division of Cardiothoracic Surgery, The Miriam Hospital, Brown University, 164 Summit Ave., Providence, RI 02906.

0022-5223/95 $3.00 + 0 **12/6/62948**

subsequent 67% or higher mortality rate from this fungal infection.[3] Among the bone marrow transplant population, invasive *Aspergillus* infection occurs in 4% to 38% of patients[4] and is a highly lethal infection. In patients having solid organ transplantation, invasive aspergillosis develops in 2.0% of renal transplant recipients[5] and 4.2% of liver transplant recipients.[6]

Medical therapy with antifungal agents for IPA in immunosuppressed patients has yielded disappointing results. In a recent review of the literature,[7] standard antifungal therapy alone with amphotericin B resulted in a greater than 94% mortality rate in patients who had bone marrow transplants. At the time of that literature review, no successful medically treated case of IPA in a liver transplant recipient had ever been reported.[7] The propensity of *Aspergillus* to invade pulmonary blood vessels with the resultant hemorrhagic pulmonary infarcts and subsequent development of a necrotic cavity[8] greatly impedes the effective penetration of systemic antifungal agents and thereby prevents attainment of therapeutic lung tissue drug levels.

Scattered reports in the 1980s documented occasional immunosuppressed patients with cancer[4, 9-12] and renal transplant recipients[5] who were cured of IPA by pulmonary resection and antifungal therapy. Because of the dismal results from antifungal medical treatment alone, we chose in 1987 to pursue a more aggressive approach with these patients. We combined surgical resection of localized IPA with standard medical therapy in our immunocompromised population of patients with hematologic diseases and liver transplant recipients, and this report documents our results.

Patients and methods

Patient population. Between January 1, 1987, and December 31, 1993, 16 consecutive immunocompromised patients were identified who underwent pulmonary resections for IPA. The group consisted of 14 patients with hematologic diseases and 2 liver transplant recipients. They were studied by retrospective review of their hospital records and radiographic studies. For this review, patients were considered to be immunocompromised if they underwent high-dose chemotherapy (with or without total body irradiation) that caused prolonged neutropenia (absolute neutrophil count [ANC] <500 cells/mm^3), with or without subsequent bone marrow rescue. Patients receiving autologous bone marrow, autologous stem cell, and allogeneic bone marrow transplants were included. Also included among the immunocompromised group were solid organ transplant recipients. By definition, the *primary procedure* refers to either the day of transplantation (bone marrow or liver), the end of high-dose chemotherapy (in the chemotherapy only group), or the start of the steroid pulse for rejection treatment.

Patients with hematologic diseases. Thirteen patients had hematologic malignancies and one had refractory aplastic anemia. Three had high-dose chemotherapy only and the rest had chemotherapy followed by marrow rescue. In addition to chemotherapy and marrow rescue, patients undergoing allogeneic bone marrow transplantation also received 600 to 1200 cGy of total body irradiation before transplantation and a posttransplantation immunosuppressive regimen of cyclosporine, corticosteroids, and in some patients methotrexate or antithymocyte globulin. Hematopoetic growth factors [granulocyte/macrophage-colony stimulating factor (GM-CSF) or granulocyte-colony stimulating factor (G-CSF)] were commonly used in patients beginning in 1991. Cultures were obtained on hospital admission in all patients before their procedure. Patients were housed in rooms with high-efficiency particulate air filtration systems. Infection control protocols have been described in more detail previously.[13]

Liver transplant recipients. Two patients in our overall group were liver allograft recipients. The standard liver transplant protocols for antibiotic prophylaxis, monitoring, infection control and surveillance procedures, immunosuppression, rejection treatment, and antibacterial and antifungal infection treatment have been described in detail previously.[6]

Diagnosis of suspected *Aspergillus* infection. All febrile patients had cultures of blood, urine, and sputum obtained. Fungal serologic testing was not routinely done in any patient, because negative results do not exclude the diagnosis.[7] Chest radiographs were done at least twice a week. Chest computed tomographic (CT) scanning was commonly done and results were believed to be suggestive of fungal infection if there was a new nodule with or without cavitation, a halo, or a hazy or sharp margin, by criteria reported previously.[14] Diagnostic bronchoscopy with bronchoalveolar lavage was done in most patients in whom a new parenchymal abnormality on chest radiograph developed. Percutaneous needle biopsy of the lung nodule was done on some patients.

Probable IPA was suspected in patients with a new pulmonary infiltrate especially if the infiltrate was nodular or cavitary on chest CT scan, with or without any of the following: (1) new fever persisting despite antibiotic treatment; (2) new respiratory symptoms such as dyspnea, cough, hemoptysis, or pleuritic chest pain; (3) sputum or pulmonary lavage fluid showing typical histologic findings or cultures positive for *Aspergillus* species; or (4) percutaneous needle biopsy material from the lung infiltrate showing typical histologic findings or culture positive for *Aspergillus* species. Most patients with strongly suspected IPA were evaluated for evidence of disseminated infection in another major site; for example, a brain CT scan was done to look for indications of cerebral aspergillosis. If no major distant site of infection was located and the suspected IPA appeared to be localized to one lung, then patients in medically operable condition underwent a thoracotomy with pulmonary resection.

Surgical treatment. All pulmonary resections were done through a posterolateral thoracotomy incision with a

Table I. *Summary of clinical presentations of patients with Aspergillus infection*

Patient No.	*Age (yr)*	*Sex*	*Primary diagnosis*	*Other medical problems*	*Primary procedure*	*Aspergillus presentation*
Hematologic disease						
1	36	F	Acute monoblastic leukemia	Tooth abscess	High-dose chemotherapy	CXR, CT, fever
2	48	M	Acute myelogenous leukemia	None	High-dose chemotherapy	Fever, CXR, cough, chest pain, CT
3	59	M	Acute myelogenous leukemia	Renal insufficiency, hypertension	High-dose chemotherapy	Fever, CXR, cough, chest pain, CT
4	32	M	Hodgkin's disease	None	Auto BMT	CXR, CT, fever, chest pain
5	46	F	Hodgkin's disease	None	Auto PSCT	CXR, fever, chest pain, cough, CT
6	43	M	Non-Hodgkin's lymphoma	Prior melanoma	Auto PSCT	Fever, CXR, CT
7	51	F	Hodgkin's disease	Hypothyroidism	Auto PSCT	Fever, dyspnea, CXR CT
8	55	M	Non-Hodgkin's lymphoma	Emphysema	Auto PSCT	Fever, cough, CXR, CT
9	47	M	Non-Hodgkin's lymphoma	None	Auto PSCT	Fever, CXR, CT
10	20	F	Aplastic anemia	Non-*Aspergillus* fungal infection on elbow	Allo BMT	Chest pain, CXR, fever
11	49	M	Acute myelogenous leukemia	Chronic hepatitis B	Allo BMT	CXR, CT, fever, respiratory failure
12	29	M	Acute myelogenous leukemia	Diffuse interstitial lung disease	Allo BMT	Fever, CXR, CT, respiratory failure
13	40	F	Chronic myelogenous leukemia	None	Allo BMT	CXR, CT
14	26	F	Acute myelogenous leukemia	None	Allo BMT	CXR, fever, dyspnea, chest pain
Liver transplant						
15	57	M	Cryptogenic cirrhosis	Chronic pancreatitis	Liver transplant (incidental hepatoma)	CXR, CT, leukocytosis
16	38	M	Transplant rejection (liver transplant 4 years earlier)	Diabetes mellitus, hypertension	Liver transplant (rejection treatment)	Fever, CXR, CT

Allo BMT, Allogeneic bone marrow transplant; *Auto BMT,* autologous bone marrow transplant; *Auto PSCT,* autologous peripheral stem cell transplant; *CT,* chest computed tomography; *CXR,* chest radiograph; *F,* female; *M,* male; *mediast,* mediastinal; *met,* metastatic; *NG,* no growth; *Sp,* species.

*Some patients with leukemia had an ANC <500 cells/mm^3 on hospital admission. Consequently, in these patients the total days ANC <500 cells/mm^3 is actually greater than the number listed and this is indicated by a plus sign.

double-lumen endotracheal tube in place. The extent of the resection was determined by the surgeon on the basis of the preoperative chest CT scan and the intraoperative findings. Three patients had intraoperative pleural irrigation with 0.9% saline solution containing amphotericin B, whereas the rest had intraoperative pleural irrigation with bacitracin and 0.9% saline solution only. Amphotericin B administration was started in all patients before the operation as soon as there was a presumed fungal infection and the agent was continued after the operation. Four patients were being treated prophylactically on an investigational protocol before any evidence of *Aspergillus* infection was found. Postoperative care was done in a routine manner for pulmonary resections except for maintenance of appropriate respiratory isolation procedures in patients with neutropenia. The time for chest tube removal was based on pleural fluid drainage and air leak. One patient with pleural involvement with *Aspergillus* had chest tubes converted postoperatively to open empyema tubes that were advanced out over 2 months on an outpatient basis.

Postoperative *Aspergillus* diagnosis. Histologic evaluation of tissue obtained from the operation was believed to be diagnostic for *Aspergillus* when it contained characteristic septate hyphae that exhibited dichotomous branching at 45 degrees, particularly if they happened to contain conidial heads (sporulating structures).[8] The histologic picture also had to demonstrate hyphae invasion, areas of

Proven site of Aspergillus infection	*Preoperative invasive diagnostic procedure*	*Method of diagnosis*		*Total days ANC <500* cells/mm³*	*Days after primary procedure ANC >500 cells/mm³*	*ANC at time of Aspergillus presentation (cells/mm³)*
		Histology	*Culture*			
Lung, nose	Bronchoscopy, nondiagnostic	Typical	NG	31	19	0
Lung	Bronchoscopy, nondiagnostic	Typical	*A. fumigatus*	46+	No WBC recovery	0
Lung	Bronchoscopy, nondiagnostic	Typical	NG	11	13	0
Lung, pleura, mediast. nodes	Bronchoscopy, positive	Typical	*A. flavus*	22	18	15,660
Lung	Bronchoscopy, nondiagnostic; needle biopsy, positive	Typical	NG	27	28	600
Lung	Bronchoscopy, nondiagnostic	Typical	NG	17	17	0
Lung	None	Typical	NG	26	30	100
Lung	Bronchoscopy, nondiagnostic	Typical	NG	19	15	1,200
Lung	Bronchoscopy, nondiagnostic	Typical	*A. fumigatus, Penicillium* sp	13	13	200
Lung	Bronchoscopy, nondiagnostic	Typical	NG	35+	23	0
Lung	Bronchoscopy, positive	Typical	*A. fumigatus*	39+	22	0
Lung	Bronchoscopy, nondiagnostic	Typical	*A. flavus, Legionella*	31+	22	2,800
Lung	Bronchoscopy, nondiagnostic	Typical	*A. terreus*	16	20	0
Lung, skin	None	Typical	*A. fumigatus*	31	20	0
Lung	Bronchoscopy, positive; needle biopsy, positive	Typical (incidental met. hepatoma in lung)	*A. terreus*	0	Never <500	23,400
Lung	Bronchoscopy, nondiagnostic; needle biopsy, nondiagnostic	Typical	*A. flavus, Legionella*	0	Never <500	3,400

infarction often with cavities containing necrotic lung (so-called mycotic lung sequestrum[11]), or thrombosis of pulmonary vessels. Although other rare fungi such as *Fusarium sp.* may be morphologically indistinguishable from *Aspergillus,* infections morphologically confirmed without culture were included in this series. However, the diagnosis of IPA was conclusively confirmed if an *Aspergillus* species was cultured from tissue.

Follow-up. Patient records, including subsequent radiographic studies, were carefully reviewed after operation for evidence of recurrence of the fungal infection. We were successful in obtaining long-term follow-up on all survivors of the index hospitalization, even those who left the local area. The majority of all long-term survivors had follow-up radiographic studies including chest CT scans. All data summaries collected from this retrospective review are expressed as the mean plus or minus the standard deviation, median, and range. Where applicable, data were compared with the Student's *t* test; *p* values less than 0.05 were considered significant.

Results

Patient demographics. The patient population ranged in age from 20 to 59 years with a mean of 42.3 ± 11.4 years (median 44.5 years). There were 10 men and 6 women. All were white. Nine of the 16 patients (56.3%) were cigarette smokers.

Clinical presentation. Table I shows a summary of the clinical presentation of each patient. Of the 14 patients with hematologic diseases, 3 had high-dose chemotherapy only. The remaining 11 had high-dose chemotherapy plus rescue with autologous bone marrow in one (No. 4), autologous peripheral

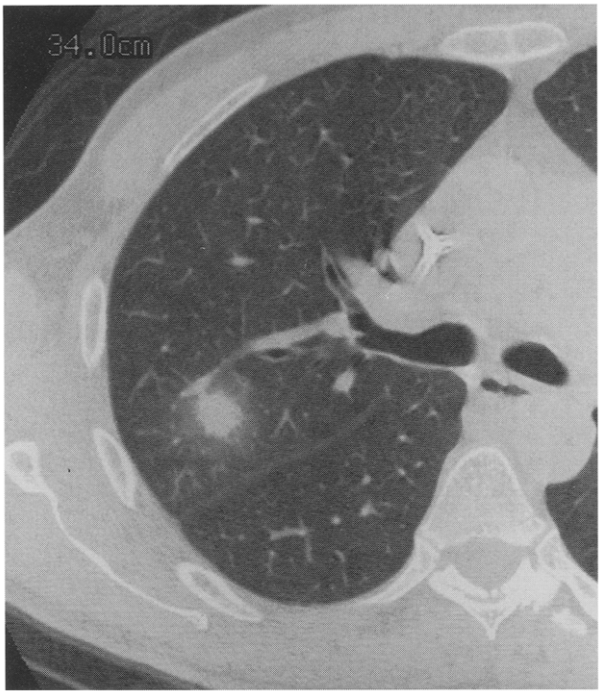

Fig. 1. Thin-section contrast-enhanced chest CT image from patient No. 9 at a level 1 cm inferior to the carina demonstrating a dense 1.5 cm diameter nodular mass in the right upper lobe of the lung with a surrounding "halo."

stem cells in five (Nos. 5 through 9), and allogeneic bone marrow in five (Nos. 10 through 14). Of the two patients who had orthotopic liver transplantation, one (No. 15) had the transplant because of end-stage liver disease caused by cryptogenic cirrhosis, which was done during the same hospitalization 48 days before the pulmonary resection for IPA. The other patient (No. 16) underwent liver transplantation 4 years earlier because of end-stage liver disease caused by non-A, non-B hepatitis, and the current hospital admission was for treatment of rejection and for a bile duct stricture, with the subsequent development of IPA.

A fever higher than 38.5° C was the initial presenting symptom of IPA in eight patients, although fever was a prominent symptom in all patients before operation, except in one liver transplant patient (No. 15) who was receiving high-dose corticosteroids for treatment of acute rejection. A new nodular or diffuse infiltrate on routine chest radiograph was the presenting abnormality of IPA in seven other patients. The remaining patient (No. 10) had pleuritic chest pain as the presenting symptom. Other symptoms of IPA included cough (usually productive) in four, pleuritic chest pain in six, and dyspnea in two with frank respiratory failure in two others. Two patients (Nos. 3 and 4, both with thrombocytopenia) preoperatively had a slight amount of blood-tinged sputum intermittently but no patient manifested frank hemoptysis. In addition, no patient had a positive blood culture for *Aspergillus.* In the column on *Aspergillus presentation* in Table I, the abnormal signs and symptoms listed for each patient are given in the chronologic order in which they developed.

The initial presenting signs or symptoms of IPA in all patients occurred a mean of 14.3 ± 6.5 days (range 8 to 29 days, median 11.5 days) after the primary procedure. In the patients with hematologic diseases, IPA initially presented after a mean of 12.9 ± 5.3 days (range 8 to 24 days, median 11.0 days). The time to presentation was not significantly different for patients with allogeneic and autologous marrow transplants. For the two patients with liver transplantation, a mean of 24.5 ± 6.4 days (range 20 to 29 days) passed after their transplant or rejection treatment before the initial presentation of IPA, and this was a significantly longer period than that in the overall group of patients with hematologic diseases ($p = 0.013$).

Radiographic findings. All patients had characteristic radiographic findings. On chest radiography, there was the appearance of a pulmonary infiltrate, usually nodular, that was commonly seen at the time symptoms occurred. Most striking was how rapidly the radiographic abnormalities progressed, from a normal chest radiograph to the sudden appearance of an enlarging nodule that often increased in size daily despite antifungal therapy. These changes were most notable in patients who had neutropenia at the time or were receiving immunosuppressive drugs. Chest CT scan findings were abnormal in all patients and generally manifested one of two patterns described previously[14]: (1) dense nodular opacity with a hazy margin or more commonly a surrounding zone of intermediate attenuation (density), called a "halo" sign, or (2) cavitary mass often with a discrete margin and a crescent-shaped area of hyperlucency surrounding or within the parenchymal opacity, called an "air crescent" sign.

One patient (No. 4) exhibited an unusual picture of diffuse lobar consolidation and apparent pleural empyema containing debris (he was shown later at operation to have an *Aspergillus* empyema plus a necrotic *Aspergillus* cavity in the lung and lymph

Table II. *Presenting radiographic opacity compared with cell counts and days after procedure*

Type of opacity	*WBC/mm³*	*ANC/mm³*	*Days after procedure*
Nodule with or without "halo" ($n = 9$)*	377.8 ± 408.6	33.3 ± 70.7	16.7 ± 7.0
Cavity ($n = 4$)*	7575.0 ± 9571.3 ($p = 0.036$)	4675 ± 6351.6 ($p = 0.04$)	42.8 ± 14.5 ($p < 0.001$)

WBC, White blood cell count.

*The data for the two patients with liver transplantation were included in the calculation of "days after procedure." Therefore $n = 10$ for the nodule group and $n = 5$ for the cavity group for that section.

node involvement with *Aspergillus*). Three patients (Nos. 3, 6, and 9) had on chest CT scan a parenchymal nodular opacity with a hazy margin. Six patients (Nos. 1, 2, 7, 10, 13, and 14) had a parenchymal nodule with a surrounding "halo" sign, as illustrated by a chest CT image from patient No. 9 (Fig. 1). Four patients (Nos. 5, 8, 11, and 12) had a gas-containing cavitary mass, and two of these patients had a classic "air crescent" sign, as shown in a representative CT image from patient No. 8 (Fig. 2). The two patients with liver transplants had both of the common radiographic pictures: a nodule with a hazy margin in patient No. 16 and a gas-containing cavitary mass in patient No. 15.

In the 13 patients with hematologic diseases with transient neutropenia who had one of the two major radiographic pictures of IPA (nodule or cavity), the white blood cell count and the ANC at the time the CT scans were obtained both significantly correlated with which of the two features appeared (Table II). Similarly, in the same 13 patients with transient neutropenia plus the 2 patients with liver transplants, a significant correlation existed between the initial type of radiographic pattern seen on chest CT scan with IPA (nodular or cavitary) and the time from the primary procedure until the radiographic study was done (Table II).

Invasive diagnostic procedures. Fourteen patients underwent flexible bronchoscopy with bronchoalveolar lavage a mean of 6.8 ± 7.2 days (range 1 to 23 days, median 3 days) after symptoms or radiographic abnormalities of IPA were recognized. One of the 14 lavage specimens (from patient No. 4) grew an *Aspergillus* species on culture, although two others (from patients Nos. 11 and 15) demonstrated a typical histologic picture of *Aspergillus* but no organism grew. All three of these patients had either cavitary lesions (Nos. 11 and 15) or diffuse lobar consolidation and empyema (No. 4) on CT scan.

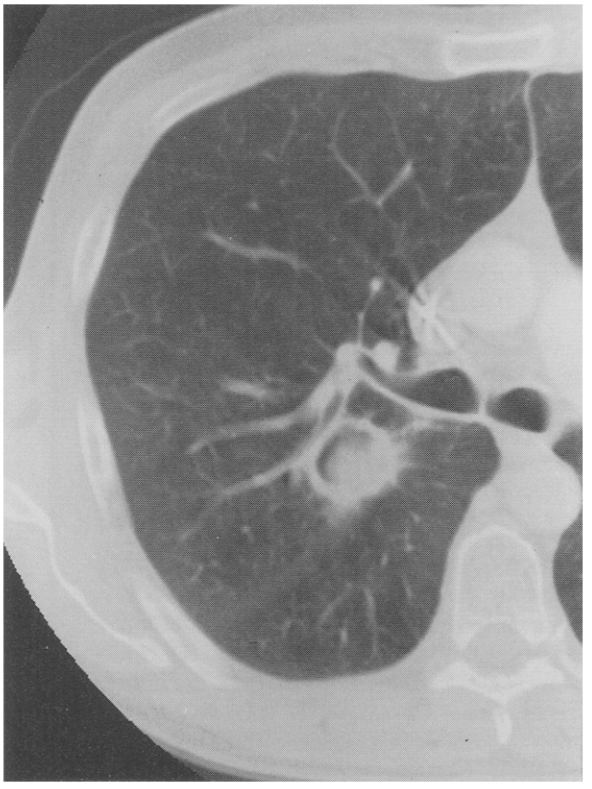

Fig. 2. Contrast-enhanced chest CT image from patient No. 8 at the level of the carina showing a gas-containing 2.5 cm diameter cavitary density in the right upper lobe. There is an intracavitary mass and an "air crescent" sign. Other more caudad images (not shown) demonstrate a direct bronchial communication with the cavity and apparent extension of this mass across the major fissure into the superior segment of the right lower lobe (confirmed at operation).

The other 11 bronchoscopic evaluations (78.6%) were nondiagnostic or demonstrated other organisms. A percutaneous needle aspiration biopsy was done in three patients and in two the specimen grew an *Aspergillus* species on culture. None of the patients had a complication from the needle biopsy.

White blood cell counts. Neither of the patients with liver transplants had neutropenia at any time during their hospitalization. However, all 14 of the patients with hematologic diseases had severe neutropenia (ANC <500 cells/mm³) during their hospitalization before the development of IPA. The mean duration of severe neutropenia in these patients was 26.0 ± 10.3 days (range 11 to 46+, median 26.5 days). Four patients with acute myelogenous leukemia or aplastic anemia were admitted to the hospital with severe neutropenia so the total neutropenic duration is unknown and is indicated in Table I with

Table III. *Summary of therapy for patients with Aspergillus infection*

	Days after primary procedure			*On day of operation*			
Patient No.	*Aspergillus presentation*	*Amphotericin B started*	*Operation done*	*Condition*	*ANC (cells/ mm^3)*	*Days since admission*	*Thoracic surgical procedure*
Hematologic disease							
1	11	13	20	Febrile, no supp O_2	700	31	Lobectomy
2	9	7	27	Febrile, no supp O_2	0	35	Pneumonectomy
3	8	8	14	Febrile, no supp O_2	1,100	24	Lobectomy
4	8	15	48	Febrile, uremic, no supp O_2	10,000	55	Bilobectomy, decortication, thoracoplasty
5	8	8	53	Febrile, no supp O_2	4,700	70	Pneumonectomy
6	9	3	33	Afebrile, no supp O_2	900	1	Lobectomy
7	21	11	25	Febrile, no supp O_2	100	31	Lobectomy
8	24	12	27	Febrile, mild dyspnea, no supp O_2	2,800	1	Lobectomy and wedge resection
9	12	10	16	Afebrile, no supp O_2	1,000	24	Multiple wedge resections
10	15	4 days before transplant	a. 18 b. 23	Febrile, no supp O_2	a. 0 b. 1,700	a. 28 b. 33	a. Lobectomy b. Wedge resection
11	9	9	48	Febrile, acidotic, ventilator support, jaundiced	15,100	59	Multiple wedge resections
12	17	1 day before transplant	49	Febrile, no supp O_2	2,700	58	Wedge resection
13	18	6 days before transplant	21	Afebrile, cough, no supp O_2	3,400	28	Lobectomy
14	11	12 days before transplant	12	Afebrile, no supp O_2	0	24	Wedge resetion
Liver transplant							
15	29	36	48	Afebrile, no supp O_2	8,300	61	Lobectomy
16	20	21	23	Febrile, no supp O_2	3,400	23	Lobectomy

A&W, Alive and well; *AML,* acute myelogenous leukemia; *Asper, Aspergillus* infection; *ATN,* acute tubular necrosis; *BMT,* bone marrow transplant; *DAH,* diffuse alveolar hemorrhage; *met.,* metastatic; *met. sq. cell car.,* metastatic squamous cell carcinoma; *MOSF,* multiple organ system failure; *POD,* postoperative day; *recurr.,* recurrent; *resp.,* respiratory; *supp O_2,* supplemental O_2.

a plus sign after the number of days the ANC was less than 500 cells/mm^3. The number of days after the end of high-dose chemotherapy or marrow rescue until the ANC reached more than 500 cells/mm^3 was a mean of 20.0 ± 5.1 days (range 13 to 30 days, median 20.0 days) for 13 patients, and one patient (No. 2) never had recovery of the ANC to greater than 500 cells/mm^3 up to the time of hospital discharge.

Nine of the patients were given hematopoetic growth factors (GM-CSF or G-CSF) after their transplant and their mean time for recovery of the

Postoperative complications	*Amphotericin B total dosage (mg)*	*Other antifungal agents*	*Outcome*	*Autopsy*	*Follow-up (months after operation)*
None	835	Itraconazole	Discharged POD 8	—	Auto BMT 4 mo later; A&W, no *Asper* (40 mo)
None	1,600	Fluconazole	Discharged POD 10	—	Died of AML, no *Asper* (10 mo)
None	1,525	Fluconazole	Discharged POD 26	—	Died of AML, no *Asper* (6 mo)
None	2,189	—	Discharged POD 32	—	Alive with recurr. Hodgkin's, no *Asper* (82 mo)
Herpes simplex pneumonia	2,823	—	Died POD 28	DAH, ATN, no *Asper*	—
None	1,054	—	Discharged POD 6	—	Died of recurr. lymphoma, no *Asper* (8 mo)
None	1,000	Itraconazole	Discharged POD 7	—	A&W, no *Asper* (8 mo)
Atrial fibrillation	1,000	—	Discharged POD 9	—	A&W, no *Asper* (3 mo)
None	1,000	—	Discharged POD 6	—	A&W, no *Asper* (4 mo)
Resp. insufficiency, coagulopathy, bleeding	1,700	Rifampin	Died POD 11 graft-vs-host disease, no *Asper*	None	—
Resp. failure, liver failure, seizures	1,504	Fluconazole, Itraconazole	Died POD 7, cerebral edema, ventilator support	DAH, ATN, met. sq. cell ca., no *Asper*	—
Resp. failure, sepsis, renal failure, MOSF, pulmonary infiltrates	1,386	Fluconazole	Died POD 20, possible *Asper* recurrence	None	—
Progressive resp. failure on POD 2	1,164	Itraconazole	Died POD 20	DAH, no *Asper*	—
Bilateral pulmonary consolidation	7,701 (liposomal)	Fluconazole, Itraconazole	Discharged POD 30	—	Died, DAH, MOSF, no definite *Asper* (3 mo)
Prolonged air leak	901	Itraconazole	Discharged POD 43	—	Alive with met. hepatoma, no *Asper* (13 mo)
Pneumonia, resp. insufficiency, prolonged air leak	1,080	—	Discharged POD 84	—	A&W, no *Asper* (8 mo)

ANC to greater than 500 cells/mm^3 was 20.2 ± 5.0 days. However, this time was not significantly less than the recovery time to an ANC greater than 500 cells/mm^3 in the four patients with marrow recovery who did not receive hematopoetic growth factors, which was a mean of 23.0 ± 4.8 days ($p = 0.366$). Finally, at the time of IPA presentation, eight patients had an ANC of zero and six patients had begun to have engraftment with a mean ANC of 3426.7 ± 6074.1 cells/mm^3 (range 100 to 15,660; median 900).

Medical therapy. A complete summary of therapeutic interventions for IPA in the patient population is shown in Table III. Antifungal medical therapy was aggressively begun with amphotericin B in all patients immediately on the suspicion of an active fungal infection. Four patients (Nos. 10, 12, 13, and 14) had begun receiving prophylactic am-

photericin B through an investigational protocol before receiving high-dose chemotherapy and marrow rescue and before IPA presentation. The total dosage of amphotericin B received was a mean of 1778.9 ± 1664.1 mg (range 835 to 7701 mg, median 1275.0 mg). Fourteen (87.5%) of the 16 patients received a total dosage greater than 1000 mg. One patient (No. 14) was treated with liposomal amphotericin B to a high total dosage of 7701 mg and was a hospital survivor. The total dosage of amphotericin B did not differ significantly between a mean of 1807.7 ± 1995.6 mg in the 11 hospital survivors and the mean dose of 1715.4 ± 648.9 mg for the five nonsurvivors ($p = 0.922$). Renal toxicity of this drug often limited the dosing schedules and total dosage in this patient population, especially in the seven patients also receiving long-term cyclosporine therapy. Six patients received itraconazole for varying lengths of time after lung resection when severe nephrotoxicity or other toxic effects forced discontinuation of amphotericin B. Five patients also received fluconazole to treat *Candida* infection, and one received rifampin in addition to amphotericin B to augment IPA treatment.

Surgical intervention. Pulmonary resection was done a mean of 30.1 ± 14.3 days (range 12 to 49 days, median 26.0 days) after the primary procedure. However, the interval from IPA presentation until operation varied greatly with a range of 1 to 45 days (mean 15.8 ± 15.5 days, median 7.5 days). The 11 hospital survivors had the lung resection a mean of 11.9 ± 12.1 days after IPA presentation compared with a mean of 24.4 ± 20.1 days in the five nonsurvivors, although this trend toward a longer delay for operation was not statistically significant ($p = 0.140$). Pulmonary resection was done a mean of 32.9 ± 22.1 days (median 29.5 days, range 1 to 70 days) after hospital admission. The 11 hospital survivors were admitted to the hospital as inpatients a mean of 28.7 ± 22.3 days before lung resection, but not statistically fewer days than the five nonsurvivors who were admitted a mean of 42.0 ± 21.0 days before operation ($p = 0.280$).

The overall condition of most patients at the time of operation was surprisingly good. On the day of operation, the ANC had recovered to greater than 500 cells/mm^3 in 12 (75%) of 16 patients, and the mean ANC for all patients was 3387.5 ± 4298.5 cells/mm^3 (range 0 to 10,000, median 1900.0). Only one of the five hospital deaths was in a patient who had severe neutropenia at the time of lung resection. For only the patients with hematologic diseases at the time of operation, the mean ANC of hospital survivors was 1844.4 ± 3176.9, which was not significantly different from the mean ANC of 5180.0 ± 5804.9 in the nonsurvivors ($p = 0.184$). Eleven (68.8%) of the 16 patients were febrile on the day of operation. Fifteen (93.8%) of 16 patients did not require supplemental oxygen on the day of operation, but the other patient (a nonsurvivor) was receiving ventilator support.

Surgical procedures done included seven lobectomies (1 death), two pneumonectomies (1 death), one lobectomy and wedge resection, four single or multiple wedge resections (2 deaths), and one bilobectomy with decortication and three-rib thoracoplasty. In addition, one patient underwent a lobectomy followed 5 days later by a contralateral wedge resection for a new focus of *Aspergillus* infection (a nonsurvivor).

During the period of this case review, four other patients (3 patients with liver transplantation and 1 patient with allogeneic bone marrow transplantation) underwent pulmonary resections (all lobectomies) because of unremitting fever and new nodular pulmonary infiltrates suggestive of IPA. Their clinical presentation was somewhat similar to that of the patients with IPA although the chest CT scan findings did not demonstrate the classic "halo" sign or the "air crescent" sign. Two were found to have *Nocardia* lung abscesses (both hospital survivors), one ventilator-dependent patient had a *Candida* lung abscess (nonsurvivor), and the patient with allogeneic bone marrow transplant had a mixed bacterial lung abscess (a hospital survivor).

Surgical pathologic findings. Resected lung on all patients showed a similar picture on gross examination consisting of hemorrhagic necrosis with varying degrees of cavitation filled with mycotic lung sequestrum[11] and surrounding consolidation. The microscopic examination confirmed the presence of hemorrhagic infarction with necrotic lung invaded by hyphae. Methenamine silver stains revealed in all patients the typical histologic features of abundant septate hyphae with dicotomous branching at 45 degrees often with vessel invasion and thrombosis. A typical example of the histologic picture (patient No. 12) is shown in Fig. 3. Despite typical histologic findings in all patients, only 9 (56.3%) of the 16 grew an *Aspergillus* species. In addition, three of these specimens had a mixed infection. All patients had IPA but three also had other sites of infection with *Aspergillus*.

Complications. Nine (56.3%) of the 16 patients had postoperative complications that ultimately re-

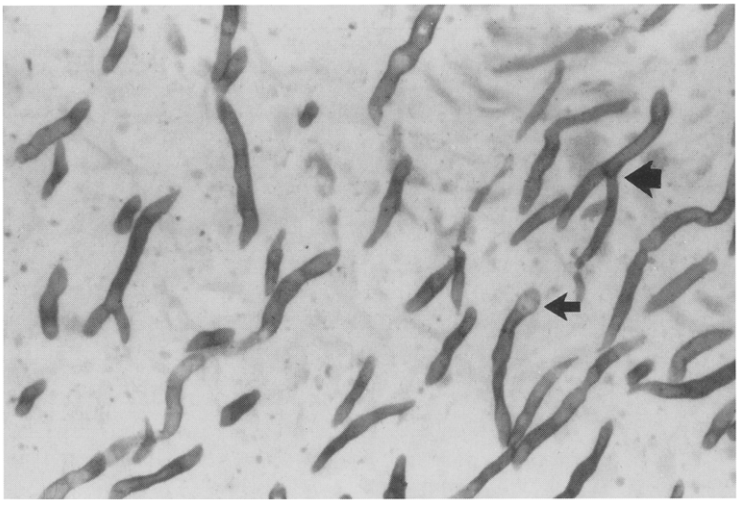

Fig. 3. Photomicrograph from the surgical specimen from patient No. 12 with a Grocott methenamine silver stain of lung demonstrating prominent septate hyphae exhibiting dichotomous branching at 45 degrees *(large arrow)* and very early conidial head (sporulating structure) formation *(small arrow)*. Fungal culture from this specimen grew *A. flavus* (original magnification ×400).

sulted in five deaths. As expected, the most common complications were of respiratory origin in 7 (77.8%) of the 9 patients. A variety of other complications occurred and are listed in Table III. The occurrence of nonoliguric renal insufficiency with a rising serum creatinine level was common in most patients (present before operation in many) and was related to amphotericin B administration, although it was especially pronounced in patients also receiving cyclosporine. Despite the immunocompromised, debilitated condition of most patients, the majority of whom were receiving steroids at the time of operation, no patient had an empyema, bronchopleural fistula, bleeding that necessitated surgical exploration, residual pleural space problems, wound dehiscence, or deep wound infection. One patient (No. 16) had a late superficial wound infection (bacterial), which healed with conservative management.

Hospital outcome. Eleven of 16 patients survived the hospitalization. The nine survivors with hematologic diseases were discharged from the hospital a mean of 14.9 ± 11.0 days (range 6 to 32 days, median 9 days) after operation. The two patients with liver transplants were hospitalized significantly longer after operation and were discharged after a mean of 63.5 ± 29.0 days (range 43 to 84 days) ($p = 0.002$).

The five deaths (31.3% overall mortality) occurred a mean 17.2 ± 8.3 days (range 7 to 28 days, median 20 days) after operation. Four of the five deaths were in patients with allogeneic bone marrow transplants. Only one of the original five patients with allogeneic marrow transplants with IPA who underwent lung resection survived the hospitalization. Two deaths (No. 11 and 13) were the result of diffuse alveolar hemorrhage (DAH) with respiratory failure, but without any evidence of residual *Aspergillus* infection in any organ. There was incidental metastatic squamous cell carcinoma in the pancreas (primary tumor not found) discovered on autopsy in one of these patients (No. 11). One hospital death (No. 10) was a result of biopsy-proven graft-versus-host disease with respiratory failure, but no clinical evidence of *Aspergillus* recurrence was seen. Another hospital death (No. 12) occurred as a result of respiratory failure with pulmonary infiltrates, sepsis, and multiple organ system failure and occurred in the only patient in the entire group of 16 in whom recurrent and possibly disseminated *Aspergillus* infection was clinically suspected; unfortunately no autopsy was obtained. The final death occurred in the only patient with autologous bone marrow transplantation (No. 5), who died 4 weeks after operation with *Herpes simplex* pneumonia and DAH in the remaining lung after a pneumonectomy.

Long-term follow-up. Long-term follow-up of hospital survivors was 100% complete, with a mean follow-up of 16.8 ± 24.0 months (range 3 to 82 months, median 8 months). Three patients have

subsequently died with recurrence of their malignancy at a mean of 8.0 ± 2.0 months (range 6 to 10 months), but none had any evidence of *Aspergillus* infection. Likewise, none of the survivors of the initial hospitalization has ever had any clinical evidence of recurrent *Aspergillus* infection.

Discussion

Aspergillus is a ubiquitous fungus commonly found in soil, stored grains, and decaying organic matter such as spoiled straw and hay, and it is even found in such extreme environments as the Sahara sands and the Arctic snow.[15] The fungus, first identified in 1729 by the priest and botanist Micheli, was probably named for the perforated globe (aspergillum) used for sprinkling holy water due to its resemblance to the radiating spores (conidial head) on the hyphae.[16] After the initial clinical description of aspergillosis in 1842, Virchow[17] in 1856 reported the first four cases with pathologic evidence of this disease on autopsy.

Aspergillus spores are airborne organisms usually present in the air, and undoubtedly inhalation of them is extremely common. Yet their virulence is low and production of disease is rare. Involvement of the lungs with this fungus is the most common because the portal of entry is usually the respiratory tract. Hinson, Moon, and Plummer[16] in 1952 classified pulmonary aspergillosis into three types. First, the noninvasive allergic form results in respiratory symptoms as a result of an immunologic reaction to the fungus in the tracheobronchial tree. Second, saprophytic disease results from colonization of preexisting cavities in the lung, leading to the formation of a tangled mass of hyphae, blood elements, and debris in the cavity termed a mycetoma (fungus ball) or classic aspergilloma. These lesions have been classified into simple or complex aspergillomas depending on the extent of surrounding parenchymal disease. The saprophytic form is the most common manifestation of pulmonary aspergillosis,[8] may require surgical excision because of bleeding (sometimes life-threatening) from erosion into surrounding pulmonary vessels, and generally is a chronic process quite unlike the invasive third type. The third type, the septicemic type or IPA, occurs almost exclusively in immunocompromised hosts. It arises in necrotizing bronchopneumonia with further invasion of lung parenchyma and pulmonary vessels leading to thrombosis and hemorrhagic infarction, and ultimately the fungus may disseminate.

The development of nosocomial IPA in an immunocompromised patient is a potentially devastating complication, occurring in as few as 4.5% of patients with bone marrow transplants of all types[18] to as many as 20% of allogeneic bone marrow transplant recipients.[19] In patients with neutropenia and acute leukemia undergoing standard chemotherapy, IPA has been diagnosed antemortem in 21%.[11] In contrast, invasive aspergillosis without neutropenia may develop in 2% of patients with renal transplants[5] and 1.5%[20] to 4.2%[6] of patients with liver transplants. However, considering the high mortality in all immunocompromised patients, the development of IPA is a serious complication.

For patients with hematologic diseases and those undergoing bone marrow transplantation, the risk of the development of IPA progressively rises with the increasing number of neutropenic days, reaching a 70% incidence by 34 or more days of neutropenia.[20] The mean neutropenic period for patients in the current series was 26.0 ± 10.3 days, which clearly places most of our patients in this high-risk group. Some series indicate that an age older than 30 years increases the incidence of IPA, as does mismatching of bone marrow allograft recipients.[18] Cytomegalovirus (CMV) infection, which itself is immunosuppressive, has been demonstrated by some to predispose patients to IPA,[19] as does the presence of higher grade graft-versus-host disease.[18] Corticosteroid therapy is another independent risk factor for aspergillosis.[21] Because therapy with corticosteroids generally accompanies the use of cyclosporine in graft-versus-host prophylaxis, corticosteroids further compound the immunosuppression of patients with allogeneic bone marrow transplants and increase their overall risk of lethal IPA.[7, 13] Other factors that may contribute to an elevated risk include damage to the mucocutaneous barriers by fungus, impaired humoral immunity related to side effects of therapy, and the loss of resistance to colonization by the use of antibiotics.[22] All of the patients with hematologic diseases in the current series had one or more of these risk factors.

In patients with solid organ transplants, predisposing factors for development of aspergillosis include recent treatment for acute rejection (both liver transplant patients in the current series were treated for rejection), recent CMV infection, and multiple transplantations.[5] Factors also found specifically in patients with liver transplants include retransplantation, reintubation, bacterial infections, prolonged antibiotic use, increased intraoperative

blood transfusion requirements, increased number of corticosteroid boluses, use of OKT3, vascular complications, rising levels of serum creatinine, Roux-en-Y biliary reconstruction, and urgent transplant status.[6] Many of these factors were present in the two patients with liver transplantation in the present series.

Establishment of an early antemortem diagnosis of IPA is important if treatment is to be successful. Symptoms are most likely to occur during the period of neutropenia, and in our series of patients with hematologic diseases symptoms began a mean of 13 days after the marrow transplant or the end of chemotherapy, when 50% of these patients had an ANC of zero. For the patients with liver transplants, presentation of IPA symptoms or signs occurred later at a mean of 25 days. The clinical presentation most commonly includes unexplained and unremitting fever not responsive to antibacterial agents,[4] a symptom present in 94% of patients in the present series and missing only in the one patient receiving high-dose corticosteroids for rejection. Pleuritic chest pain, seen in 38% of our patients, is seen frequently, along with dyspnea and cough.[23] Hemoptysis may occur because of the vasculotropic nature of the fungus, which leads to pulmonary vessel invasion. But the reported 31% incidence of hemoptysis in IPA is not nearly as high as the 52% to 80% occurrence in classic saprophytic aspergillomas.[24] Interestingly, only 13% of patients in our series manifested even a minor episode of hemoptysis with IPA.

The development of a characteristic rounded infiltrate on the chest radiograph is a universal finding and when accompanied by a fever in an immunocompromised patient should strongly suggest IPA.[24] Mori and associates[14] described the two major radiographic patterns of IPA seen on chest CT scans: nodular with or without a surrounding "halo" and cavitary with or without an "air crescent" sign. The nodular pattern appears to be the earlier presentation because it significantly correlates with a lower white blood cell count, lower absolute neutrophil count, and earlier occurrence after transplantation.[14] This association was also found in our series (see Table II). Because the cavitary pattern generally is seen after engraftment, this implies that neutrophil recovery is necessary for pulmonary cavitation to occur. Przyjemski and Mattii[25] proposed that proteolytic enzymes released from the influx of granulocytes cause dissolution of necrotic lung and separation of sequestra from the surrounding lung parenchyma leading to cavity formation. This hypothesis is further strengthened by the fact that the most frequent presentation of IPA was cavitary in 91% of patients with renal transplantation who never had neutropenia.[5]

A positive sputum culture for *Aspergillus* is highly suggestive of infection, but may only indicate colonization. Bronchoscopy with bronchoalveolar lavage tends to be nondiagnostic and usually is not helpful because even a positive result for *Aspergillus* may indicate only colonization and not invasive infection.[26] In the present series, only 19% of lavage samples had positive histologic results and all were in patients with advanced cavitary disease. Percutaneous needle biopsy of the nodular infiltrate is another diagnostic option and showed positive results in two of three of our patients. However, needle biopsy often carries an unacceptably high risk of bleeding complications in these patients with thrombocytopenia. Additionally, because a nondiagnostic result will generally not change therapeutic plans if surgical resection is an option, this modality probably should be reserved for patients who would be treated with medical therapy only.

Recently, a commercial test kit for *Aspergillus* infection has been described for detection of *Aspergillus* galactomannan antigen in serum, urine, or both. Although a false positive result may occur in patients receiving certain anticancer agents such as cyclophosphamide, this test reportedly facilitates very early detection in those patients at high risk for IPA, such that empiric antifungal therapy may be started promptly and the results of medical therapy are possibly improved.[27]

Definitive diagnosis of IPA early in its course is often difficult and a treatment delay can be uniformly fatal in these immunocompromised patients.[24] Therefore it is entirely appropriate to institute empiric antifungal therapy with amphotericin B when IPA is clinically suspected.[13] Unfortunately, even early aggressive medical treatment of IPA results in a high mortality. Meyer and associates[23] reported a 100% mortality rate with medical treatment alone for IPA in their immunocompromised population. Wingard and colleagues[4] and Peterson and associates[19] found the same 100% mortality rate in their bone marrow transplant populations. Denning and Stevens[7] in their extensive 1990 review found an overall 94% mortality rate with medical therapy of IPA in 13 collected series of bone marrow transplant recipients.

For patients with solid organ transplants, the

mortality rate from IPA in patients with renal transplantation treated medically was lower at 38% although 60% of survivors lost their allograft kidney because rejection episodes were not treated while they were being treated for IPA.[5] However, the mortality rate from IPA in liver transplant recipients with medical therapy has been shown to be much worse and in multiple series approaches 100%.[28]

Scattered early anecdotal reports have appeared of IPA cures resulting from combining pulmonary resection with antifungal medical therapy in immunocompromised patients. Wingard and associates[4] in their bone marrow transplant population had only one survivor with IPA, and that patient underwent pulmonary resection of the infection site in addition to amphotericin B therapy. This was also the experience of Meyer and colleagues[23] in one patient 15 years earlier at the Memorial Sloan-Kettering Cancer Center. In their 1987 review, Kibbler and associates[11] reported their own series plus patients from the literature for a total of eight surgical cures of IPA with no surgical mortality in patients with neutropenic leukemia. For solid organ transplantation, Weiland and colleagues[5] reported three survivors of lung resection and amphotericin B treatment of IPA in their renal transplant population (also, all allograft kidneys survived).

In view of the dismal results of medical therapy of IPA and these promising early surgical results, we adopted an aggressive surgical approach in 1987 for the present series in which immunocompromised patients with clinical evidence strongly suggestive of IPA underwent pulmonary resection along with amphotericin B therapy. In our series, all three patients receiving high-dose chemotherapy and five of six autologous marrow rescue patients survived, free of recurrent *Aspergillus* infection. The one death in the autologous marrow group was caused by *Herpes simplex* pneumonia and later DAH in the remaining lung after pneumonectomy for removal of a lung destroyed by prior radiation therapy and cavitary IPA. Results after pulmonary resection in patients with allogeneic bone marrow transplants with IPA have been less rewarding for us and others.[24] Four of five of our patients with allogeneic transplantation did not survive the hospitalization: two died of respiratory failure from DAH, another died of graft-versus-host complications, and the fourth patient died with multiple organ system failure but possibly had disseminated *Aspergillus* infection. DAH, which is probably a subset of idiopathic interstitial pneumonitis (a common cause of death in allogeneic bone marrow transplantation[29]), is a poorly understood, high-mortality condition that caused three of the five postoperative deaths in our series. It appears to be associated with renal insufficiency, advanced age, and white blood cell recovery, but it is not related to *Aspergillus* infections.[30] Finally, both patients with liver transplants survived lung resection for IPA and are still living with no evidence of recurrent *Aspergillus* infection. The overall survival from IPA for our surgically treated patients with hematologic diseases is 64% and survival is 100% for our liver transplant group.

Since we began our study, several other surgical series have been reported. Lupinetti and associates[24] reported on five pediatric patients with leukemia treated with chemotherapy and allogeneic bone marrow rescue who underwent pulmonary resection for IPA. One patient operated on two months before transplant was cured of IPA although later died of CMV pneumonia; the other four died 24 to 194 days after operation of disseminated *Aspergillus* infection (2 patients), *Aspergillus* pneumonia (1 patient), and central nervous system leukemia (1 patient). Young and associates[31] reported 100% hospital survival in eight patients with neutropenia with malignancies (4 had bone marrow transplants) who underwent pulmonary resections (7 lobectomies and 1 multiple wedge resections) for IPA. Wong, Waters, and Walesby[26] later reported a series of 16 patients with neutropenia (14 with high-dose chemotherapy only and 2 with allogeneic bone marrow transplantation) who underwent pulmonary resections (13 by lobectomy or pneumonectomy and 3 by wedge resection) for IPA, with only one postoperative death caused by CMV pneumonia and no recurrent *Aspergillus* infection.

The outlook for improvements in medical therapy in the near future for IPA that might challenge these most recent surgical results is slightly encouraging.[7] Trials are in progress with the minimally toxic and very promising oral drug itraconazole (an intravenous preparation will be available soon), liposomal amphotericin B with its putative lower toxicity and improved penetration, prophylactic amphotericin B in patients with neutropenia, who are at high risk for the infection (this did not prevent IPA in 4 patients in our series), and combination medical therapy with amphotericin B to achieve synergy with flucytosine or rifampin. However, even the optimal dos-

age and duration of therapy of amphotericin B for treatment of deep mycoses is still not clear and possibly higher dosages may be advisable.[7] Although the most common species, *A. fumigatus* and *A. flavus,* are generally sensitive to amphotericin B, in vitro susceptibility testing, despite its 5- to 21-day turnaround time, may play an important role when other therapeutic agents such as flucytosine (which is not effective with all isolates) are used singly or in combination or when less common *Aspergillus* species are treated.[7]

At present, it is not clear which is the most effective management strategy for IPA in immunocompromised patients. The persistently high mortality rates with current medical management sways us to advocate adding the more aggressive surgical approach, as described in this retrospective series and prior recent reports.[24, 26, 31] Contrary to what might be expected, pulmonary resection for localized IPA in selected patients can be done safely with low morbidity and mortality despite low or nonexistent white blood cell counts, thromboctyopenia, and corticosteroid therapy, with only rare recurrence of the *Aspergillus* infection. Results from these series suggest that early, complete resection with lobectomy or occasionally wedge resection for smaller fungal lesions along with excision of sufficient normal tissue to prevent contamination of uninfected lung should be done as soon as the characteristic clinical and radiographic pictures appear, without waiting for positive cultures or other confirmatory tests or a long trial of antifungal medical therapy. Delaying surgery may result in life-threatening hemoptysis,[31] greater risk for systemic dissemination as further vascular invasion by the fungal hyphae occurs,[32] and increased risk for pleural fungal invasion with empyema formation. The best survival results from the current series and others[11, 31] favor early resection, preferably within the first week of diagnosis.

The exact role that surgical treatment plays in various patient subsets in the treatment of IPA has yet to be defined and awaits prospective clinical trials. From our experience and that of others,[24, 26, 31] patients with multiple loci of infection, allogeneic bone marrow transplant recipients, and possibly ventilator-dependent patients are less likely to benefit from this aggressive surgical approach. However, aside from these caveats, most immunocompromised patients with hematologic disease and solid organ transplant recipients in whom this almost uniformly fatal complication of IPA develops may expect a greatly improved likelihood of survival, with almost 70% of all patients in this series cured of the fungal infection for the long term.

We extend our special appreciation to Dr. Susan L. Speaks for providing the photomicrograph (Fig. 3) used in this manuscript.

REFERENCES

1. Williams DM, Krick JA, Remington JS. Pulmonary infection in the immunocompromised host. Am Rev Respir Dis 1976;114:359-64.
2. Degregorio MW, Lee WMF, Linker CA, Jacobs HA, Ries CA. Fungal infection in patients with acute leukemia. Am J Med 1982;73:543-8.
3. Albeda SM, Talbot GH, Gerson SL, Miller WT, Cassileth PA. Pulmonary cavitation and massive hemoptysis in invasive pulmonary aspergillosis. Am Rev Respir Dis 1985;131:115-20.
4. Wingard JR, Beals SU, Santos GW, Merz WG, Saral R. *Aspergillus* infections in bone marrow transplant recipients. Bone Marrow Transplant 1987;2:175-81.
5. Weiland D, Ferguson RM, Peterson PK, Snover DC, Simmons RL, Najarian JS. Aspergillosis in 25 renal transplant patients. Ann Surg 1983;198:622-9.
6. Castaldo P, Stratta RJ, Wood RP, et al. Clinical spectrum of fungal infections after orthotopic liver transplantation. Arch Surg 1991;126:149-56.
7. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. Rev Infect Dis 1990;12:1147-201.
8. Suen HC, Wright CD, Mathisen DJ. Surgical management of pulmonary aspergillosis. Chest Surg Clin North Am 1993;4:671-81.
9. Fisher BD, Armstrong D, Yu B, Gold JWM. Invasive aspergillosis: progress in early diagnosis and treatment. Am J Med 1981;71:571-7.
10. Shamberger RC, Weinstein HJ, Grier HE, Levey RH. The surgical management of fungal pulmonary infections in children with acute myelogenous leukemia. J Pediatr Surg 1985;20:840-4.
11. Kibbler CC, Milkins SR, Bhamra A, Spiteri MA, Noone P, Prentice HG. Apparent pulmonary mycetoma following invasive aspergillosis in neutropenic patients. Thorax 1988;43:108-12.
12. Schattenberg A, DeVries F, DeWitte T, Cohen O, Donnelly JP, DePauw BE. Allogeneic bone marrow transplantation after partial lobectomy for aspergillosis of the lung. Bone Marrow Transplant 1988;3:509-12.
13. Iwen PC, Reed EC, Armitage JO, et al. Nosocomial invasive aspergillosis in lymphoma patients treated with bone marrow of peripheral stem cell transplants. Infect Control Hosp Epidemiol 1993;14:131-9.
14. Mori M, Galvin JR, Barloon TJ, Gingrich RD, Stan-

ford W. Fungal pulmonary infections after bone marrow transplantation: evaluation with radiography and CT. Radiology 1991;178:721-6.
15. Rippon J. Medical mycology: the pathogenic fungi and pathogenic actinomycetes. 3rd ed. Philadelphia: WB Saunders, 1988:618-50.
16. Hinson KFW, Moon AJ, Plummer NS. Bronchopulmonary aspergillosis: review and report of eight cases. Thorax 1952;7:317-33.
17. Virchow R. Beitrage zur Lehre von den beim Menschen vorkommenden pflanzlichen Parasiten. Virchows Arch Pathol Anat 1856;9:557-93.
18. Meyers JD. Fungal infections in bone marrow transplant patients. Semin Oncol 1990;17:10-3.
19. Peterson PK, McGlave P, Ramsay NKC, et al. A prospective study of infectious diseases following bone marrow transplantation: emergence of *Aspergillus* and cytomegalovirus as the major causes of mortality. Infect Control 1983;4:81-9.
20. Gerson SI, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Casileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984;100:345-51.
21. Armstrong D. Treatment of opportunistic fungal infections. Clin Infect Dis 1993;16:1-9.
22. Milliken ST, Powles RL. Antifungal prophylaxis in bone marrow transplantation. Rev Infect Dis 1990;12: S374-9.
23. Meyer RD, Young LS, Armstrong D, Yu B. Aspergillosis complicating neoplastic disease. Am J Med 1973;54:6-15.
24. Lupinetti FM, Behrendt DM, Giller RH, Trigg ME, de Alarcon P. Pulmonary resection for fungal infection in children undergoing bone marrow transplantation. J THORAC CARDIOVASC SURG 1992;104: 684-7.
25. Przyjemski C, Mattii R. The formation of pulmonary mycetoma. Cancer 1980;46:1701-4.
26. Wong K, Waters CM, Walesby RK. Surgical management of invasive pulmonary aspergillosis in immunocompromised patients. Eur J Cardiothorac Surg 1992; 6:138-43.
27. Rogers TR, Hynes KA, Barnes RA. Value of antigen detection in predicting invasive pulmonary aspergillosis. Lancet 1990;336:1210-3.
28. Kusne S, Torre-Cisneros J, Manez R, et al. Factors associated with invasive lung aspergillosis and the significance of positive *Aspergillus* culture after liver transplantation. J Infect Dis 1992;166:1379-83.
29. Armitage JO. Bone marrow transplantation. N Engl J Med 1994;330:827-38.
30. Robbins RA, Linder J, Stahl MG, et al. Diffuse alveolar hemorrhage in autologous bone marrow transplant recipients. Am J Med 1989;87:511-8.
31. Young VK, Maghur HA, Luke DA, McGovern EM. Operation for cavitating invasive pulmonary aspergillosis in immunocompromised patients. Ann Thorac Surg 1992;53:621-4.
32. Shamberger RC, Weinstein HJ, Grier HG, Levey RH. The surgical management of fungal pulmonary infections in children with acute myelogenous leukemia. J Pediatr Surg 1985;20:840-4.

Discussion

Dr. Zwi Steiger *(Detroit, Mich.).* I just have one question and a comment. Have you done any resections for *Aspergillus* infection before transplants to avoid possible complications? We, too, had massive hemoptysis in immunocompromised patients. The hemoptysis was attributed to *Aspergillus* infection with unfortunate consequences that, in retrospect, could have been avoided by an elective resection of localized disease. On the urging of the oncologists and infectious disease physicians, we started resecting these foci, with favorable results. Compared with resection of *Aspergillus*-infected chronic tuberculosis cavities, these procedures are not technically difficult.

Dr. Robinson. The three patients who initially were treated with high-dose chemotherapy only and in whom *Aspergillus* infection later developed underwent lung resection and survived. Two of the three patients subsequently had high-dose chemotherapy and bone marrow transplantation 3 to 4 months later and did well. This approach has been described in the literature with good results, and I think it is a reasonable course to pursue.

Mr. Robin K. Walesby *(London, England).* I have a wide experience with this condition in London and I reported the cases of 16 patients 2 years ago (Wong K, Waters CM, Walesby RK. Surgical management of invasive pulmonary aspergillosis in immunocompromised patients. Eur J Cardiothorac Surg 1992;6:138-43). My experience has now unfortunately risen to 30 patients with this condition.

I compliment the authors on this paper and their results, which are much the same as mine. I have found that it is important to overresect lung tissue in these situations. I have had to reoperate on patients on four occasions either to turn a wedge resection into a lobectomy or to change a lobectomy into a completion pneumonectomy when the disease recurred in the remainder of the lung. Unfortunately, my hematologists are always opposed to lobectomy because their chemotherapy is deleterious to lung function. There is always a conflict between the hematologist who wants the surgeon to leave as much lung tissue as possible and the surgeon who needs to take out as much lung as is necessary because of the diffuse and invasive nature of the disease. Although there is invariably a discrete nodular aspergilloma, that is only part of the story. The disease is much more diffuse and can affect the whole lobe or the whole lung, as the description of IPA might lead one to believe.

Finally, can I ask you whether you use aprotinin (Trasylol)? I have had problems in the past with excess bleeding. These resections are exceedingly demanding because all tissues are matted together by the inflammatory process. Even though preoperative infusion with

clotting factors and platelets is done before operation I have produced a dramatic decrease in blood losses with the use of preoperative aprotinin.

Dr. Robinson. We have not used any supplemental methods to decrease bleeding problems in addition to platelet transfusions and replacement of clotting factors. This approach has worked well for us. However, I know other surgeons who have had problems with bleeding in these patients, and this is a significant concern. So far we have not had to use any other therapy for hemostasis.

I would agree with your recommendation to do wider resections in these cases. We tend to do lobectomies, and after this experience we continue to favor a wide resection. Wedge resections were done in only four patients, but most were in patients who had several foci of *Aspergillus* infection in the same lung. However, I would agree that a wider resection is probably preferred.