Fungal endocarditis

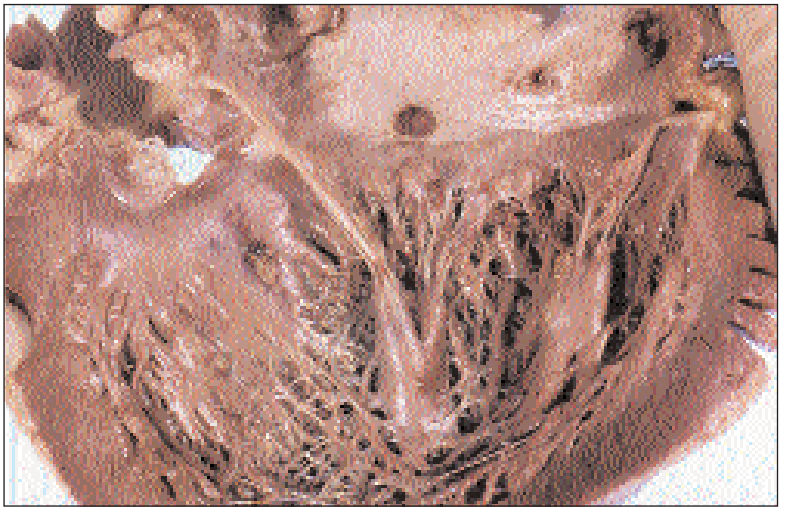
Fungal endocarditis is a serious condition that affects particular groups of patients. This article reviews the aetiology, clinical features and relevant investigations required for diagnosis as well as the treatment necessary for a successful outcome.

Infective endocarditis caused by fungi accounts for approximately 1% of all cases of endocarditis. Certain patient groups tend to be particularly susceptible and many of the presenting features, both clinical and echocardiographic, differ from infective endocarditis caused by other microorganisms. Specific investigations are usually required for diagnosis and intensively-monitored treatment with potentially toxic antifungal agents is essential. Cardiac surgery is nearly always necessary to achieve a cure.

Patient at risk

Patients with abnormal heart valves, patients after cardiac surgery, those receiving long-term antibiotics or intravenous feeding and those with long-term central venous catheters are most at risk (Woods et al, 1989). Patients receiving treatment for bacterial endocarditis on native or prosthetic valves, immunocompromised individuals such as patients with malignancy or acquired immunodeficiency syndrome (AIDS) and those being treated with steroids, chemotherapy or other immunosuppressive agents are particularly susceptible (*Figure 1*).

Figure 1. Large* Candida albicans *vegetations are visible on the mitral valve and myocardium of this 46-year-old woman dying of acute lymphoblastic leukaemia.



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Neonates requiring prolonged intensive care and parenteral nutrition are vulnerable and fatal fungal endocarditis (FE) has been reported after bone marrow transplantation. Intravenous drug abusers are presenting with FE with increasing frequency and the right heart is most commonly affected.

In specialist cardiac surgical units, FE remains a significant threat to patients requiring redo valve surgery for bacterial endocarditis and in particular for those requiring long-term mechanical circulatory support, such as left ventricular assist devices, as a result of the antibiotics required to prevent driveline site infection.

Microbiology and pathology

Fungi are eukaryotes – possessing a diploid number of chromosomes, a nuclear membrane and sterols in their plasma membrane. They have two basic morphological forms, spores and hyphae. Spores are unicellular fungi which reproduce asexually by blastoconidia formation (budding) or fission, e.g. *Candida* spp. or *Cryptococcus* spp. Hyphae are multicellular fungi which reproduce asexually and/or sexually, e.g. *Aspergillus* spp. Dimorphism exists when the fungus exhibits the spore or hyphal form, e.g. histoplasmosis or coccidioidomycosis. *Candida* spp. appear in tissue as both budding yeasts and tubular elements called pseudohyphae.

Approximately 75% of all cases of FE are caused by *Candida* spp., the rest being caused by *Aspergillus* spp. and a range of other fungi. *Histoplasma* spp. and *Cryptococcus* spp. occur rarely.

Microbiology

Fungal blood cultures require special media, e.g. BACTEC (BD Diagnostics, Sparks, MD, USA), but *Aspergillus* spp., *Histoplasma* and *Phycomyces* rarely grow in blood cultures. Although *Candida* spp. are relatively easy to grow, most other fungi require concentration of the blood by lysis centrifugation and culture on a solid medium such as Mycosel agar, blood agar, Sabouraud or other media (*Figure 2*).

Fungi can be positively stained in tissue preparations using lactophenol cotton blue or Grocott silver stains (*Figures 3* and *4*). Stains for mucopolysaccharides such as periodic acid–Schiff (PAS) are also suitable for demonstrating fungal hyphae and spores.

Specific identification of the fungus will help target treatment. When *Candida* species are found in blood cultures, differentiation between *C. albicans* and non-albicans species can be made using the germ-tube assay.

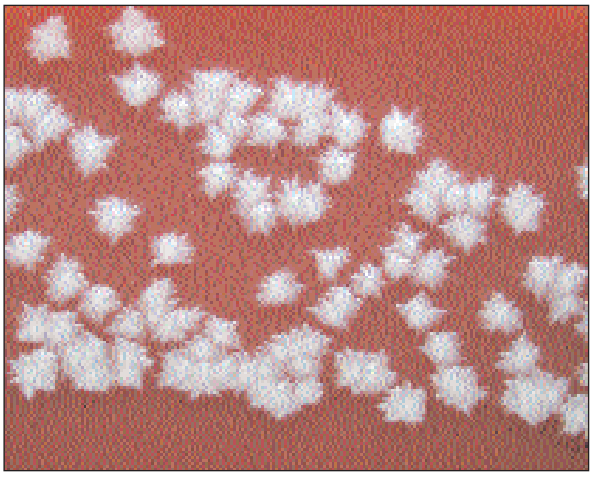


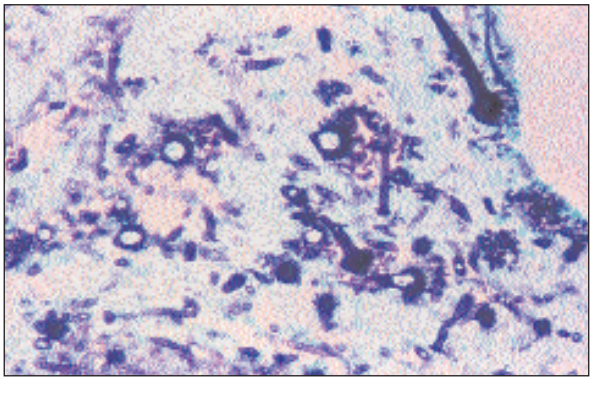
Figure 2.* Candida *colonies grown on blood agar.

Most candidaemias are caused by *C. albicans* and although most are susceptible to fluconazole, non-albicans species exhibit variable resistance.

Disseminated fungal infections with organisms such as *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis* or *Blastomyces* spp. rarely cause FE in the absence of cardiac foreign bodies (e.g. prosthetic valves, pacemaker wires) (Blair et al, 1980). They may be diagnosed by bone marrow culture or histological examination of excised vegetations, emboli or valves.

In immunocompromised patients with long-term intravenous (IV) catheters, prolonged antibiotic use and leucopenia, the respiratory, gastrointestinal and genitourinary mucosa and skin are often heavily colonized by *Candida* spp. and the intestinal mucosa may also be damaged by cytotoxic agents. Fungaemia may result and cause myocardial lesions and non-valvular endocarditis (*Figure 1*) (Woods et al, 1989). Unusual fungi may be responsible, e.g. *Trichosporon* spp. or *Fusarium* spp. (Anaissie et al, 1986). If the pathogen is adherent to the tip of an indwelling IV catheter, vegetations may occur on the wall of the superior vena cava, the right atrium, tricuspid or pulmonary valves and may result in pulmonary infarction and abscess (*Figures 5–7*). Patients with AIDS and on long-term fluconazole to prevent oropharyngeal thrush may be

Figure 3.* Aspergillus *species may be isolated from blood cultures or directly from vegetations or emboli removed surgically. They are recognized by their conidiophores – swollen ends of hyphae from which radiate large numbers of sterigmata (short lengths of narrower hyphae) ending in short chains of spores.



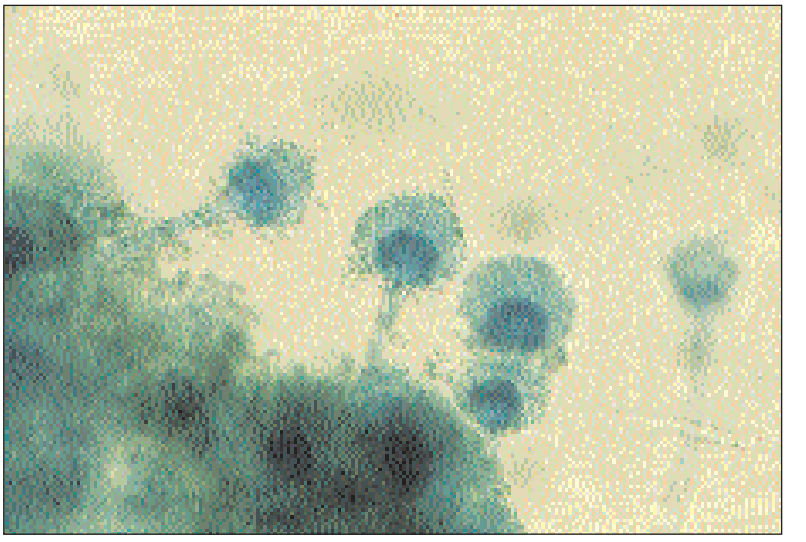
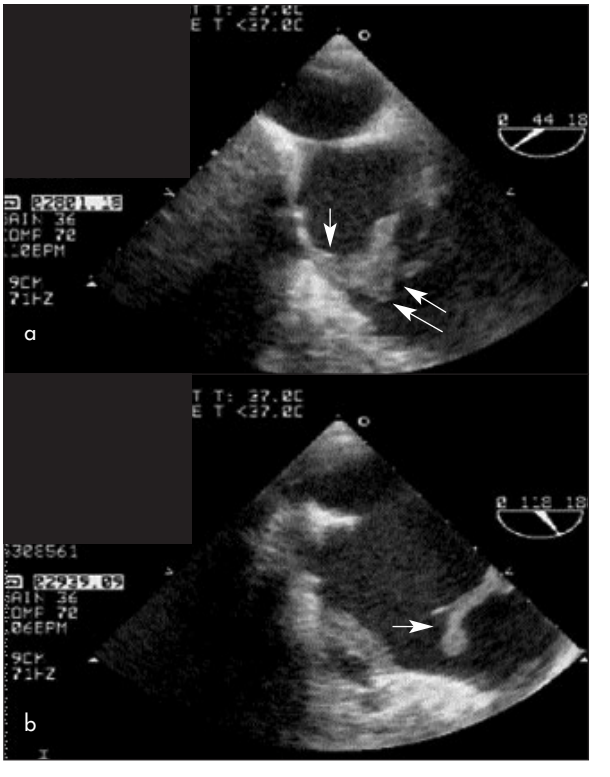


Figure 4. High power view of* Aspergillus conidiophore *showing conidiospores. Stain: lactophenol cotton blue.

Figure 5. Transoesophageal echocardiogram from a 48-year-old woman receiving chemotherapy with epirubicin (via a Hickman line) for breast cancer following mastectomy and axillary clearance. She developed neutropenic septicaemia caused by* Candida tropicalis. *a. The echocardiogram showed a large (20 mm) vegetation on the anterior tricuspid valve leaflet, moderate tricuspid regurgitation and (b) a large pedunculated mobile mass (25 mm long) attached to the superior vena cava and floating in the right atrium.



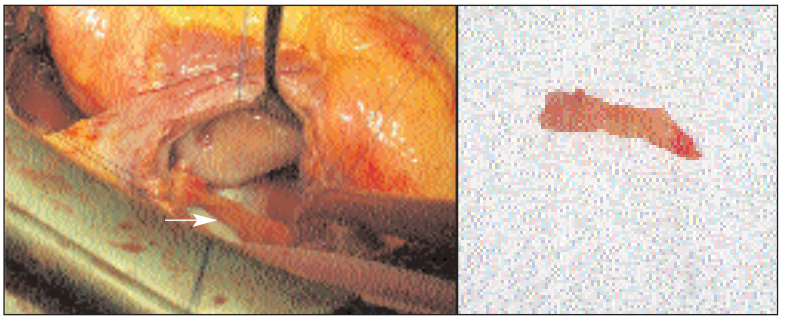


Figure 6. Open heart surgery was necessary to remove the mass from the superior vena cava (arrow) of the patient in Figure 5.

prone to *C. krusei*. FE occurring while receiving prolonged antibiotic therapy is frequently caused by *C. albicans* or *T. glabrata*.

Pathology

Fungal vegetations consist of the fungal pathogen adherent to a fibrin–platelet nidus on the damaged endocardium of the atria, ventricles or valves (Calderone et al, 1978). Vegetations are macroscopically large (10–33 mm) and friable, and prone to embolize. Diffuse myocarditis can occur. Characteristic histopathological findings and special histochemical stains such as PAS (*Figure 8*) and Gomori-methenamine silver may help diagnosis.

Figure 7. The tricuspid valve and its large vegetation (arrow) were also removed from the patient in Figure 5. The valve was replaced by a tissue valve prosthesis and the patient treated with intravenous amphotericin B for 4 weeks and oral voriconazole for 1 year. The large fungal mass can be seen attached to the destroyed tricuspid valve.

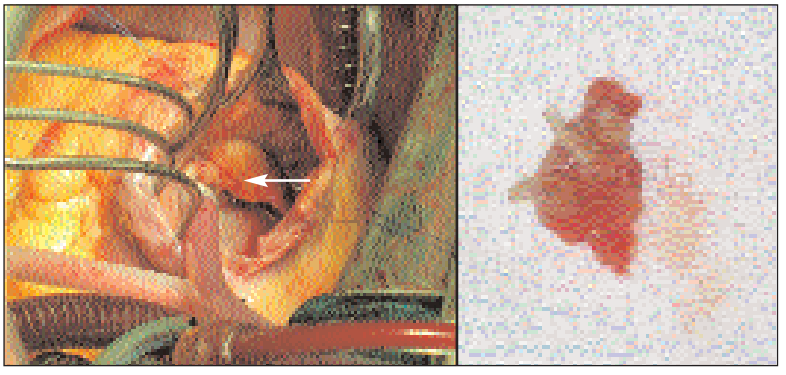
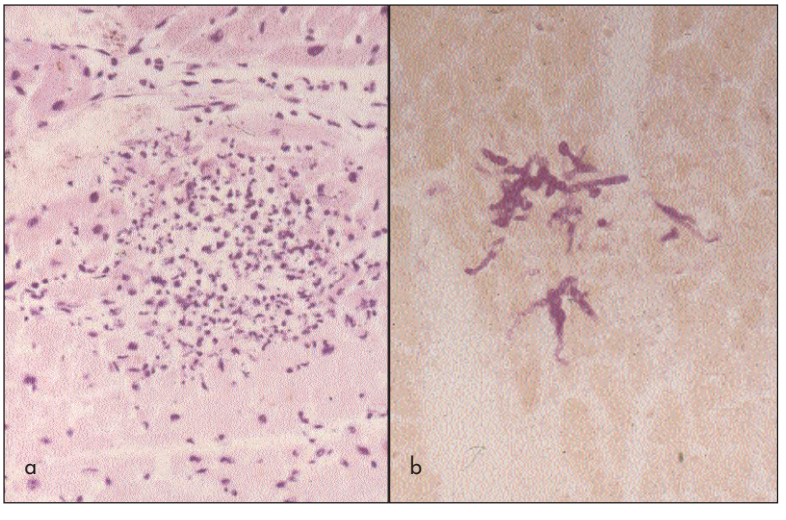


Figure 8. Fungal myocardial abscess (a) stained with haematoxylin and eosin appears as an acute inflammatory focus but fungal hyphae can be seen clearly (b) when stained by the periodic acid–Schiff method.



Clinical presentation

Unlike the typical presentation of acute or subacute bacterial endocarditis, FE is characterized by frequent negative blood cultures and few physical signs (Kammer and Utz, 1974; Rubinstein et al, 1975; McLeod and Remington, 1978; Moyer and Edwards Jr, 1992; Rubinstein and Lang, 1995). Fever, cardiac murmurs, splenomegaly and the occurrence of peripheral arterial emboli to large vessels supplying the limbs (30%), brain (55%), gut and kidneys (55%), and to the coronary arteries are the most common signs (Andriole et al, 1962; Vo et al, 1981). Sometimes multiple, these large emboli cause considerable functional and neurological damage, such as stroke, and lead to the associated high mortality. Metastatic abscesses are not an infrequent complication – the heart and kidneys being involved most commonly (Rubinstein et al, 1975). Chorioretinitis and endophthalmitis are serious and examination of the retina is essential (Edwards Jr et al, 1974). Maculopapular skin rashes, petechiae, nodules and pustules may occur (McLeod and Remington, 1978; Moyer and Edwards Jr, 1992).

A high index of suspicion should exist in those patients who are particularly susceptible, especially if pyrexia, rigors and evidence of peripheral emboli recur after prolonged and apparently successful antibiotic therapy.

Complications

Valvular regurgitation results from ulceration, tear and rupture of chordae tendineae, or perforation of the cusps themselves. Abscesses of the heart may occur, mainly in the aortic valve ring, especially when prosthetic valves are infected. They can spread to surrounding structures such as the interventricular septum and can cause a fistula between cardiac chambers and the aorta. Septal abscesses can lead to heart block and aortic root abscesses may produce a sinus of Valsalva aneurysm, involve the coronary ostia or cause valve obstruction. Pericarditis can complicate FE (Incarvito et al, 1981). Bulky, friable vegetations on the valves or endocardium produce emboli in over 80% of FE caused by *Aspergillus* spp. and in 33–75% of cases involving *Candida* spp. (Ramey et al, 1970, Kammer and Utz, 1974; Rubinstein et al, 1975; McLeod and Remington, 1978; Vo et al, 1981; Moyer and Edwards Jr, 1992; Rubinstein and Lang, 1995).

Glomerulonephritis (caused by antifungal immune complex deposition), meningitis, cerebral abscess, haemoptysis and haemopneumothorax have been reported.

Investigations

Normochromic normocytic anaemia, leucocytosis and hepatorenal dysfunction may occur. Erythrocyte sedimentation rate and C-reactive protein levels are usually elevated initially and are useful for indicating the effectiveness of the antifungal treatment. Urinalysis may show microscopic haematuria, red and white cell casts, and proteinuria.

A chest radiograph may show cardiomegaly and evidence of heart failure, pulmonary infarcts and lung abscesses. An electrocardiogram may show rhythm disturbances, heart block, myocardial infarction, ST or T wave abnormalities as a result of myocarditis or pericarditis.

Fungal blood cultures (3–6 sets) should be taken. Although frequently negative, most are positive with *Cryptococcus neoformans*, *Coccidioides immitis* and *Saccharomyces* spp., 83–95% with *Candida* spp., 11% with *Aspergillus* spp. and 0% with unusual fungi such as *Penicillium* spp., *Histoplasma* and *Phycomyces* (Kammer and Utz, 1974; McLeod and Remington, 1978; Moyer and Edwards Jr, 1992). Culture of a peripheral arterial embolus may provide the best and only clue of the presence of FE and the specimen can be examined microscopically for hyphae. All skin lesions (for *Aspergillus* spp.), oropharyngeal lesions (for *Histoplasma* spp.), lung lesions (in IV drug abusers), spleen and bone marrow (in immunocompromised individuals) should be taken for culture when FE is seriously suspected (McLeod and Remington, 1978; Vo et al, 1981; Moyer and Edwards Jr, 1992).

Serology has been useful in cryptococcosis and histoplasmosis – using a latex agglutination test for cryptococcal and *Histoplasma* antigen (Microbiology Resource Committee, 1987; Paya et al, 1987). A complement-fixation test and immunodiffusion test for coccidioidomycosis and paracoccidioidomycosis respectively may be useful. Although *Candida* precipitins and *Aspergillus* antigens and antibodies might provide supportive diagnostic evidence of fungal infection, their sensitivity and specificity are disappointing. Investigational approaches to diagnosis include detection of unique fungal metabolites by gas liquid chromatography, or antigen- or antibody-based methods and detection of immunodominant fungal antigens by radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), latex agglutination or immunoblot. Polymerase chain reaction techniques may be able to identify traces of fungal DNA or cell wall constituents. While results of some newer tests to identify *Candida* cell wall mannan, *Candida* cytoplasmic enolase antigen and *Aspergillus* galactomannan are promising, problems still exist.

Transthoracic echocardiography and transoesophageal echocardiography (TOE) are most important in establishing a diagnosis, for defining the anatomical extent of the valvar disease, fistulae and abscesses and for guiding the surgical strategy (*Figure 5*). TOE is especially useful when prosthetic valves are involved. Vegetations are typically large and visible on valves but may not be seen if attached to the myocardium.

Treatment

In general, a combination of surgery and effective medical therapy is necessary if a cure is to be achieved. Unfortunately, in many cases the patient's underlying condition makes it impossible to offer cardiac surgery and in itself determines the individual's prognosis. For those patients at risk of fungaemia, nystatin prophylaxis (1 MU/day) may be worthwhile.

Medical therapy

The polyene antifungal agents, e.g. amphotericin B and nystatin, bind to ergosterol in the plasma membrane and disrupt it, whereas the imidazole agents, e.g. fluconazole and itraconazole, block ergosterol synthesis by binding to cytosolic P450 necessary for the conversion of lanosterol to ergosterol. The pyridine analogue, flucytosine, becomes incorporated into RNA and/or DNA and thus blocks protein or DNA synthesis.

Erythrocyte sedimentation rate and C-reactive protein levels are usually elevated initially and are useful for indicating the effectiveness of the antifungal treatment.

A combination of amphotericin B (1–3 mg/kg IV every 24 hours, total dose 2–2.5 g) and 5-flucytosine (5-FC) (150–200 mg/kg orally per day in four divided doses) is usually recommended for susceptible fungi, although where possible high doses of amphotericin B may be preferable. Adverse effects of amphotericin include vomiting and diarrhoea, electrolyte disturbances, cardiovascular, renal and hepatic toxicity, blood dyscrasias, fever and neurological disorders. Esters of amphotericin, lipid complexes of amphotericin (Amphocil, ABLC, Cambridge Laboratories, Wallsend) and amphotericin encapsulated in liposomes (AmBisome, Gilead Sciences, Great Abington, 1–3 mg/day) may offer reduced toxicity and allow bigger dosage to be used.

Bone marrow depression and hepatic necrosis are still serious adverse effects of 5-FC. Blood counts and liver function tests should be monitored and plasma concentrations should be kept between 25 and 50 mg/litre.

Fluconazole (400 mg/day), itraconazole (200–400 mg/day) and voriconazole may be used orally as well as intravenously for the treatment of FE caused by *Candida*, *Aspergillus*, *Cryptococcus*, *Fusarium* and

Histoplasma. All of these agents have potentially serious side effects. A microbiologist should be consulted for advice when considering all antifungal agents.

Surgery

Cardiac surgery should be performed once bulky vegetations are diagnosed in order to prevent embolization. Otherwise persistent infection and fungaemia, valve destruction, regurgitation and heart failure, abscess, fistula or false aneurysm formation are the usual indications. Fungal prosthetic valve endocarditis requires excision of the prosthesis, radical debridement of infected tissue (including abscess cavities and sinus tracts), reconstruction using biological tissue when possible and prolonged oral suppressive antifungal therapy (Utley et al, 1975).

Prognosis

Data suggest a high mortality for patients with FE. Survival rates are better among patients receiving combined surgical and antifungal treatment, in those infected with *Candida* and in those who have univalvular involvement. Prognosis has improved with the introduction of echocardiography and an increased awareness of FE. However, FE recurs in around 30% of affected individuals. Close follow-up is required and patients should remain on long-term antifungal therapy.

Future developments

Because of the toxicity associated with the currently available antifungal drugs, efforts are being made to develop new agents. These include drugs that target fungal cell wall formation such as nikkomycins which inhibit chitin synthase, the echinocandin/pneumocandin/lipopeptide class which inhibit glycan synthesis and pradimicins which bind to mannan. Newer azole drugs are aimed at having broader spectrum of activity, increased efficacy and less toxicity. The allylamines, e.g. naftifine and terbinafine, inhibit squalene epoxidase, another enzyme in the biosynthetic pathway of ergosterol. Immunomodulators may prove to be important adjuncts to therapy in immunocompromised patients. The expanding array of recombinant cytokines, especially interferon-gamma, the colony-stimulating factors, the various interleukins or interleukin antagonists as well as passive immunotherapy with monoclonal antibodies may all prove of worth in these unfortunate patients that are prone to FE. BJHM

KEY POINTS

- Fungal endocarditis affects special patient groups including immunocompromised individuals, intravenous drug abusers, patients receiving prolonged antibiotic therapy or intravenous nutrition, patients with valve disease and those undergoing cardiac surgery.
- Fever, cardiac murmurs, splenomegaly, large mobile, friable vegetations and peripheral emboli are typical features.
- Myocardial abscesses, particularly of the aortic root and fistula formation, are serious complications as is prosthetic valve fungal endocarditis.
- Fungal blood cultures and echocardiography are the most useful diagnostic tests, although serology and histology, and culture of infected tissue and resectable peripheral emboli may be helpful in establishing the diagnosis.
- A combination of cardiac surgery and effective antifungal agents (which need to be given over a prolonged period) are usually necessary if a cure is to be achieved.

Figure 1 *is reproduced courtesy of Dr John Gosney, Royal Liverpool University Hospital, Liverpool,* Figure 5 *is reproduced courtesy of Dr Chris Bellamy, Glan Clywd Hospital, Rhyl, Wales, and* Figure 6 *is reproduced courtesy of Mr Aung Oo, The Cardiothoracic Centre, Liverpool.*
Conflict of interest: none.

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