

Cardiac Fungal Infections: Review of Autopsy Findings in 60 Patients

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An autopsy study of 60 patients with fungal infections of the heart was undertaken. The patients ranged in age from 2 months to 79 years. Fifteen of the patients had undergone cardiac surgery; neoplasms were found in 13, renal failure in eight, bacterial infections in five, liver disease in five, gastrointestinal disorders in five, and immune disease in four; two had been intravenous drug abusers; other miscellaneous disorders were observed in three. The fungal infection was limited to the myocardium in 27 patients and to the endocardium in 17 patients. Myocardium and endocardium were involved in nine patients and pericardium and myocardium in five; two patients had pericarditis alone. The most frequent organism was *Candida* (62 per cent). *Aspergillus* (12 per cent) and *Phycomycetes* (12 per cent) were also found frequently. In 51 patients (85 per cent) other deep organs, usually lung, kidney, brain, or spleen were involved. Cultures for fungus had been positive in 26 patients prior to death, and postmortem cultures were positive in 29 patients. Patients who had undergone cardiac surgery had a higher incidence of endocarditis (93 per cent), with *Candida* (53 per cent) being the most frequent cause. Patients who had received antineoplastic drugs, antibiotics, or corticosteroids had a higher incidence of myocarditis (79 per cent), again most often due to *Candida* (60 per cent). *HUM PATHOL* 15:935-942, 1984.

Fungal infections involving the heart are rare; they are usually associated with disseminated fungemia and are usually fatal.¹ Most reports have indicated an association with either intravenous drug abuse or open heart surgery.²⁻³⁵ The overall incidence of fungemia appears to be increasing, probably as a consequence of the prolonged use of antibiotics, corticosteroids, and antineoplastic drugs. We have therefore assessed the clinical settings and pathologic findings in patients with fungal infections of the heart.

MATERIAL AND METHODS

Necropsy protocols and clinical records of 60 patients with fungal infections of the heart were reviewed for age, sex, clinical diagnosis, drug therapy, and surgical intervention. Of the 60 cases, 32 were filed at the Armed Forces Institute of Pathology

(AFIP), nine at the Nashville Veterans Administration (VA) Hospital, and 19 at two private hospitals. Fungi were identified by their characteristic morphologies in histologic sections from the heart with hematoxylin-eosin, methenamine silver, and periodic acid-Schiff stains.³⁶ Premortem blood cultures for fungus had been positive in 26 patients, and postmortem cultures were positive in 29 patients.

RESULTS

Clinical Observations

The average age at the time of death was 48.5 ± 17.7 years (range, 2 months to 79 years). There were more men (42 patients) than women, since most of the patients were from military or VA hospitals. The most common underlying factors were cardiac surgery (25 per cent) and malignant neoplasms (22 per cent) (table 1). Nine of the 13 patients with malignancies had hematopoietic-lymphoid neoplasms. Renal failure was the third most common underlying disorder, while the remainder of the patients had infections, liver disease, gastrointestinal disease, and immune disorders with equal frequency. Two patients had been intravenous drug abusers. Twelve patients had undergone noncardiac surgery: renal transplantation (14 patients), exploratory laparotomy (three patients), antrectomy (two patients), abdominal vessel grafting (two patients), and Levine shunt (one patient).

Cardiac surgery. Cardiac surgery had been performed for rheumatic valvular heart disease (seven patients), aortic stenosis (three patients), valvular endocarditis (four patients), and congenital subaortic stenosis (one patient) (table 2). The aortic valve had been replaced in seven patients, the mitral valve in four patients, and both valves in three patients. One patient had undergone mitral annuloplasty, and in one patient a ventriculoaortic conduit had been inserted.

Drug therapy. Forty-six patients in this study (77 per cent) had received one or more drugs prior to death: antibiotics (34 patients, 57 per cent), corticosteroids (14 patients, 23 per cent), and corticosteroids and broad-spectrum antibiotics simultaneously (six patients, 10 per cent). Six of 13 patients with neoplasms had received chemotherapy immediately prior to death, and one patient had received chemotherapy (methotrexate) for a nonneoplastic disorder. Antifungal agents had been used in five patients (8 per cent) prior to death.

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TABLE 1. Clinical Observations at Autopsy in 60 Patients with Fungal Involvement of the Heart

	No. of Patients	Per Cent	Mean Age (yr)	Male:Female Ratio
Cardiac surgery*	15	25.0	46.1	10:5
Neoplasia	13	21.7	44.9	11:2
Renal failure	8	13.3	42.9	7:1
Infection	5	8.3	45.1	4:1
Liver disease	5	8.3	47.2	2:3
Gastrointestinal disease	5	8.3	67.3	3:2
Immune disease	4	6.7	55.0	0:4
Intravenous drug abuse	2	3.3	35.0	2:0
Other	3	5.0	63.7	3:0
Total	60	100	48.5 ± 17.7	42:18

* One patient who had undergone aortic and mitral valve replacement had a history of intravenous drug abuse.

Pathologic Findings

Site of involvement. The myocardium was the single most frequent site of mycotic infections (41 patients, 68 per cent), either alone (27 patients) or in combination with endocarditis (9 patients) or pericarditis (five patients) (table 3). Twenty-six patients (43 per cent) had endocarditis; nine of these patients also had mycotic infections of the myocardium. Two patients had isolated pericardial involvement. Fungal myocarditis varied from microscopic abscesses to transmural involvement of the myocardium with central necrosis, with or without hemorrhagic borders. Some specimens showed infiltration by neutrophils, in others neutrophils and lymphocytes were intermixed, and still others had virtually no inflammatory cell infiltrates.

Organisms. Thirty-seven patients (62 per cent) were infected by *Candida* spp (table 4 and Fig. 1) and 11 patients (18 per cent) by *Aspergillus* spp (Fig. 2).

TABLE 2. Pathogenesis and Type of Surgery in 15 Autopsy Patients Who Had Undergone Cardiac Surgery

	No. of Patients
Pathogenesis	
Rheumatic heart disease	7
Calcific aortic stenosis	3
Endocarditis	4
Congenital heart disease	1
Type of cardiac surgery	
Aortic valve replacement	7
Mitral valve replacement	4
Aortic and mitral valve replacement	3
Other (placement of ventriculoaortic conduit)	1

TABLE 3. Site and Distribution of Fungal Involvement of the Heart

	No. of Patients	Per Cent
Myocardium	27	45.0
Endocardium	17	28.3
Myocardium + endocardium	9	15.0
Pericardium + myocardium	5	8.3
Pericardium	2	3.3

Phycomycetes infected seven patients (12 per cent) and *Cryptococcus* two patients (3 per cent) (Fig. 3). *Histoplasma capsulatum*, *Curvularia lunata*, and *Helminthosporium* each infected one patient; all three of these patients had undergone cardiac surgery. *Candida* usually involved the myocardium (62 per cent), but 28 patients with candidal infections also had endocarditis (46 per cent). In contrast, *Aspergillus* and *Phycomycetes* were present almost exclusively in the myocardium, or in the myocardium in combination with the endocardium, and only one patient had endocarditis alone. Of 11 patients who had altered immunity (due to immune disorders or renal transplants), five had aspergillosis. *Phycomycetes* was the most common cause of pericarditis (three patients).

Extracardiac infection. Distant foci of mycotic infection were present in 51 patients (85 per cent) (table 5) but in only 60 per cent of the patients who had undergone cardiac surgery. Distant sites included lung (55 per cent), kidney (43 per cent), brain (26 per cent), spleen (20 per cent), gastrointestinal tract (17 per cent), and liver (13 per cent). Other sites included thyroid gland, pancreas, skin, prostate, bladder, adrenal glands, bone marrow, and lymph nodes, and disseminated vascular invasion was observed as well. *Candida*, *Cryptococcus*, and *Phycomycetes* were most commonly disseminated. All patients with pericarditis had extracardiac infections, and more than 90 per cent of the patients with myocarditis alone had distant mycotic infections. One third of the patients had infections in only one distant site, while in 22 per cent four or more distant organs were involved (table 6).

Cardiac surgery. More than 90 per cent of the fungal infections in the hearts of patients who had undergone cardiac surgery involved the endocardium, either alone or in combination with the myocardium (table 7). The mitral and aortic valves were involved most frequently (table 8). The pulmonary valve was involved in only one patient, who had undergone mitral and aortic valve replacement for rheumatic valvular disease; aspergillosis involved all four valves in this patient. Of the patients who had undergone cardiac surgery and had endocarditis, nearly two thirds had candidiasis, and 20 per cent had aspergillosis. *Cryptococcus* was found in only one

TABLE 4. Type of Fungal Organisms Identified at the Various Sites in the Heart

Site	Candida	Aspergillus	Phycomycetes	Cryptococcus	Other	Total	Per Cent
Myocardium	18	6	3	0	0	27	45.0
Endocardium	14	1	0	0	2	17	28.3
Myocardium + endocardium	3	3	1	1	1	9	15.0
Pericardium + myocardium	2	1	2	0	0	5	8.3
Pericardium	0	0	1	1	0	2	3.3
Total	37 (62%)	11 (18%)	7 (11.7%)	2 (3.3%)	3 (5%)	60	

patient, and no patients who had undergone cardiac surgery had Phycomycetes infection.

Drug therapy. Candidiasis was most frequent in patients who had received antineoplastic, antibiotic, or corticosteroid therapy, accounting for 71 per cent (10 of 14), 65 per cent (22 of 34), and 36 per cent (5 of 14) of infections, respectively (tables 9 and 10). In 14 patients who had received corticosteroid therapy the frequencies of Candidal (36 per cent) and Aspergillus (29 per cent) infections were almost equal, while Phycomycetes was isolated in 22 per cent of these patients (table 9). Isolated myocardial involvement occurred in nearly half of the patients who had received antibiotics and in 64 per cent and 79 per cent of the patients who had received corticosteroids or had neoplasms, respectively. Endocardial involvement (with or without myocardial or pericardial involvement) occurred less frequently in all three groups.

Premortem and postmortem cultures. The organisms most frequently identified in premortem cultures were *Candida* spp and *Cryptococcus* spp (table 11). In one patient each *H. capsulatum*, *C. lunata*, and *Helminthosporium* were found in premortem cultures. *Candida* spp, *Aspergillus*, and *Cryptococcus neoformans* were the fungi most commonly isolated after death. The frequency of postmortem isolates (48 per cent) was only slightly greater than that of premortem isolates (43 per cent). Mycotic endocarditis was usually the underlying disease when a fungus was isolated prior to death (52 per cent versus 43 per cent for pericarditis and 34 per cent for myocarditis), but the three sites were almost equally involved when fungi were grown after death (table 12). These percentages are based on the total number of patients, since all autopsy protocols did not specify the cultures performed.

DISCUSSION

Although mycotic infections of the heart are uncommon, several authors have suggested that the incidence may be increasing.^{1,25,37,39} Of our 28 patients from private and VA hospitals, 50 per cent had died during the preceding two years (1981 and 1982), 71 per cent during the preceding five years, and only 29 per cent during the period from 1971 to 1977. Since the autopsy rate declined in these hospitals during

that time, the incidence of mycotic infection of the heart is apparently increasing. Patients who had undergone cardiac surgery constituted the largest group (25 per cent). Those with neoplasms were second; most of these patients had hematopoietic-lymphoid neoplasms. Fungal infection of the heart has complicated intravenous drug abuse,^{1,2,13,16,25,30} but only two patients in this study had been intravenous drug abusers. Both had endocarditis caused by *Candida* spp, as reported previously.¹ Seventy per cent of the patients in this series had received antibiotics or corticosteroids before death, and only five patients had been treated specifically with antifungal agents. Forty-five per cent of our patients had aspergillosis, an increasing hazard in hospitals,⁴¹ particularly in immunocompromised patients.^{42,43} Pericarditis caused



FIGURE 1. Candidal myocarditis. A 12-year-old girl had undergone cardiac surgery for congenital subvalvular aortic stenosis. Scattered microabscesses, containing polymorphonuclear leukocytes as well as budding yeasts and pseudohyphae of *Candida*, were found in the myocardium at autopsy. (Methenamine silver stain. $\times 630$.)

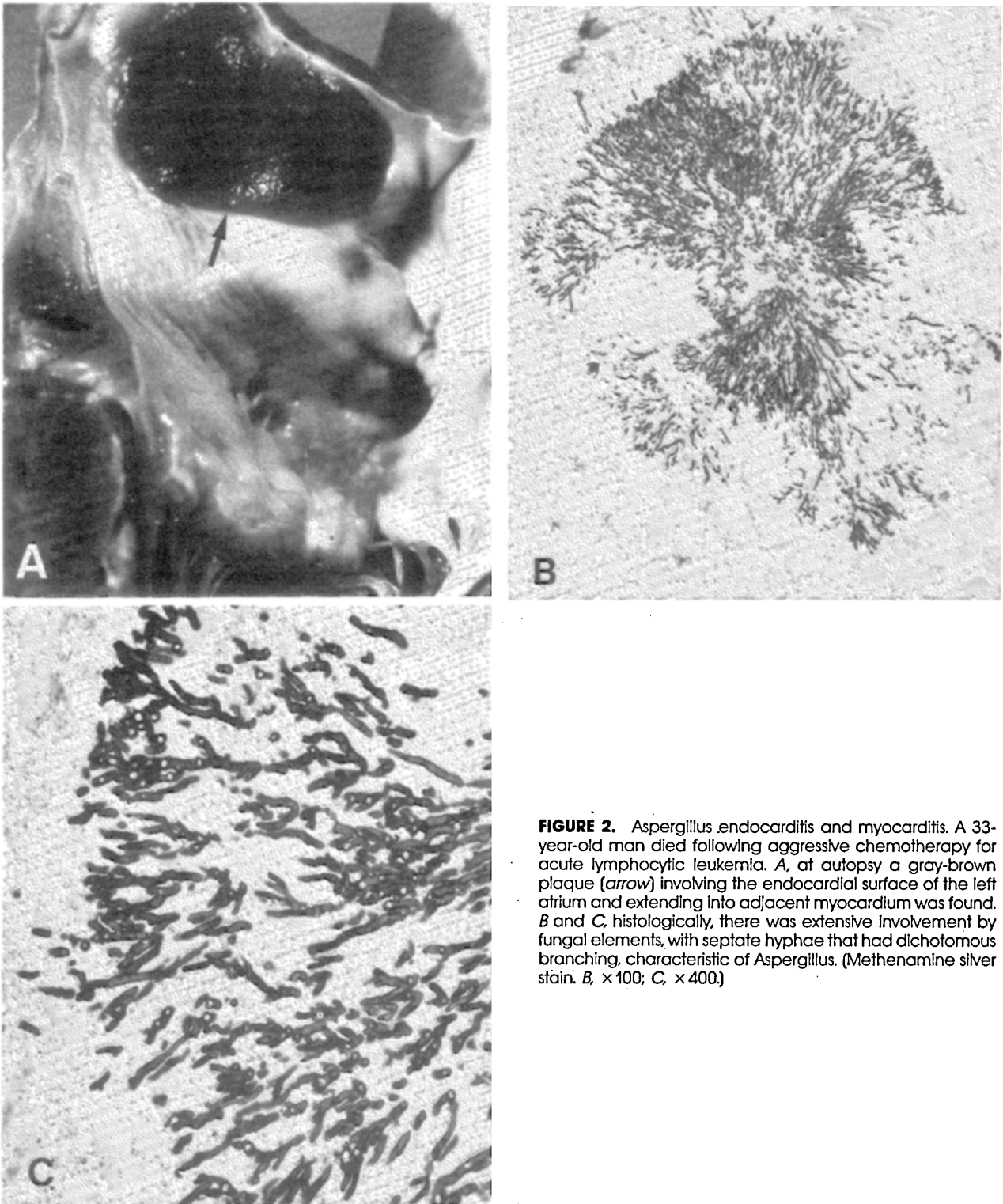


FIGURE 2. *Aspergillus* endocarditis and myocarditis. A 33-year-old man died following aggressive chemotherapy for acute lymphocytic leukemia. A, at autopsy a gray-brown plaque (arrow) involving the endocardial surface of the left atrium and extending into adjacent myocardium was found. B and C, histologically, there was extensive involvement by fungal elements, with septate hyphae that had dichotomous branching, characteristic of *Aspergillus*. (Methenamine silver stain. B, $\times 100$; C, $\times 400$.)

by *Aspergillus* spp, which has a high frequency in patients with neoplastic disorders,⁴⁴ was found in only one of our patients, who had received a renal transplant.

Cardiac Surgery

Fourteen of the 15 patients who had undergone cardiac surgery had endocarditis, an incidence similar

to that reported by others.^{39,45} Infection in prosthetic valves may result from paravalvular leaks or other conditions (cloth wear, turbulence, stasis, platelet aggregation) that favor platelet-fibrin thrombi, which act as a nidus for infection,³⁴ from introduction of organisms during the surgical procedure, or from systemic fungemia. The organism most frequently reported by others,^{34,47} and found in our series as well,

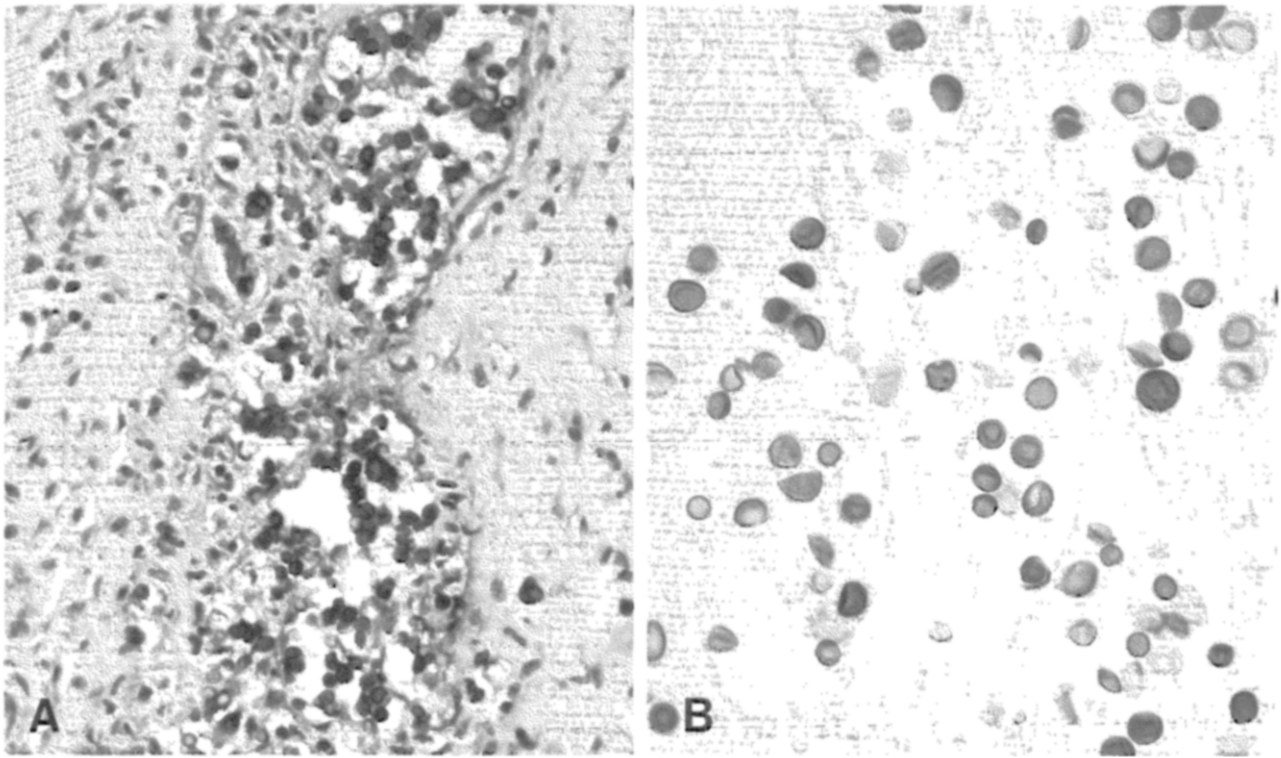


FIGURE 3. Cryptococcal pericarditis. A 43-year-old man with chronic renal failure who had received prolonged corticosteroid therapy died following progressive pneumonia. The pericardial cavity was obliterated by fibrous and fibrinous adhesions, and numerous mucicarmine-positive yeast forms, characteristic of *Cryptococcus*, were present. (Mucicarmine stain, A, $\times 250$; B, $\times 630$.)

was *Candida*. Walsh et al.,³⁹ however, found equal frequencies of *Aspergillus* and *Candida* in their patients who had undergone open heart surgery, and they postulated that environmental factors may have played a role. Rubinstein et al.¹ also observed that *Aspergillus* most frequently infected patients who had undergone cardiovascular surgery. In our series

aspergillosis was always associated with myocardial involvement; this finding may be due to the invasive nature of *Aspergillus* spp, causing elaboration of oxalic acid, which is toxic to tissue.⁴⁸ Premortem cultures were most often positive in patients with candidal infections and the endocardium was the usual site of infection.

TABLE 5. Fungal Organisms Found at Extracardiac Sites at Necropsy

Location	No. of Patients	Percentage of All Patients
Lungs	33	55.0
Kidneys	26	43.3
Brain	16	25.7
Spleen	12	20.0
Gastrointestinal tract	10	16.7
Liver	8	13.3
Thyroid	5	8.3
Blood vessel (embolus)	3	5.0
Skin	3	5.0
Pancreas	3	5.0
Bladder	2	3.3
Adrenals	2	3.3
Prostate	2	3.3
Lymph nodes	1	1.7
Ureter	1	1.7
Gallbladder	1	1.7
Peritoneum	1	1.7

TABLE 6. Number of Extracardiac Organs Involved

No. of Organs	No. of Patients	Percentage of All Patients
0	8	13.3
1	20	33.3
2	9	15.0
3	9	15.0
4 or more	13	21.5
Unknown	1	1.7

TABLE 7. Distribution of Organisms in Fungal Infections of the Heart in 15 Patients Who Had Undergone Cardiac Surgery

Site	<i>Candida</i>	<i>Aspergillus</i>	Other	Total
Myocardium	1	0	0	1 (6.7%)
Endocardium	4	1	2	7 (46.7%)
Myocardium + endocardium	3	2	2	7 (46.7%)
Total	8 (53.3%)	3 (20%)	4 (26.7%)	15 (100%)

TABLE 8. Distribution of Organisms in Fungal Infections of the Heart by Type of Cardiac Surgery Undergone

Organism	No. of Patients	Type of Cardiac Surgery			
		Aortic Valve Replacement	Mitral Valve Replacement	Aortic and Mitral Valve Replacement	Other
Candida	8 (53.3%)	2	2	2	2
Aspergillus	3 (20.0%)	2	0	1	0
Cryptococcus	1 (6.7%)	0	1	0	0
Other	3 (20.0%)	2	1	0	0

TABLE 9. Antineoplastic, Antibiotic, and Corticosteroid Therapy for Various Types of Fungal Infections

	Candida	Aspergillus	Phycomycetes	Cryptococcus	Other	Total
Neoplasia	10	0	4	0	0	14
Antibiotic therapy	22	6	4	0	2	34
Steroid therapy	5	4	4	1	0	14
Total	37	10	12	1	2	62

Drug Therapy

The majority of our 60 patients had received some type of drug therapy prior to death. Antibiotics had been used in 34 (57 per cent), corticosteroids in 14 (23 per cent), and chemotherapeutic agents in seven of the 14 patients with neoplasms. Candida was the organism found most frequently in patients who had received antibiotics (22 of 34), whereas of the 14 patients who had received corticosteroids the incidences of Candida (36 per cent) and Aspergillus (29 per cent) were almost equal, while Phycomycetes in-

fection occurred in 21 per cent of the patients. Patients who had received antibiotics, steroids, or chemotherapy had the greatest frequency of isolated myocardial involvement (36 patients), whereas ten had isolated fungal endocarditis and five had myocarditis combined with endocarditis. Pericardial involvement was uncommon in patients who had received antibiotics (four patients) or corticosteroids (four patients), and five of these eight patients had myocarditis combined with pericarditis.

Of our 60 patients, only five had received antifungal treatment, despite positive premortem blood

TABLE 10. Distribution of Fungal Infection of the Heart in Patients Who Had Received Drug Therapy

Site	Candida	Aspergillus	Phycomycetes	Other	Total
Total no. of patients receiving antibiotics					
Myocardium	12	3	1	0	16 (47.2%)
Endocardium	7	1	0	1	9 (26.5%)
Myocardium + endocardium	1	2	1	1	5 (14.7%)
Pericardium + myocardium	2	0	1	0	3 (8.8%)
Pericardium	0	0	0	1	1 (2.9%)
Total	22 (64.7%)	6 (17.6%)	3 (8.8%)	3 (8.8%)	34
Total no. of patients receiving corticosteroids					
Myocardium	4	3	2	0	9 (64.3%)
Endocardium	1	0	0	0	1 (7.1%)
Myocardium + endocardium	0	0	0	0	0
Pericardium + myocardium	0	1	1	0	2 (14.3%)
Pericardium	0	0	0	2	2 (14.3%)
Total	5 (35.7%)	4 (28.6%)	3 (21.4%)	2 (14.3%)	14
Total no. of patients who had neoplasms or received chemotherapy					
Myocardium	9		2		11 (78.6%)
Endocardium	0		0		0
Myocardium + endocardium	0		0		0
Pericardium + myocardium	1		2		3 (21.4%)
Total	0		0		0
	10 (71.4%)		4 (28.6%)		14

TABLE 11. Types of Organisms in Premortem and Postmortem Blood Cultures in Patients with Fungal Cardiac Involvement

Positive Cultures	Premortem		Postmortem	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Candida	19		16	
Aspergillus	2		9	
Phycomycetes	0		1	
Cryptococcus	2		1	
Others	3		2	
Total	26		29	

cultures in 26 patients. Rubinstein et al.¹ reported a 20 per cent survival rate in patients with fungal endocarditis, emphasizing that successful treatment depends on early diagnosis.

Site and Type of Fungus

In this series cardiac fungal infection was most frequent in the myocardium (68 per cent), with or without endocardial or pericardial involvement. The most common organism was *Candida* (62 per cent), which involved the myocardium in 23 patients (38 per cent). *Aspergillus* was second in frequency (18 per cent), and ten of 11 patients with *Aspergillus* infection had myocarditis. *Phycomycetes* caused myocarditis in six of seven patients but did not cause endocarditis. Walsh et al.³⁹ reported a high frequency of candidiasis and aspergillosis (47 per cent) in patients who had undergone abdominal surgery. Twelve of our 60 patients had undergone noncardiac surgery, and the majority of these patients had fungal myocarditis. Franklin et al.⁴⁹ reported a high incidence (62 per cent) of myocardial involvement in patients with systemic candidiasis. In patients with cardiac involvement arrhythmias, conduction disturbances, and changes in the QRS complex tended to develop. Edwards et al.⁵⁰ showed that candidal myocarditis was not diffuse but rather formed multiple small microabscesses with intervening normal tissue. In our series we found a high incidence of candidal involvement of the myocardium and endocardium. Myocardial involvement occurred more frequently in patients who had received drug therapy, while endocardial involvement occurred more often in patients who had undergone cardiac surgery.

Fungal Blood Cultures

Premortem blood cultures had been positive in 26 patients in this study. The actual percentage of positive premortem cultures may be higher, because we do not know how many patients had cultures. The frequencies of fungal involvement of the myocardium and endocardium were equal, while the pericardium was infrequently involved. *Candida* spp were most commonly isolated. *Candida*, therefore, should not be uniformly regarded as a contaminant in blood cultures. An important sign may be the persistence of *Candida* in blood cultures. Postmortem

TABLE 12. Site of Fungal Involvement in Patients with Positive Blood Cultures

	Premortem		Postmortem	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Myocardium	14	43.7	21	53.8
Endocardium	15	46.8	14	35.8
Pericardium	3	9.3	4	10.2

cultures were positive slightly more frequently than were premortem cultures. The organisms cultured most frequently in postmortem specimens were *Candida* and *Aspergillus*.

It is difficult to diagnose fungal infection of the heart clinically, but the frequency may be increasing among patients who are receiving antibiotics, corticosteroids, or antineoplastic therapy. Fungal cardiac involvement is usually accompanied by extracardiac involvement, and other sites (e.g., sputum, cerebrospinal fluid, urine, skin) are therefore accessible for culture. Precipitin tests and antibody titers to specific fungal organisms may also be useful in providing early diagnoses. Survival rates can be improved by the implementation of a high index of suspicion, early diagnosis, and aggressive antifungal treatment.

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