Postgraduate Medical Journal (September 1979) **55**, 632–641

Fungal endocarditis: patients at risk and their treatment

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Summary

Fungal endocarditis is not rare. It usually develops in patients with abnormal or surgically traumatized hearts, to whose blood fungi have gained access, perhaps during temporary (often iatrogenic) impairment of host defences. Although the blood is cleared rapidly, the fungus can establish itself in the endocardium, where it grows slowly. Thus, clinical and laboratory procedures (including blood and urine cultures) that have permitted early diagnosis and treatment of bacterial endocarditis, are not reliable in early fungal endocarditis. Greater reliance must be placed on serological monitoring of patients who have had transient fungaemia and are at risk of endocarditis. The clinician must consider factors that enhance fungal proliferation and invasion and be cognizant of its dangers – even in the absence of clear signs of infection. Prophylactic measures should be employed to protect the patient at risk, including topical, oral and systemic use of appropriate antifungal agents. Early therapy, the extent and duration of which can be determined by (1) obtaining the MIC of transitory blood or urine isolates – which should not be ignored – and (2) monitoring serology, might eliminate early invaders of the endocardium. Sixty-four reported cures of fungal endocarditis caused by *Candida*, the most common fungal pathogen, are tabulated, 29 were of classic fungal endocarditis requiring surgery, 3 of whom were seen later by others as fatal recurrences. Those treated early (shortly after candidaemia was diagnosed – mostly in patients on treatment for bacterial endocarditis or after cardiac surgery) survived without need for surgical removal of vegetations or valve replacement. Despite strong suggestive evidence that the first 35 patients tabulated had fungal endocarditis, histological proof exists for only a few who had surgery.

Cures of endocarditis caused by other fungi are noted. Improved surgical and medical therapy has improved the prognosis even of patients with the far-advanced disease. However, development of classic fungal endocarditis has been reported one or more years after cardiac surgery and late recurrences after intensive therapy of fungal endocarditis, that had led to clinical recovery of 2 years or more, have been reported. Serological monitoring of vulnerable patients might alert the physician to recurrence early enough for efficacy of drug therapy, averting fatal outcome or the need for further surgery.

Introduction

Fungal endocarditis (FE) is rarely diagnosed early enough for prompt intensive therapy that has halved the fatality of bacterial endocarditis from 95% (Weinstein, 1975). Fungaemia still tends to be ignored when it is transitory, and serological tests are not widely used. The incidence of resultant FE is difficult to estimate. From 10 to 20% of clinical infective endocarditis is abacterial (Lerner and Weinstein, 1966; Tumulty, 1967; Rabinovich, Smith and January, 1968); 30% of those detected only at post-mortem had been blood culture-negative (Cherubin and Neu, 1971). Such cases should be systemically studied serologically and by special stains for fungi, since fungi can grow in heart valves

0032-5473/79/0900-0632$02.00

without causing sepsis or notable changes in cardiac signs until late in the course of the disease. Methods to increase the efficacy and safety of antifungal-drug administration permit early treatment of cases diagnosed serologically. Over 60 cases of endocarditis caused by *Candida* have been reported cured; some were followed-up long enough to be virtually certain recoveries.

Factors that predispose to fungal endocarditis

Iatrogenic factors

Major surgery, severe accidental injury, and diseases necessitating antibiotic therapy and indwelling intravenous (i.v.) catheters for nutritional, therapeutic or diagnostic purposes, can lead to FE. Use of antibiotics that suppress enteric bacteria enhance the growth of *Candida*, which can enter the blood through toxin-irritated gut, by mycelial invasion (Seelig, 1966b; 1968) yeast persorption (Krause, Matheis and Wulf, 1969; Stone, 1974; Stone *et al.*, 1973, 1974), or directly during intestinal surgery. Environmental fungi can reach the blood *via* indwelling catheters and i.v. needles and flourish in peri-catheteral sleeve thrombi (Anderson and Yardley, 1972) or in the endocardium, traumatized by tubes that reach the heart (Law *et al.*, 1972; MacMillan, Law and Holder, 1972). Intratracheal intubation can push oral *Candida* into the lower respiratory passages and lead to pulmonary infection, serving as the focus for endocardial invasion, as with primary pulmonary fungal pathogens (Buchbinder and Roberts, 1972). Abortions or other gynaecological procedures, and urethral or dental instrumentation (e.g. areas prone to candidal colonization) can mediate entry into the circulation, thereby increasing the risk of endocarditis in patients with valvular disease or other structural cardiac abnormalities.

Emergent fungi during bacterial endocarditis therapy might be responsible for antibacterial-refractory endocarditis and are readily missed clinically and pathologically unless specifically sought. They have been disregarded as contaminants or treated only when repeatedly cultured from patients deteriorating clinically (Ellis and Spivack, 1967; Toala *et al.*, 1970; Editorial, 1971). Suppression of bacteria alone increases the growth of fungi when both are present in the endocardium.

Iatrogenic measures can suppress host defences, e.g. directly by antibiotics (Seelig, 1966a, b), or by suppression of enteric flora as in gnotobiotic animals (Abrams and Bishop, 1965). Major surgery, and other serious trauma, e.g. burns, decreases both phagocytosis and intracellular killing (Alexander, Hegg and Altmeier, 1968). Pump-oxygenator-denaturation of immunoglobulins has been implicated in post-cardiotomy infections (Lee *et al.*, 1961; Hairston *et al.*, 1969).

Patients vulnerable to fungal endocarditis

Fungi, being facultative pathogens, might cause endocarditis predominantly in patients with temporarily subnormal host defences and cardiac abnormalities. Metabolic abnormalities impair immunological defences against *Candida* (Edwards *et al.*, 1978). Not only do neutrophils and monocytes have candidacidal phagocytic activity, but lymphocytes (particularly thymic (T) cells) participate in resistance to fungi. Patients with auto-immune disease might be particularly vulnerable to FE as in rheumatic valvular disease. Similarly, cardiac patients with genetic defects such as chronic granulomatous diseases (CGD) who have subnormal phagocytic killing capacity (Lehrer and Cline, 1969a, b) or with thymic abnormalities (Hermans, Ulrich and Markowitz, 1969; Montes *et al.*, 1972) who are susceptible to refractory, usually superficial, *Candida* infections might be particularly vulnerable to FE.

There are similar cellular immune defects at the extremes of life. Neonates (particularly prematures) have subnormal phagocytic (Gluck and Silverman, 1957) and intracellular killing capacity (Miyamoto, 1965; Cocchi and Marianelli, 1967; Coen, Gursh and Kauder, 1969). Quie (1969) correlated white blood cell (WBC) metabolic defects of infancy and those seen in CGD. Uhr (1966) noted that premature infants often have subnormal delayed sensitivity reactions such as are seen in patients with genetically abnormal immune mechanisms, who are susceptible to mucocutaneous candidiasis (Kirkpatrick, Rich and Bennett, 1971). Perhaps the susceptibility of geriatric patients to fungal endocarditis might be partially attributed to impaired cellular defences, such as shown by Tillotson and Finland (1969) for pulmonary macrophages of the aged. The susceptibility of diabetics to fungal endocarditis might be an expression of such decreased phagocytic response to experimental fungal infections as has been demonstrated in alloxanized animals (Schauble and Baker 1957; Sheldon and Bauer, 1959, 1960; Bybee and Rogers, 1964). (Addicts who repeatedly inject pathogens, are a separate category of FE patients.)

Possible role of magnesium deficiency in fungal endocarditis

The loss or inactivation of magnesium (Mg) or its deficiency because of metabolic abnormalities (Seelig, 1979b) might contribute to defence impairment. Antibiotics which predispose to *Candida* infections and which adversely affect Mg metabolism include tetracyclines which chelate Mg and inhibit

dependent enzymes (Eagle and Saz, 1966) that participate in glycolytic intracellular killing (Karnovsky, 1962; Rogers, 1964) and the aminoglycosides that cause renal Mg wasting (Holmes, Hesling and Wilson, 1970; Bar, Wilson and Mazzaferri, 1975; Keating *et al.*, 1977). Both groups decrease phagocytic uptake (Munoz and Geister, 1950; Forsgren, 1974) and intracellular killing capacity (Alexander and Good, 1968). Magnesium is necessary for WBC clumping and adherence of bacteria (Allison, Lancaster and Crosthwaite, 1963; Allison and Lancaster, 1965) and is involved in phagocytosis and mobility (Wilkins and Bangham, 1964; Brennan, Seelig and Lichtman, 1979). Antibacterial-suppression of phagocytosis is reversible by Mg (Downey and Pisano, 1966). Cardiac surgery patients develop hypomagnesaemia (Scheinman, Sullivan and Hyatt, 1969; Holden, Ionescu and Woller 1972; Khan, Hodge and Bassett, 1973; Holden, 1979), possibly contributed to by the use of acid-citrate-dextrose pump-prime (Killen, Grogan and Collins, 1971). This might be a factor in their susceptibility to FE.

It is conceivable that antenatal and infantile magnesium deficiency might contribute to cardiac abnormalities (Seelig, 1978, 1979a, b) and infantile and later metabolic immunological disorders. For example, thymic abnormalities have developed in Mg-deficient rats (Bois, 1968; Alcock *et al.*, 1973; Hass, McCreary and Laing, 1979). Neonatally thymectomized mice are susceptible to *Candida* infection (Salvin, Peterson and Good, 1965). Humoral immunological defects also develop with Mg-deficiency (Alcock and Shils, 1974; Elin, 1975; Larvor, 1979). Whether phagocytic, T-cell and other immunological dysfunctions might be contributed to by therapeutic measures that cause Mg-loss or inactivation remains to be ascertained.

Fungal pathogens in endocarditis

The most common FE pathogens are *Candida* spp., most commonly after cardiac surgery and complicating bacterial endocarditis therapy (Seelig *et al.*, 1973, 1974; Engleman *et al.*, 1973; Rubinstein *et al.*, 1975; Stone, 1975; Turnier *et al.*, 1975; Utley, Mills and Roe, 1975; Premsingh *et al.*, 1976; Gladstone *et al.*, 1976; Watanakunakorn, 1977; Rotheram and Magovern, 1977; Arnon and Ehrlich, 1977; Eilard *et al.*, 1978; Wain *et al.*, 1979). Fungal endocarditis is usually a valvular infection although mural infection occurs in severely immunosuppressed hosts (often with indwelling catheters) and in other patients with disseminated candidiasis. *Aspergillus* is the next most frequently reported fungal pathogen in FE, also usually after cardiac surgery (Kammer and Utz, 1974; Carrizosa *et al.*, 1974; Harford, 1974; Rubinstein *et al.*, 1975). *Histoplasma capsulatum* can also cause endocarditis (Merchant *et al.*, 1958; Hartley, Reinsberg and Sinaly, 1967), as have the Cryptococcaceae : (1) *Cryptococcus neoformans* (Merchant *et al.*, 1958; Shelburne and Carey, 1962; Stein, Harken and Dexter, 1966; Cherubin and Neu, 1971; Naveh *et al.*, 1975); (2) *Torulopsis* sp. (Lees *et al.*, 1971; Rubinstein *et al.*, 1975; Utley *et al.*, 1975; Sharpe *et al.*, 1975; Eilard *et al.*, 1978); and (3) *Saccharomyces* (Stein, Folkens and Hruska, 1970). In his tabulation of cases of mucormycosis, Baker (1970) listed several with *Mucor* endocarditis (Torack, 1957; Gloor, Löffler and Scholer, 1961; Suga, Hagal and Kashima, 1963). Several had *Mucor*-invaded thrombi in pulmonary vessels, such as caused mural endocarditis in a boy with myelogenous leukaemia (Buchbinder and Roberts, 1972). Two more cases of *Mucor* endocarditis have been reported (Erdos, Butt and Weinstein, 1972; Khicha, Berroya and Escano, 1972). *Blastomyces* endocarditis, *Coccidioides* endocarditis (Merchant *et al.*, 1958) and *Paecilomyces* fungal endocarditis (Uys, Don and Schrire, 1963; Silver, Tuffnel and Bigelow, 1971; Haldane *et al.*, 1974), and *Phialophora* FE has also been reported (Pierach *et al.*, 1973; Rubinstein *et al.*, 1975).

Experimental fungal endocarditis

Fungal endocarditis models include heart surgery in dogs (Cooper *et al.*, 1961), advancing peripherally inserted polyethylene i.v. tubes containing *Candida* to the hearts of rabbits (Freedman and Johnson, 1972), inserting a polyethylene catheter across the aorta and injecting *Candida* (Sande, Bowman and Calderone, 1977), and securing an intraventricular catheter and injecting *Aspergillus* (Carrizosa, Kohn and Levinson, 1975). Most animals showed rapid clearance of fungaemia, despite progression of FE. *Candida* antibodies developed in all rabbits that survived at least 12 days, and rose progressively in those with persistent FE (Sande *et al.*, 1977). *Candida* organisms injected i.v. or persorbed are rapidly phagocytosed by tissue macrophages of liver and spleen (Taschdjian *et al.*, 1971; Meister *et al.*, 1977; Stone *et al.*, 1974), and even in heart valves (Calderone, Rotondo and Sande, 1978). The subsequent course depends on the fungal load, host defences and whether antifungal therapy is given.

Treatment of fungal endocarditis

FE when diagnosed late has a poor prognosis. Emphasis must be placed on prevention, early diagnosis, and adequate sustained therapy, monitored by serological tests rather than culture.

Prevention of fungal endocarditis

Vulnerable patients should be protected against

outgrowth of intestinal *Candida* by oral administration of non-absorbable antifungal antibiotics before surgery. Oral lavage with antifungal solutions before insertion of intratracheal appliances is advisable, as is their topical use in high risk patients who are to have instrumentation at sites where *Candida* colonization is likely (e.g. dental operative procedures, prostatectomy and gynaecological operative procedures). *Candida* endocarditis has developed after gynaecological surgery (Sweeney and Dineen, 1960; Gladstone *et al.*, 1976) and therapeutic abortion (Goenen *et al.*, 1977).

Indwelling i.v. catheters should be inserted under sterile conditions and secured firmly to prevent invasion by skin organisms; there should be minimal manipulation under ward conditions. Fluids for total parenteral nutrition provide excellent media for fungal growth (Maki, Goldmann and Rhame, 1973; Miller and Grogan, 1973; Goldmann and Maki, 1973). Laminar air-flow rooms, used for total parenteral nutrition-solution preparation, can become contaminated with *Candida* (Bodey, 1973). Intravenous catheters, particularly those which extend to the heart, should be closely monitored for growth of *Candida* at the catheter tip and in the blood. Flushing of the catheter with solutions of amphotericin B has been suggested (Brennan *et al.*, 1972). Now that antifungal therapy has been improved, withholding its use when transitory candidaemia develops is more hazardous than is its treatment. Endocarditis has persisted for many months after clearance of *Candida* from the blood (Hart, Russell and Remington, 1969; Seelig *et al.*, 1974; Montague and Sugg, 1974; Rubinstein *et al.*, 1975).

Fungal serology can indicate deep fungal infection, but how to interpret findings, particularly of the *Candida* antibodies, is under dispute (Kozinn *et al.*, 1972, 1976; Kozinn, 1978; Goldstein and Hoeprich, 1972; Gaines and Remington, 1973; Taschdjian *et al.*, 1973; Bacon, Davidson and Smith, 1974; Everett, LaForce and Eickoff, 1975; Remington, Gaines and Gilmer, 1972; Harding, Sandford and Merz, 1976; Holder, Kozinn and Law, 1977; Merz *et al.*, 1977). Rising titres or conversion of negative to positive values in susceptible patients provide a valuable clue to clinical endocarditis caused by *Candida* sp. or *Torulopsis* sp. – the latter because of cross-antigenicity of these fungi (Harris *et al.*, 1972; Seelig *et al.*, 1973, 1974; Iannini *et al.*, 1976; Galgiani and Stevens, 1977; Arnon and Ehrlich, 1977; Kemp and Solotorovsky, 1964; Taschdjian *et al.*, 1973). Such *Candida* precipitins have risen in advancing experimental *Candida* endocarditis, in contrast to their transitory rise and then fall in septicaemic animals without endocarditis, as their infection cleared (Sande *et al.*, 1977). Monitoring *Candida* serology for months and then at not longer than yearly intervals is advisable in patients with heart disease, who have had transient candidaemia

Treatment of early fungal endocarditis

Such early FE, as was described by Ratcliffe and Pryce (1968) 2 weeks after cardiac surgery, and by Strauss and Merz (personal communication) in a post-cardiotomy patient who then had gastric surgery (both with candidaemia; the latter with *Candida* precipitins) resemble the early experimental model (Calderone *et al.*, 1978). At this stage, low-dose antifungal therapy might be curative. Most of the patients in Table 1 had antifungal treatment within days to weeks of *Candida* being detected. Twenty-two were being treated for bacterial endocarditis or sepsis when *Candida* was cultured (cases 1, 3–6, 8–12, 14–16, 21, 23–25, 27, 28, 30, 31, 34; Table 1). *Candida* sp. alone was found in 14 of the cardiac surgery patients (cases 7, 13, 19–23, 26–29, 32, 33, 35) and in 3 of those who had other surgical procedures (cases 2, 31) or with other valvular disease (case 16). Whether the candidaemia of the drug addict (case 34) reflected early FE is uncertain. Four were treated on the basis of rising titres: 2 prophylactically (cases 21, 22) and 2 with evidence of endocarditis but without culture of *Candida* (cases 23, 28); 10 had their treatment monitored by serological determinations (cases 19, 21–23, 26–31). One of the patients, whose *Candida* precipitins rose after a transient fall, and whose agglutinations did not fall during 5 months of observation (case 23) is a questionable cure, as are those with unspecified follow-up. One of Arnon and Ehrlich's (1977) 5 cases is not listed because he died of combined fungal and bacterial infection; *Candida* spp. had been cultured early; serology became positive by the 23rd post-operative day.

Eilard *et al.* (1978) reported cure of a cardiac surgery patient who developed fungaemia due to *Torulopsis*. Hairston and Lee (1970) reported a one-year follow-up of a patient from whose prosthesis (replaced because of bacterial endocarditis) *Aspergillus* sp. was cultured: she remains well 8 years later (R. H. Sade and P. Hairston, personal communication). A child with *Rhodotorula* fungaemia, presumed to have endocarditis, was successfully treated with a one-year course of flucytosine (Naveh *et al.*, 1975). A diabetic 57-year-old man who developed *Rhodotorula* fungaemia during treatment for staphylococcal endocarditis responded to amphotericin B therapy (Shelburne and Carey, 1962).

Two patients with *Histoplasma* endocarditis recovered. one on standard amphotericin B dosage (Derby, Coolidge and Rogers, 1962) and one on 50%

of that dosage (Drutz *et al.*, 1968). Possibly low-dose, short-term courses of i.v. amphotericin B (Medoff *et al.*, 1972) or of the newer oral imidazoles might prove useful in early forms of FE.

Treatment of advanced fungal endocarditis

Advanced FE has been reported as cured in 29 cases (Table 2). Antifungal therapy was amphotericin B alone or with other antifungal drugs, before and after replacement of infected valves, with cardiac irrigation using high concentration of amphotericin B one g/l (Kay *et al.*, 1968; Turnier *et al.*, 1975). The vegetations must be removed because of their impenetrability by such solutions (Rubinstein *et al.*, 1974). Long-term treatment and follow-up are necessary (Rubinstein *et al.*, 1975; Premsingh *et al.*, 1976), preferably with monitoring of *Candida* precipitins or agglutinins or both (Seelig *et al.*, 1974; Galgiani and Stevens, 1977; Kelly Smith and Hsieh, 1978). Dr Stevens (Borelli *et al.*, 1979) proposed that cases be categorized as 5- or 10-year remissions rather than cures. In fact, 3 of the tabulated patients reported as cured later died of recurrences (cases 59–61). Six were well at 3 years' (or more) follow-up (cases 36–38, 41, 50, 63), which brings the total 3 years + cures for *Candida* FE to 11, including early and probable cases treated promptly, usually with antifungal drugs alone (cases 3, 4, 12, 20, 31). Four were clinically and serologically negative at follow-up at 3 years or less (cases 39, 48, 51, 62). The absence of clinical recurrence in most is not assurance of recovery; 2 have had positive serology and are in doubt (cases 50, 63) even though one has been free of overt disease for 5 years (case 50).

Drug toxicity has often prevented completion of an adequate course of therapy. New orally-effective imidazoles, and combinations of antifungal drugs, may permit more effective and tolerable therapy to be sustained long enough for complete elimination of fungi from the heart. Fourteen of the cases in Tables 1 and 2 received combination systemic therapy (cases 20, 31, 34, 42, 48–51, 60–63). Seven were given the drugs sequentially (cases 15, 16, 31, 32, 41, 42, 46), usually because of intolerance. Six were given oral doses of imidazoles (cases 19, 35, 42, 50, 60, 63) – even of derivatives rapidly inactivated (clotrimazole) or not absorbed when given by mouth (miconazole). Two improved with an imidazole plus amphotericin B (cases 50, 63) despite *in vitro* antagonism (Schachter *et al.*, 1976; Dupont and Drouhet, 1979).

Two patients with advanced *Aspergillus* endocarditis recovered following removal of infected tissue and with amphotericin B and flucytosine therapy (Lawrence, Schockman and McVaugh, 1971; Carrizosa *et al.*, 1974.)

Immunotherapy in refractory advanced fungal endocarditis

Kelly Smith and Hsieh (1978) found that transfer factor produced marked transient improvement in 3 patients who became septic and refractory to antifungal therapy after maximal therapy for advanced *Candida* endocarditis. All had depressed cell-mediated immunity characterized by anergy and monocytopenia, probably mediated by their overwhelming infection. The first patient (No. 61) died suddenly after having rapidly responded to a single dose of transfer factor, becoming afebrile, free of petechiae, clearing of candidaemia, and restoration of immunoreactivity: his negative *Candida* skin test and serology became positive, and his WBC count rose. At post-mortem he was almost free of *Candida* sp. Two patients given transfer factor responded similarly: one was also treated with amphotericin B, but died of recrudescence of FE within one year; the other was free of FE as determined by culture of his prosthesis removed later for bacterial infection. Specific transfer factor has promise as adjunctive therapy with established antifungal and surgical therapy of refractory FE, similar to the transfer factor-improved response to amphotericin B of other refractory fungal infections (Kent and Kendall, 1965; Kirkpatrick, Rich and Smith, 1972; Graybill *et al.*, 1973; Stevens, 1977).

Other means of stimulating host defences include autologous vaccines – given parenterally or orally (Beemer *et al.*, 1976; Beemer, Kutlin and Pinto, 1977) – and chemotherapeutic stimulation of cellular immunity such as levamisole (Renoux and Renoux, 1972; Tripodi, Parks and Brugmans, 1973). Use of nystatin, orally, to release enteric fungal antigens for stimulation of immunoresponsiveness (Beemer *et al.*, 1976) suggests that combined oral and i.v. polyene therapy reported curative (cases 2, 5, 9) and combined i.v. amphotericin B with orally effective antifungal drugs, might thereby have had more *in vivo* efficacy than anticipated from *in vitro* studies. Drugs effective against isolated organisms cure or fail in patients depending on their immunocompetence (comment by D. W. R. Mackenzie, this Symposium). The preliminary finding of restored drug-response in far-advanced FE (Kelly Smith and Hsieh, 1978) suggests that iatrogenic temporary suppression of host defences that may allow for fungal establishment in diseased valves during transitory fungaemia should be considered and appropriate therapy instituted. Early treatment with low-dosage antifungal drugs, then, might obviate the heroic measures required for advanced fungal endocarditis.

Acknowledgments

Appreciation is expressed to Drs W. Merz and R. Strauss for the data on the patient whose clinically unsuspected early *Candida* endocarditis was detected only at post-mortem, and to Dr J. Kelly Smith, for alerting me to his experience with transfer factor and to Drs Richards, Cerrutti, Jakara, Sade, Hairston, Gonen, Seabury, Temple, Dismukes and Curtis for follow-up data.

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