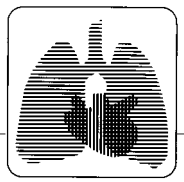

reviews

Fungal Endocarditis, 1995–2000

Lígia C. Pierrotti, MD; and Larry M. Baddour, MD

One hundred fifty-two cases of fungal endocarditis (FE) were identified in the English-language literature between January 1, 1995, and June 30, 2000. Although the median age of patients (44 years) was relatively young, injection drug use was identified as a risk factor in only 4.1% of cases. Other factors, including underlying cardiac abnormalities (47.3%), prosthetic valves (44.6%), and central venous catheters (30.4%), were more commonly identified as predisposing conditions and reflect the changing epidemiology of the syndrome. Unfortunately, mortality remains unacceptably high, particularly for patients with Aspergillus-related FE. Novel therapies are needed to improve patient outcomes. ***(CHEST 2002; 122:302–310)***

Key words: fungal; infective endocarditis; mold-related; yeast-related

Abbreviations: FE = fungal endocarditis; IE = infective endocarditis; NVE = native valve endocarditis; PVE = prosthetic valve endocarditis; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography

Fungal endocarditis (FE) is an uncommon occurrence. Previously published series[1,2] reported fungi as causes of infective endocarditis in 1.3 to 6% of cases. Advances in medical and surgical therapies, including reconstructive cardiovascular surgery, implantation of intracardiac prosthetic devices, prolonged use of IV catheters, exposure to multiple broad-spectrum antibiotics, and immunosuppression, have been implicated as causes of the perceived increase in the number of cases of fungemia and FE seen during the last 2 decades.[3,4]

FE has been characterized by excessive mortality (> 50%) and morbidity, regardless of treatment. A combined medical-surgical approach seems to offer an improved outcome. However, there are no clinical trials to support or refute this opinion, largely because of the rarity of the syndrome. We reviewed clinical features, echocardiographic findings, microbiologic data, treatment, and outcome of all FE cases reported in the English-language literature between January 1, 1995, and June 30, 2000, to provide a current characterization of the syndrome.

*From the Hospital das Clinicas (Dr. Pierrotti), University de São Paulo, São Paulo, Brazil; and the University of Tennessee Medical Center at Knoxville (Dr. Baddour), Knoxville, TN.
Manuscript received July 12, 2001; revision accepted September 10, 2001.
Correspondence to: Larry M. Baddour, MD, University of Tennessee, Medical Center at Knoxville, 1924 Alcoa Highway U-114; Knoxville, TN 37920-6999; lbaddour@mc.utmck.edu

Materials and Methods

Case Identification

To identify previously published cases of FE in the English-language literature, we performed a computerized search of the MEDLINE database for cases published between January 1, 1995, and June 30, 2000. The key words used in the search were *endocarditis*, *fungal*, *fungi*, *mycoses*, and *fungemia*. In addition, the reference list of each citation was examined to verify that all published cases were collected for this review.

Case Definition

The Duke criteria were used to define cases that were included in the analysis. According to the Duke criteria,[5] infective endocarditis (IE) can be defined as *definite IE*, clinical and echocardiographic criteria or pathologic features (demonstration of microscopic findings of a vegetation or fungi in valvular tissue or embolus obtained at autopsy or surgery); or *possible IE*, findings consistent with IE that fall short of a definitive definition and are not rejected.

Clinical Features

Demographic information, echocardiographic findings, microbiology data, treatment modalities, histopathologic findings, and clinical outcome, including complications and relapses, were recorded for all cases.

Prosthetic valve endocarditis (PVE) was defined as *early PVE*, when infection symptoms and signs developed within 60 days of valve replacement surgery, and *late PVE*, when infection symptoms and signs occurred > 60 days after surgery. One patient with an intra-atrial pacemaker infection and three patients with

Gore-Tex patch (W.L. Gore and Associates; Flagstaff, AZ) infections were categorized as PVE. *Complicated endocarditis* was defined as the presence of congestive heart failure, embolic phenomenon, valvular insufficiency, or prosthetic valve dehiscence. *Relapse* was defined as the return of symptoms and signs of endocarditis after an initial response to treatment that was caused by the same microorganism as was initially isolated. *Long-term suppressive therapy* was defined as treatment after the completion of acute treatment and administered for at least 6 months.

Statistical Analysis

Statistical analysis was performed with software (Epi Info; Centers for Disease Control and Prevention [in association with the World Health Organization]; Atlanta, GA). Categorical data were analyzed using a χ^2 or Fisher exact test, and the unpaired Student *t* test was used for continuous variables (age and follow-up). A p value < 0.05 was considered significant.

Results

To our knowledge, 152 cases of FE were reported between January 1, 1995, and June 30, 2000.[6–96] Because of the variability in the amount of clinical data mentioned in each case, the denominator used to analyze individual demographics features was usually < 152.

Gender and Age

Gender and age were cited in 119 cases; 80 patients (67.2%) were men, and 39 patients (32.8%) were women (age range, 1 week to 84 years; mean age, 40.3 years; median age, 44 years). When patients with PVE and native valve endocarditis (NVE) were compared, there was a difference in age; the mean and median ages were 49.7 years and 53 years for patients with PVE, and 34.1 years and 33 years for patients with NVE, respectively ($p < 0.001$, *t* test).

Predisposing Factors

Predisposing factors were listed in 148 cases out of the total of 152. The most common predisposing conditions (Table 1) included underlying anatomical cardiac conditions in 70 patients (47.3%), prosthetic cardiac devices in 66 patients (44.6%), central venous catheters in 45 patients (30.4%), and previous antibiotic use in 30 patients (20.3%). A variety of other predisposing conditions were less frequently seen. In four cases, there was no mention of predisposing factors. Five patients (3.4%) had no predisposing factor identified.

The underlying cardiac structural abnormality was specified in 24 of 70 cases (34.3%). Fourteen pa-

Table 1—*Predisposing Conditions in FE

Predisposing Factors	Yeast (n = 101)	Mold (n = 39)	Microorganism Not Mentioned (n = 10)	Yeast Plus Mold (n = 1)	Total (n = 152)†
Underlying cardiac abnormality	50 (49.5)	16 (41.0)	4	0	70 (47.3)
Prosthetic valve	46 (45.5)	15 (38.5)	5	0	66 (44.6)
Central venous catheter	40 (39.6)	4 (10.3)	0	1	45 (30.4)
Broad-spectrum antibiotics	24 (23.8)	4	1	0	30 (20.3)
Malignancy	6	7	0	0	13 (8.8)
Parenteral nutrition	9	1	0	0	11 (0.4)
Abdominal surgery	10	0	1	0	11 (0.4)
Solid-organ transplant	2	7	0	1	10 (0.8)
Pacemaker	5	2	0	0	7 (0.7)
IV drug user	6	0	0	0	6 (0.1)
Diabetes mellitus	4	1	0	0	5 (0.4)
Previous IE	2	1	1	0	4 (2.7)
HIV positive	4	0	0	0	4 (2.7)
Corticosteroid use	0	1	2	0	3 (2.0)
Alcohol abuse	2	1	0	0	3 (2.0)
Bone marrow transplant	0	3	0	0	3 (2.0)
Hemodialysis	0	0	1	0	1 (0.7)
Necrotizing fasciitis	0	0	1	0	1 (0.7)
Brain injury	0	1	0	0	1 (0.7)
Not mentioned	4	0	0	0	4

*Data are presented as No. (%) or No. Note that four cases did not address the predisposing factors; therefore, 148 cases were used for calculation of percentages, rather than the total of 152 cases.

†One culture-negative case with broad-spectrum antibiotics, parenteral nutrition, and underlying cardiac abnormality as predisposing conditions was included.

tients had congenital valvulopathy, 6 patients had rheumatic valvulopathy, and 1 patient had congenital and rheumatic valvulopathy. Prior IE was described in three patients, and, in one of the patients, it was associated with congenital and rheumatic valvulopathy.

Clinical and Echocardiographic Findings

Previously unrecognized or changing heart murmurs were described in 24 of 31 patients in whom there was mention of auscultatory findings at hospital admission. Echocardiograms were performed in 102 patients and not performed in 5 patients. There was no mention of echocardiography in 45 patients. Echocardiography demonstrated vegetations in 83 of 102 patients (81.4%); vegetations were described as large in 42 patients (50.6%) and mobile in 16 patients (19.3%). Myocardial abscess (5.9%) was infrequently seen on echocardiographic examination. At least 44 of 102 patients underwent transesophageal echocardiography (TEE). The type of echocardiographic procedure was not described in 32 cases. Three patients had normal transthoracic echocardiographic results but did not undergo TEE. Both transthoracic echocardiography (TTE) and TEE results were described in 16 patients, and in only one patient was a vegetation seen on TEE that was not visualized on transthoracic study. In that patient, the vegetation was attached to the mitral valve, a well-known anatomic problem area for TTE sensitivity.

TTE identified 88.9% of vegetations in patients with NVE and 76.5% in of vegetations in patients with PVE. TEE identified 92.0% of vegetations in patients with NVE and 61.1% of vegetations in patients with PVE. Large vegetations were noted in 35 cases of NVE compared with 7 cases of PVE ($p = 0.03$, Mantel-Haenszel test).

Table 2—*Microorganisms Isolated From FE Patients

Variables	Fungus	Data
Yeast (n = 101)	Candida species	95/101 (94.1)
	C albicans	46
	C parapsilosis	17†
	Candida tropicalis	8†
	Candida glabrata	2
	Candida krusei	3
	Candida lusitaniae	1
	Candida chaetamion	1
	Candida zeylanoides	1
	Not specified	18
	Trichosporon inkin	1
	Histoplasma capsulatum	2
	Saccharomyces cervisiae	1
	Cryptococcus neoformans	1
	Hansenula anomala	1
Mold (n = 39)	Aspergillus species	28/39 (71.8)
	A fumigatus	15
	Aspergillus nidulans	1
	Aspergillus flavus	2
	Aspergillus terreus	5
	Aspergillus niger	2
	Not specified	3
	Scedosporium apiospermum	1
	Scedosporium prolificans	1
	Phaeocremonium parasiticum	1
	Acremonium species	1
	Fusarium dimerum	1
	Phialemonium curvatum	1
	Microascus cinereus	1
	Bipolaris spicifera	1
	Scopulariopsis brevicaulis	3
Yeast plus mold	*F solani* and *C parapsilosis*	1
Not mentioned		10
Negative culture		1

*Data are presented as No. (%) or No. unless otherwise indicated.
†In association with *C albicans* (one case each).

Microbiology

Table 2 summarizes the types of fungi and the frequency with which they were identified. Yeasts caused 101 infections, and Candida species were recovered in 95 patients (94.1%); in 2 of the 95 cases, polymicrobial IE was caused by two different Candida species. In one other case, *Candida parapsilosis* was isolated with a mold, *Fusarium solani. Candida albicans* was the pathogen in 46 cases (45.5%).

Thirty-nine patients had mold infections, and in 28 patients (71.8%), Aspergillus species were recovered. *Aspergillus fumigatus* was most commonly identified and was recovered in 15 patients. The infecting fungus was not described in 10 patients.

The distribution of yeasts and molds causing prosthetic valve vs native valve infections was not statistically different (data not shown). Similar findings were seen for PVE differentiated into early and late categories.

Almost one half of identified pathogens (46.5%) were recovered in blood cultures; 25.2% were recovered from an intracardiac site, and 28.3% were recovered from both blood cultures and intracardiac sites. The site of microorganism isolation was not mentioned in 24 cases. Positive blood culture results were more frequent in yeast-related IE cases than in mold-related cases (81.2% vs 30.8%; $p < 0.001$, Mantel-Haenszel test).

Diagnosis

Clinical and microbiologic features of each case were analyzed according to the Duke criteria. IE

cases were defined as either definite (n = 120) or possible (n = 23) in 143 patients. The IE category was not specified in the remaining nine cases,[12,88] although the Duke criteria were used to define these cases, and they were not rejected. Among all cases classified as definite, 89.2% were based on pathologic criteria.

The interval between valve replacement and onset of infection was available in only 54 cases and ranged from 1 day to 24 years. Twenty-six cases (45.6%) and 31 cases (54.4%) were classified as early PVE and late PVE, respectively; 9 cases could not be classified because of lack of information. There was no statistical difference in the age distributions for the two groups ($p = 0.35$, t test). Twenty-two patients had mechanical prostheses, 23 patients had biological prostheses, and in 17 patients did not have a specified prosthesis. One patient had an intra-atrial pacemaker, and three patients had cardiac patches, two of which were Gore-Tex.

Complications

Complications were reported in 100 patients (Table 3). Embolic phenomena were most commonly seen and described in 61 patients. Congestive heart failure and sepsis, the next most common complications, were seen in 16 patients each. Complications were not described in 52 patients. Seventy-four patients (48.7%) had complicated IE, with a similar distribution among yeast endocarditis and mold endocarditis cases and among NVE and PVE patients.

Therapy

Medical therapy was described in 118 cases; 111 patients (94.0%) received antifungal therapy, and no medical therapy was administered in 7 patients. Seventy-five patients (49.3%) received acute therapy, and 36 patients (23.7%) received chronic suppressive therapy after completion of acute treatment. Amphotericin B-containing compounds were used in 102 patients (91.9%) as acute therapy. Ninety-three patients were treated with conventional amphotericin B (with 5-fluocytosine or azole compounds in 26 cases); 2 patients received liposomal amphotericin B alone, and 7 patients received both conventional and lipid-associated amphotericin B. Four patients were treated with fluconazole alone, one patient received 5-fluocytosine alone, and there was no information regarding treatment for four other patients.

Long-term (≥ 6 months) suppressive therapy was administered to 13 patients after acute treatment. Eleven patients and 2 patients had FE caused by yeasts and molds, respectively. Eight patients with yeast infections were administered fluconazole; the remaining three patients received itraconazole, ketoconazole, or amphotericin B. Itraconazole was administered to the two patients with FE caused by molds (*Aspergillus niger* in both cases). In five other patients, suppressive therapy was administered but no specific duration of therapy was mentioned. Instead, the duration of therapy was labeled as lifelong, prolonged, or long-term.

Surgical intervention was common. Seventy-eight of 119 patients (65.5%) had surgery. No data regarding surgery were available for 33 patients. Intracardiac surgery was the most common type of surgical intervention and was performed in 63 patients. Embolectomy was performed in four patients, and both intracardiac surgery and embolectomy were performed in seven cases.

Among PVE patients, 79.6% patients underwent surgery, whereas only 53.8% of NVE patients underwent surgery ($p = 0.03$, Mantel-Haenszel test). In addition, surgery was performed more frequently among late PVE than early PVE patients (89.6% vs

Table 3—*Complications of FE

Complications	Yeast (n = 61)	Mold (n = 29)	NM (n = 8)	Yeast Plus Mold (n = 1)	Total (n = 100)†
Emboli	39 (63.9)	20 (69.0)	1	0	61
Congestive heart failure	11 (18.0)	3 (10.3)	2	0	16
Sepsis	12 (18.0)	3 (10.3)	1	1	16
Valvular regurgitation	7	2	0	0	9
Organ failure	4	4	1	0	9
Miscellaneous‡	4	3	5	0	12
Dehiscence	3	2	0	0	5
Valvular stenosis	1	0	0	0	1

*Mentioned in 100 cases. Data are presented as No. (%) or No. NM = not mentioned.

†Includes one culture-negative case with emboli.

‡Includes pneumonia (n = 1), disseminated intravascular coagulation and pulmonary edema (n = 1), hemolytic anemia (n = 1), thrombus and pneumonia (n = 1), paravalvular abscess (n = 1), perianular complications not specified (n = 5), bradyarrhythmia (n = 1), and metabolic and hematological abnormalities (n = 1).

65.2%; p = 0.003, Mantel-Haenszel test). Both medical and surgical therapy were used in 83.3% of complicated FE cases and in 54.5% of uncomplicated FE cases (p = 0.002, Mantel-Haenszel test).

A limited number of cases included a gross description of vegetations seen intraoperatively or at postmortem examination. In 17 of 28 cases (60.7%) in which comments were included, the vegetations were described as large. Fungi were seen on histopathologic examination of resected cardiac and/or embolic tissue in 46 of 49 cases (93.9%) that included this information.

Outcome

The mortality rate among 122 patients with IE was 56.6%; outcome data were not described for 30 patients. The ages of patients who survived did not differ statistically from those of patients who died (p = 0.50, *t* test).

The mortality rate among patients with mold IE was higher than that of patients with yeast IE (82.1% vs 40.3%; p < 0.001, Mantel-Haenszel test). The mortality rates among PVE and NVE cases, stratified by age and microorganism (yeast or mold), were not different (50.0% vs 66.1%; p = 0.23, Mantel-Haenszel test).

Fifty percent of patients who received antifungal therapy died. All seven patients who did not receive antifungal therapy died (p = 0.01, Mantel-Haenszel test).

There was a trend toward higher survival for patients with yeast-related endocarditis who had undergone valve surgery (68.3% of patients who underwent surgery survived, compared with 52.2% of patients who did not have surgery; p = 0.20, Mantel-Haenszel test). The mortality rates for patients who received medical therapy and for patients with combined medical-surgical intervention were both approximately 50%. The mortality rates did not differ for complicated and uncomplicated FE cases, regardless of whether the patients underwent medical or combined medical and surgical therapy.

Follow-Up

Follow-up was mentioned in 36 of 53 patients who survived (range, 42 days to 17 years). Follow-up was longer for PVE cases (mean and median of 3.6 years and 1.5 years, respectively) than for NVE cases (mean and median of 1.2 years and 1 years, respectively) [p = 0.03, *t* test]. The period of follow-up did not differ for yeast IE cases vs mold IE cases, for patients who did or did not undergo surgery, or for patients who did or did not receive lifelong suppressive therapy.

Relapse occurred in five patients (two yeast-related and three mold-related) after a variable period ranging from 1 week to 7 months after initial response and completion of acute therapy. In one patient, two relapses caused by *C albicans* occurred in NVE after acute medical therapy with fluconazole was discontinued. After the second relapse and acute treatment, 17 months of suppressive therapy with fluconazole was administered; no additional relapse was noted during a 34-month follow-up. In the other four patients, one relapse was diagnosed. One patient received suppressive therapy, underwent no surgery, and relapse occurred just after suppressive therapy was stopped. In the other three patients, no suppressive therapy was administered, and relapse occurred after valve replacement.

Discussion

FE is a rare illness that deserves attention. Because of a rapidly evolving epidemiology that is largely caused by advances in medical and surgical techniques, fungal infection syndromes, including FE, are relatively new complications that can threaten the success of novel therapies. In our opinion, FE should be classified as an emerging infectious disease.

FE involves a younger population. The mean age of adult patients in one review[97] was 44.3 years. In the current review, which included both children and adults, the mean and median ages were 40.3 years and 44 years, respectively.

In past years, injection drug use was considered a prominent risk factor for the development of FE.[98] In both the review by Ellis and colleagues[97] and in the current review, injection drug use was described in a minority (13% and 4.1%, respectively) of patients. In contrast, therapeutic interventions, including intravascular catheter use, valve surgery, immunosuppressive treatment, and broad-spectrum antibiotic use, were much more prevalent as risk factors for the subsequent development of FE.

Several factors positively and negatively impact our ability to diagnose FE. These factors are important because, in years past, the diagnosis was not made until postmortem examination for a sizable portion of patients. The rarity of the syndrome coupled with negative blood culture results in most mold cases and some yeast cases compromised our ability to secure an early diagnosis. However, the large vegetations that characterize this illness seem to increase the sensitivity of TTE and should prompt a consideration of FE in the setting of (blood) culture-negative endocarditis.

Establishing a definitive diagnosis of infective endocarditis is frequently a problem in which blood

culture results are negative and histopathologic evidence of endocardial infection is not available. This could impact the findings of a literature review if the cases are not valid. Clinical criteria have been established to satisfy a case definition of infective endocarditis in a setting in which histopathologic evidence is not available, and these criteria have enjoyed widespread application. In the current literature review, Duke clinical criteria were infrequently needed to secure a diagnosis of FE because histopathologic evidence was obtained in 34 of 37 mold cases (91.9%) and in 67 of 77 yeast cases (87.0%). The routine availability of cardiac and/or embolic tissue for histopathologic examination and culture was, in part, due to the generally accepted doctrine that patients with proven or suspected FE undergo valve replacement in combination with medical therapy for attempted cure.

Despite a recognized dismal outcome in patients with mold endocarditis and a less-than-acceptable outcome in patients with yeast endocarditis, the choice of medical therapy has not changed in decades. Amphotericin B, as exemplified in the current literature review, remains the mainstay of medical therapy. Histopathologic and microbiologic findings of resected intracardiac tissue indicate that amphotericin B is slow to clear fungi. In one extreme example,[99] Candida species could be cultured from resected valvular tissue after 190 days of amphotericin B. Mortality caused by Aspergillus endocarditis in both recent literature reviews is $> 90\%$, and surgical intervention with valve replacement did not improve mortality rates as compared with rates for patients who received antifungal therapy alone.

It is less clear whether the tenet that FE is a stand-alone indication for valve surgery in cases of Candida-related endocarditis is correct. Both literature surveys indicate that there may be a survival benefit to valve replacement, but they should not be overinterpreted because the data were collected retrospectively from a series of case reports. Treatment bias is inevitable in this setting because patients who are more ill are often deemed nonsurgical candidates and suffer increased mortality. Data from another investigation[100] suggested that surgical intervention did not improve outcome over that of medical therapy alone in patients with uncomplicated Candida prosthetic valve endocarditis. There are, however, potential weaknesses in the interpretation of these data. First, the number of patients in both treatment groups was small ($n = 10$ and $n = 3$, respectively). Second, follow-up data were not available in 5 of the 13 cases; in 3 other cases, the duration of follow-up was ≤ 1 year. Thus, late relapses of FE may have been missed. Third, at least four patients received long-term antifungal suppressive therapy that could have prevented FE relapse and death. Considering all of the clinical information to date, valve replacement should probably be offered with aggressive medical therapy until prospectively collected data are generated that direct clinicians to do otherwise.

Relapsing FE is a complication seen in as many as 30 to 40% of patients who have FE develop and who survive to complete short-term therapy.[6,9] Relapsing FE was less often seen (3.3%) in the current literature survey for at least two reasons. First, follow-up information was limited. Only 36 of the 53 patients who survived had information regarding follow-up, and for those patients listed, only 12 patients had follow-up of > 2 years. It is well recognized that relapses can occur late in FE cases and that short-term (< 2 years) follow-up will miss episodes of late relapse. Second, the newly adopted long-term suppressive therapy[100–102] was administered to 13 patients and likely prevented relapsing FE that would have occurred without the use of suppressive treatment.

Long-term suppressive therapy for FE is being used in two clinical scenarios. In one, the patient is deemed a nonsurgical candidate, usually for medical or surgically technical reasons, and suppressive therapy is administered after the patient's response to acute antifungal treatment. Because the patient is not considered curable without valve replacement, long-term (life-long) suppressive therapy is given. In the second scenario, long-term suppressive therapy is administered to patients who undergo valve replacement and acute treatment. Because the relapse rate is high and cure with suppressive treatment may not be achievable,[101] some cardiothoracic surgeons advocate long-term (life-long) suppressive antifungal treatment. Thus, potentially all patients who survive long enough to complete acute treatment, which can include valve replacement, may be considered candidates for chronic suppressive antifungal therapy.

FE has gained more attention in the recent literature. With our continued expansion of medical and surgical techniques, it is expected that an increasing number of these cases will occur. Advances in therapy are also needed to diminish the high mortality rate that currently characterizes FE.

ACKNOWLEDGMENT: The authors thank Mandana Mobasseri for data collection and Sandra R. Tallant for administrative assistance and article preparation.

References

1 Bayer AS, Scheld M. Endocarditis and intravascular infections. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Philadelphia, PA: Churchill Livingstone, 2000; 857–902

2 Karchmer AW. Infections on prosthetic valves and intravascular devices. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Philadelphia, PA: Churchill Livingstone, 2000; 903–917
3 Fernandez-Guerrero M, Verdejo C, Azofra J, et al. Hospital-acquired infective endocarditis not associated with cardiac surgery: an emerging problem. Clin Infect Dis 1995; 20: 16–23
4 Rubinstein E, Lang R. Fungal endocarditis. Eur Heart J 1995; 16:84–89
5 Durack DT, Lukes AS, Bright DK, et al. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994; 96:200–209
6 Baddour LM. Long-term suppressive therapy for *Candida parapsilosis*-induced prosthetic valve endocarditis. Mayo Clin Proc 1995; 70:773–735
7 Gentry LO, Nasser MM, Kielhofner M. Scopulariopsis endocarditis associated with duran ring valvuloplasty. Tex Heart Inst J 1995; 22:81–85
8 Grigg A, Clouston D. Disseminated fungal infection and early onset microangiopathy after allogeneic bone marrow transplantation. Bone Marrow Transplant 1995; 15:795–797
9 Fernández-Guerrero ML, Verdejo C, Azofra J, et al. Hospital-acquired infectious endocarditis not associated with cardiac surgery: an emerging problem. Clin Infect Dis 1995; 20:16–23
10 Hosking MC, MacDonald NE, Cornel G. Liposomal amphotericin B for postoperative *Aspergillus fumigatus* endocarditis. Ann Thorac Surg 1995; 59:1015–1017
11 Migrino RQ, Hall GS, Longworth DL. Deep tissue infections caused by *Scopulariopsis brevicaulis*: report of a case of prosthetic valve endocarditis and review. Clin Infect Dis 1995; 21:672–674
12 Del Pont JM, De Cicco LT, Vartalitis C, et al. Infective endocarditis in children: clinical analyses and evaluation of two diagnostic criteria. Pediatr Infect Dis J 1995; 14:1079–1086
13 Muehrcke DD, Lytle BW, Cosgrove DM. Surgical and long-term antifungal therapy for fungal prosthetic valve endocarditis. Ann Thorac Surg 1995; 60:538–543
14 Schwint OA, Venara M. Tricuspid valve endocarditis. Pediatr Pathol Lab Med 1995; 15:535–537
15 Tolan M, Clarke S, Schofield P, et al. Homograft replacement of fungal endocarditic pulmonary valve. Eur J Cardiothorac Surg 1995; 9:528–530
16 Wells CJ, Leech GJ, Lever AM, et al. Treatment of native valve Candida endocarditis with fluconazole. J Infect 1995; 31:233–235
17 Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis 1995; 20:1531–1534
18 Chaumentin G, Boibieux A, Piens MA, et al. *Trichosporon inkin* endocarditis: short-term evolution and clinical report. Clin Infect Dis 1996; 23:396–397
19 Casson DH, Riordan FA, Ladusens EJ. Aspergillus endocarditis in chronic granulomatous disease. Acta Paediatr 1996; 85:758–759
20 Girmenia C, Martino P, De Bernardis F, et al. Rising incidence of *Candida parapsilosis* fungemia in patients with hematologic malignancies: clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. Clin Infect Dis 1996; 23:506–514
21 Gilbert H, Peters ED, Lang SJ, et al. Successful treatment of fungal prosthetic valve endocarditis and review. Clin Infect Dis 1996; 22:348–354
22 Hogevik H, Alesting K. Fungal endocarditis: a report on seven cases and a brief review. Infection 1996; 24:17–21
23 Kothari SS, Sharma M, Saxena A, et al. Right atrial mass due to fungal endocarditis in an infant. Indian Pediatr 1996; 33:593–595
24 Mayayo E, Moralejo J, Camps J, et al. Fungal endocarditis in premature infants: case report and review. Clin Infect Dis 1996; 22:366–368
25 Mansour AJ, Safi J, Markus MR Jr, et al. Late failure of surgical treatment for bioprosthetic valve endocarditis due to *Candida tropsilosis*. Clin Infect Dis 1996; 22:380–381
26 Mathew J, Gaisor R, Thannoli N. Images in cardiovascular medicine: fungal mass on the tricuspid valve [letter]. Circulation 1996; 94:2040
27 Nguyen MH, Nguyen ML, Yu VL, et al. Candida prosthetic valve endocarditis: prospective study of six cases and review of the literature. Clin Infect Dis 1996; 22:262–267
28 Schønheyder HC, Jensen HE, Gams W, et al. Late bioprosthetic valve endocarditis caused by *Phialemonium aff. curvatum* and *Streptococcus sanguis*: a case report. J Med Vet Mycol 1996; 34:209–214
29 Sergi C, Weitz J, Hofmann WJ, et al. Aspergillus endocarditis, myocarditis and pericarditis complicating necrotizing fasciitis: case report and subject review. Virchows Arch 1996; 429: 177–180
30 Whitby S, Madu EC, Bronze MS. Case report: *Candida zeylanoides* infective endocarditis complicating infection with the human immunodeficiency virus. Am J Med Sci 1996; 12:138–139
31 Adli NM, Condos WR Jr, Tami LF, et al. Aspergillus mitral endocarditis [letter]. Circulation 1997; 96:4431
32 Banerjee U, Gupta K, Venugopal P. A case of prosthetic valve endocarditis caused by *Cryptococcus neoformans var. neoformans*. J Med Vet Mycol 1997; 35:139–141
33 Berenguer J, Rodríguez-Tudela JL, Richard C, et al. Deep infections caused by *Scedosporium prolificans*: a report on 16 cases in Spain and a review of the literature; *Scedosporium prolificans* Spanish Study Group. Medicine 1997; 76:256–265
34 Centers for Disease Control and Prevention. *Candida albicans* endocarditis with a contaminated aortic valve allograft: California, 1996. JAMA 1997; 277:1271–1272
35 De Leval L, Deleixhe M, Kulbertus H. Tricuspid valve endocarditis [letter]. Heart 1997; 77:501
36 Diekema DJ, Messer SA, Hollis RJ, et al. An outbreak of *Candida parapsilosis* prosthetic valve endocarditis. Diagn Microbiol Infect Dis 1997; 29:147–153
37 Heath CH, Lendrum JL, Wetherall BL, et al. *Phaeoacremonium parasiticum* infective endocarditis following liver transplantation. Clin Infect Dis 1997; 25:1251–1252
38 Hartyánszky IL, Pintér M, Kádár K, et al. Candida endocarditis in an infant. Pediatr Cardiol 1997; 18:440–442
39 Hollingsed MJ, Morales JM, Roughneen PT, et al. Surgical management of catheter tip thrombus: surgical therapy for right atrial thrombus and fungal endocarditis (*Candida tropicalis*) complicating pediatric sickle-cell disease. Perfusion 1997; 12:197–201
40 Heitmann L, Cometta A, Hurni M, et al. Right-sided pacemaker-related endocarditis due to Acremonium species. Clin Infect Dis 1997; 25:158–160
41 Joly V, Belmatoug N, Leperre A, et al. Pacemaker endocarditis due to *Candida albicans*: case report and review. Clin Infect Dis 1997; 25:1359–1362
42 Kanda Y, Akiyama H, Onozawa Y, et al. Aspergillus endocarditis in a leukemia patient diagnosed by a PCR assay. Kansenshogaku Zasshi 1997; 71:269–272
43 Khan ZU, Sanyal SC, Mokaddas E, et al. Endocarditis due to *Aspergillus flavus.* Mycoses 1997; 40:213–217

44 Klingspor L, Stintzing G, Tollemar J. Deep Candida infection in children with leukemia: clinical presentation, diagnosis and outcome. Acta Paediatr 1997; 86:30–36
45 Lejko-Zupanc T, Kozelj M. A case of recurrent *Candida parapsilosis* prosthetic valve endocarditis: cure by medical treatment alone. J Infect 1997; 35:81–82
46 Nandakumar R, Raju G. Isolated tricuspid valve endocarditis in nonaddicted patients: a diagnostic challenge. Am J Med Sci 1997; 314:207–212
47 Ohmori T, Iwakawa K, Matsumoto Y, et al. A fatal case of fungal endocarditis of the tricuspid valve associated with long-term venous catheterization and treatment with antibiotics in a patient with a history of alcohol abuse. Mycopathologia 1997; 139:123–128
48 Pauzner R, Goldschmied-Reouven A, Hay I, et al. Phaeohyphomycosis following cardiac surgery: case report and review of serious infection due to Bipolaris and Exserohilum species. Clin Infect Dis 1997; 25:921–923
49 Shmuely H, Kremer I, Sagie A, et al. *Candida tropicalis* multifocal endophthalmitis as the only initial manifestation of pacemaker endocarditis. Am J Ophthalmol 1997; 123: 559–560
50 Sons H, Dausch W, Kuh JH. Tricuspid valve repair in right-sided endocarditis. J Heart Valve Dis 1997; 6:636–641
51 Yates AB, Mohrotra D, Moffitt JE, et al. Candida endocarditis in a child with hyperimmunoglobulinemia E syndrome. J Allergy Clin Immunol 1997; 99:770–722
52 Alam M, Higgins R, Alam Z, et al. Aspergillus fungal mass detected by transesophageal echocardiography. J Am Soc Echocardiogr 1998; 11:83–85
53 Chim CS, Ho PL, Yuen ST, et al. Fungal endocarditis in bone marrow transplantation: case report and review of literature. J Infect 1998; 37:287–291
54 Doshi J, Tharacan JM, Manohar SR. Peripartum fungal endocarditis of native mitral valve. Indian Heart J 1998; 50:199–200
55 Gerritsen JG, Dissel JT, Verwey HF. *Candida tropicalis* endocarditis. Circulation 1998; 98:90–91
56 Guinvarc'h A, Guilbert A, Marmorat-Khuong A, et al. Disseminated *Fusarium solani* infection with endocarditis in a lung transplant recipient. Mycoses 1998; 41:59–61
57 Inoue Y, Yozu R, Ueda T, et al. A case report of *Candida parapsilosis* endocarditis. J Heart Valve Dis 1998; 7:240–242
58 Katsoulis J, Aggarwal A, Darling AH. Very rapid echocardiographic appearance of Aspergillus endocarditis. Aust N Z J Med 1998; 28:60–61
59 Kennedy HF, Simpson EM, Wilson N, et al. *Aspergillus flavus* endocarditis in a child with neuroblastoma. J Infect 1998; 36:126–127
60 Kuehnert MJ, Clark E, Lockhart SR, et al. *Candida albicans* endocarditis associated with a contaminated aortic valve allograft: implication for regulation of allograft processing. Clin Infect Dis 1998; 27:688–691
61 Navabi MA, Ajami H, Amirghofran A, et al. Aspergillus endocarditis: rare but serious Aspergillus ball obstructing the pulmonary artery. Eur J Cardiothorac Surg 1998; 14: 530–532
62 Paterson D, Dominguez EA, Chang FY, et al. Infective endocarditis in solid organ transplant recipients. Clin Infect Dis 1998; 26:689–694
63 Remsey ES, Lytle BW. Repair of fungal aortic prosthetic valve endocarditis associated with periannular abscess. J Heart Valve Dis 1998; 7:235–239
64 Román JA, Vilacosta I, Sarriá C, et al. Clinical course, microbiologic profile, and diagnosis of periannular complications in prosthetic valve endocarditis. Am J Cardiol 1998; 83:1075–1079
65 Scapellato PG, Desse J, Negroni R. Acute disseminated histoplasmosis and endocarditis. Rev Inst Med Trop Sao Paulo 1998; 40:19–22
66 Schett G, Casati B, Willinger B, et al. Endocarditis and aortal embolization caused by *Aspergillus terreus* in a patient with acute lymphoblastic leukemia in remission: diagnosis by peripheral-blood culture. J Clin Microbiol 1998; 36:3347–3351
67 Takeda S, Wakabayashi K, Yamazaki K, et al. Intracranial fungal aneurysm caused by Candida endocarditis. Clin Neuropathol 1998; 17:199–203
68 Verghese S, Mullasari A, Padmaja P, et al. Fungal endocarditis following cardiac surgery. Indian Heart J 1998; 50:418–422
69 Vivas C. Endocarditis caused by *Aspergillus niger*: case report. Clin Infect Dis 1998; 27:1322–1323
70 Wang JH, Liu YC, Lee SS. Candida endocarditis following percutaneous transluminal coronary angioplasty. Clin Infect Dis 1998; 26:205–206
71 Wendt B, Haglund L, Razavi A, et al. *Candida lusitaniae*: an uncommon cause of prosthetic valve endocarditis. Clin Infect Dis 1998; 26:769–770
72 Ariffin H, Ariffin W, Tharam S, et al. Successful treatment of *Candida albicans* endocarditis in a child with leukemia: a case report and review of the literature. Singapore Med J 1999; 40:533–536
73 Aspesberro F, Beghetti M, Oberhänsli I, et al. Fungal endocarditis in critically ill children. Eur Pediatr 1999; 158:275–280
74 Baratella MC, Dan M, Fabbri A. Candida endocarditis of the right heart. Heart 1999; 82:100
75 Camin AM, Michelet C, Lanaganay T, et al. Endocarditis due to *Fusarium dimerum* four years after coronary artery bypass grafting. Clin Infect Dis 1999; 28:150
76 Darwazeh A, Berg G, Faris B. *Candida parapsilosis*: an unusual organism causing prosthetic heart valve infective endocarditis. J Infect 1999; 38:130–131
77 Célard M, Dannaoui E, Piens MA, et al. Early *Microascus cinereus* endocarditis of a prosthetic valve implanted after *Staphylococcus aureus* endocarditis of the native valve. Clin Infect Dis 1999; 29:691–692
78 Fedalen PA, Fisher CA, Todd BA, et al. Early fungal endocarditis in homograft recipients. Ann Thorac Surg 1999; 68:1410–1411
79 Mathew R, Ranjit MS, Rajamini MR. Postoperative endocarditis due to *Candida tropicalis*. J Assoc Physicians India 1999; 47:921–922
80 Marín P, García-Martos P, García-Doncel A, et al. Endocarditis by *Aspergillus fumigatus* in a renal transplant. Mycopathologia 1999; 145:127–129
81 Sobottka I, Deneke J, Pothmann W, et al. Fatal native valve endocarditis due to *Scedosporium apiospermum* (*Pseudallescheria boydii*) following trauma. Eur J Clin Microbiol Infect Dis 1999; 18:387–389
82 Vaideeswar P, Sivaraman A, Deshpande JR, et al. Neonatal candidal endocarditis: a rare manifestation of systemic candidiasis. Indian J Pathol Microbiol 1999; 43:165–168
83 Viertel A, Ditting T, Pistorius K, et al. An unusual case of Aspergillus endocarditis in a kidney transplant recipient. Transplantation 1999; 68:1812–1813
84 Román AR, Rodriguez-Bailón I, Gómez-Doblas JJ. Fungal whip beats the heart. Circulation 1999; 100:1249
85 Abad C, Maynar M, Ponce G, et al. Implantation of a composite bifurcated cryopreserved aorta-iliac femoral homograft in a patient with *Candida albicans* endocarditis [letter]. J Cardiovasc Surg 2000; 41:317–319

86 Veraldi GF, Gugliemi A, Genna M, et al. Occlusion of the common iliac artery secondary of fungal endocarditis: report of a case. Surg Today 2000; 30:291–293
87 Gumbo T, Taege AJ, McWhorter S, et al. Aspergillus valve endocarditis in patients without prior cardiac surgery. Medicine 2000; 79:261–268
88 Netzer RO, Zollinger E, Seiler C, et al. Infective endocarditis: clinical spectrum, presentation and outcome: an analysis of 212 cases 1980–1995. Heart 2000; 84:25–30
89 Picarelli D, Surraco J, Zúñiga J, et al. Surgical management of active infective endocarditis in a premature neonate weighing 950 grams. J Thorac Cardiovasc Surg 2000; 119:380–381
90 Rao K, Saha V. Medical management of *Aspergillus flavus* endocarditis. Pediatr Hematol Oncol 2000; 17:425–427
91 Sorrell VL, Koutlas TC, Ohl C. Fungal endocarditis at the aortotomy site after aortic valve replacement. Clin Cardiol 2000; 23:387–389
92 Melamed R, Leibovitz E, Abramson O, et al. Successful non-surgical treatment of *Candida tropicalis* endocarditis with liposomal amphotericin-B (AmBisome). Scand J Infect Dis 2000; 32:86–89
93 Ledesma D, Pearce W. Images in clinical medicine. N Engl J Med 2000; 342:1015
94 Kreiss Y, Vered Z, Keller N, et al. *Aspergillus niger* endocarditis in an immunocompetent patient: an unusual course. Postgrad Med J 2000; 76:105–106
95 Kirchgatterer A, Auer J, Täuber K, et al. Fungal endocarditis of the mitral valve. Clin Cardiol 2000; 23:55
96 Gouëllo JP, Asfar P, Brenet O, at al. Nosocomial endocarditis in the intensive care unit: an analysis of 22 cases. Crit Care Med 2000; 28:377–382
97 Ellis ME, Al-Abdely H, Sandridge A, et al. Fungal endocarditis: evidence in the world literature, 1965–1995. Clin Infect Dis 2001; 32:50–62
98 McLeod R, Remington JS. Fungal endocarditis. In: Rahimtoola SH, ed. Infective endocarditis. New York, NY: Greene and Stratton, 1978
99 Utley JR, Mills J, Roe BB. The role of valve replacement in the treatment of fungal endocarditis. Thorac Cardiovasc Surg 1975; 69:255–258
100 Nguyen MH, Nguyen ML, Yu VL, et al. Candida prosthetic valve endocarditis: prospective study of six cases and review of the literature. Clin Infect Dis 1996; 22:262–267
101 Muehrcke DD, Lytle BW, Cosgrove DM. Surgical and long-term antifungal therapy for fungal prosthetic valve endocarditis. Ann Thorac Surg 1995; 60:538–543
102 Baddour LM. Long-term suppressive therapy for fungal endocarditis. Clin Infect Dis 1996; 23:1338–1339