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Clinical Aspects of Invasive Candidiasis
Endocarditis and Other Localized Infections

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Abstract

Candida endocarditis was previously considered a rare disease. However, its incidence is increasing, partly as a consequence of increased use of prosthetic intravascular devices. In patients with prosthetic valve endocarditis, *Candida* infection may occur via a two-step process; firstly, post-operative transitory candidaemia occurs during the intensive care unit stay, leading to colonization of the prosthetic valve and subsequent biofilm formation, with reduced susceptibility to antifungal agents. This theory lends support for pre-emptive antifungal therapy with agents that display activity against biofilm-associated *Candida* in patients with prosthetic heart valves at risk of candidaemia.

Current guidelines recommend treatment with amphotericin B with or without 5-fluorocytosine, or an echinocandin, with valve replacement where possible. Recent data suggest that amphotericin B shows reduced activity against *Candida* biofilm, and poor penetration into vegetations and blood clots in experimental models of infectious endocarditis, whereas echinocandins, and in particular anidulafungin, display potent *in vitro* activity against sessile *Candida* cells within biofilms. The incidence of ocular candidiasis has been decreasing among inpatients with candidaemia, possibly because of earlier identification and treatment of candidaemia. The therapeutic approach includes prolonged treatment with fluconazole or voriconazole. The role of systemic echinocandins may be limited since they achieve undetectable vitreous concentrations. Vitrectomy with local instillation of amphotericin B, azoles or echinocandins may play a role in the treatment of chronic complications such as epiretinal membrane formation. The role of *Candida* in CNS infections is unclear. Diffuse encephalitis in candidaemia is misleading, since alterations of the mental status are generally attributed to candidaemia-associated sepsis syndrome, and neuroimaging studies and cerebrospinal fluid cultures are rarely performed as part of the diagnostic work-up. Osteomyelitis caused by *Candida* is considered infrequent. In contrast, *Candida* is frequently implicated in nosocomial non-postneurosurgery spondylodiscitis. Optimal management of such cases may require surgical debridement and, after initial intravenous antifungal therapy, prolonged administration of oral azoles.

The role of *Candida* in endocarditis is fairly well established. With the increasing numbers of patients at risk of *Candida* endocarditis, there is a need for agents with potent efficacy against *Candida* biofilms. Echinocandins

represent a potential therapeutic option in this setting. Antifungal agents may also be of use in the treatment of complications in patients with ocular candidiasis and in CNS infections.

Once *Candida* gains access into the bloodstream, secondary infection may occur in a number of organs and tissues, such as the eyes, kidneys, skin, joints and bones, CNS and endocardium, including heart valve prosthesis or other intracardiac devices. Moreover, persistent fungaemia resulting from intravascular *Candida* infection may further facilitate metastatic seeding of the above organs. In neutropenic haemato-oncology patients with chronic haematogeneous candidiasis attributable to intestinal tract damage by cytotoxic chemotherapy, liver and spleen localizations are common. These are described in detail elsewhere.[1]

This paper reviews the epidemiology and treatment of *Candida* infection in endocarditis and other clinical entities.

1. *Candida* Endocarditis

Candida endocarditis has long been considered to be a rare and often fatal infectious disease with a presentation similar to that of subacute bacterial endocarditis. Until recently, most data were from case reports or very small series.[2] Initially, most patients were intravenous drug addicts or cardiosurgery patients with prosthetic heart valves.[2-5] During the 1980s, however, several cases of catheter-related, right-sided *Candida* endocarditis were observed in immunocompromised/oncology patients and major abdominal surgery patients requiring indwelling central venous catheterization for parenteral nutrition and/or cytotoxic chemotherapy.[6,7] The number of reported cases has increased during the last decade, probably as a consequence of increased use of prosthetic intravascular devices, advances in the surgical techniques (including reconstructive heart surgery), and increases in the number of immunocompromised patients. In addition, a growing number of individuals are at high risk for nosocomial candidaemia; for example, those admitted to the intensive care unit (ICU) or those with other forms of health care-associated (HCA) invasive fungal infections.[2,8]

A recent prospective 1-year survey of *Candida* bloodstream infections (BSIs) in seven university hospitals in western France assessed the epidemiology and clinical features of *Candida* endocarditis.[9] Of 190 cases of *Candida* BSI, 7 (3.7%) were complicated by endocarditis (4 on native valves, 2 on artificial [biological] valves and 1 involving a pacemaker). Indeed, the ICE-PCS (International Collaboration on Endocarditis – Prospective Cohort Study) recently indicated that *Candida* endocarditis accounted for 33 (1.2%) of 2749 cases of definite infectious endocarditis. Patients with *Candida* endocarditis were more likely to have prosthetic valves or short-term indwelling catheters, and to have an HCA *Candida* infection.[10] It should be noted that during recent decades, the number of patients undergoing open heart surgery and carrying prosthetic implants has increased. A high proportion of the patients who undergo such operations are critically ill, require prolonged ICU monitoring, and therefore have several of the risk factors for developing nosocomial candidaemia.[11] Most of these patients undergo post-operative splanchnic hypoperfusion, leading to intestinal intramucosal acidosis and increased intestinal mucosal permeability.[12] These patients are also at risk of developing ventilator-associated pneumonia (VAP) requiring antibacterial therapy with associated endotoxaemia, which may damage the intestinal mucosal barrier, thereby favouring *Candida* translocation.[13] Implantation of a contaminated allograft can also occur. All the aforementioned factors might predispose to the spread of *Candida* species into the systemic circulation and development of candidaemia. Thus, the scenario of a patient with a prosthetic heart valve or other intravascular prosthetic device who develops candidaemia is becoming more common.

The risk of developing prosthetic valve endocarditis (PVE) in candidaemic patients with prosthetic heart valves was addressed in a retrospective study by Nasser et al.[8] Overall, *Candida* PVE was documented in 11 of 44 (25%) patients: 7 patients were diagnosed at the same time as candidaemia (group 1), while the remaining 4 (group 2) were diagnosed several weeks after an episode of early postoperative candidaemia. It is noteworthy that in both groups, PVE was diagnosed late after valve replacement (after a mean of 270 days in group 1, and after a mean of 246 days in group 2),[8] suggesting that the episodes had a similar pathogenic mechanism. Thus, *Candida* PVE may be a two-step process: the first step is represented by a post-operative transitory candidaemia occurring during the ICU stay, which leads to colonization of prosthetic valve and subsequent biofilm formation. After the initial colonization, the fungus, slowly growing on the prosthesis surface, becomes less susceptible to antifungal agents. This speculation lends support for pre-emptive antifungal therapy with agents that display antibiofilm activity in patients with prosthetic heart valves who are at risk of candidaemia.

The current Infectious Diseases Society of America (IDSA) guidelines on the treatment of candidiasis recommend intravenous lipid formulation of amphotericin B with or without 5-fluorocytosine, in addition to valve surgery as first-line treatment for *Candida* endocarditis (table I).[14] Recent *in vitro* studies have shown reduced activity of amphotericin B against *Candida* biofilm,[15] and poor penetration into vegetations and blood clots in experimental models of infectious endocarditis,[16] whereas echinocandins, and in particular anidulafungin, display potent *in vitro* activity against sessile *Candida* cells within biofilms,[17,18] and caspofungin has been successfully used in anedoctal cases of *Candida* endocarditis.[9,10] Thus, the echinocandins may have a favourable impact on the management of this infection.

2. Ocular Candidiasis

Contrary to endocarditis, the incidence of ocular candidiasis has been decreasing among inpatients with candidaemia, with recent incidence estimates of less than 2%.[19] It has been suggested that this trend is related to earlier identification and treatment of candidaemia.[20] The clinical presentation may be very indolent, with progression from corioretinitis to vitritis or frank endophthalmitis, especially in patients who are not able to articulate ocular symptoms,[20] and *Candida* endophthalmitis may occur as a late relapsing of candidiasis. Thus, retinal examination is mandatory in all patients with candidaemia and should be repeated after 2 weeks in patients that show no signs of ocular disease at the first fundoscopy. The therapeutic approach includes prolonged treatment with fluconazole or voriconazole (table I). The role of systemic echinocandins might be limited since they achieve undetectable vitreous concentrations. Vitrectomy with local instillation of amphotericin B, azoles or echinocandins may play a role in the treatment of chronic complications such as epiretinal membrane formation.[19,20]

3. CNS and Osteoarticular Infections

Diffuse encephalitis in the setting of candidaemia is very misleading since alterations of the mental status are generally attributed to the candidaemia-associated sepsis syndrome. In addition, neuroimaging studies and cerebrospinal fluid cultures do not usually contribute to diagnosis. These complications worsen an already ominous prognosis.[21,22] Osteomyelitis caused by *Candida* is considered infrequent and, when it does occur, it can usually be traced back to the spinal column. However, in our recent experience of nosocomial non-postneurosurgery spondylodiscitis, we observed 3 (27%) of 11 cases caused by *Candida* species.[23] Optimal management may require surgical debridement and, after initial intravenous antifungal therapy, prolonged administration of oral azoles.

4. Conclusions

The role of *Candida* in endocarditis is fairly well established. With the increasing incidence of *Candida* endocarditis, and the increasing num-

Table I. Infectious Diseases Society of America guidelines for management of endocarditic and localized infections. Adapted from Pappas et al. with permission[14]

Condition	Therapy guidelines
Endocarditis (NVE or PVE)	LFAmB (3–5 mg/kg/day) with or without 5-fluorocytosine (25 mg/kg qid) is recommended. Alternatives include AmB-d (0.6–1.0 mg/kg/day) with or without flucytosine, or an echinocandin[a]. Step-down therapy to fluconazole (400–800 mg [6–12 mg/kg] daily) should be considered for susceptible *Candida* isolates in stable patients with negative blood culture results. Valve replacement is strongly recommended and antifungal treatment should continue for at least 6 weeks after valve replacement. In patients unable to undergo valve replacement, long-term suppression with fluconazole (400–800 mg [6–12 mg/kg] daily) is recommended (lifelong in patients with PVE)
Endophthalmitis	AmB-d (0.7–1.0 mg/kg/day) plus 5-fluorocytosine (25 mg/kg qid) is recommended. Surgical intervention is recommended for patients with severe endophthalmitis or vitreitis. Fluconazole 400–800 mg daily (loading dose of 12 mg/kg, then 6–12 mg/kg daily) is acceptable for less severe endophthalmitis. LFAmB (3–5 mg/kg/day), voriconazole (6 mg/kg q12h for two doses then 3–4 mg/kg q12h) or an echinocandin[b]are alternatives for patients intolerant of or experiencing treatment failure with primary therapy. Duration of therapy is at least 4–6 weeks, as determined by repeat examinations to verify resolution
CNS candidiasis	LFAmB (3–5 mg/kg/day) with or without 5-fluorocytosine (25 mg/kg qid) is recommended for initial several weeks of therapy, followed by fluconazole (400–800 mg [6–12 mg/kg] daily). Treatment should continue until all signs and symptoms, CSF abnormalities and radiologic abnormalities have resolved. Removal of infected ventricular devices is recommended
Osteoarticular infection	
osteomyelitis	Fluconazole (400 mg [6 mg/kg] daily) for 6–12 months or LFAmB (3–5 mg/kg/day) for several weeks followed by fluconazole for 6–12 months. Alternatives include an echinocandin[b]or AmB-d (0.5–1.0 mg/kg) for several weeks followed by fluconazole for 6–12 months. Surgical debridement in selected cases is advised
septic arthritis	Fluconazole (400 mg [6 mg/kg/daily) for at least 6 weeks or LFAmB (3–5 mg/kg/day) for several weeks followed by fluconazole to completion is recommended. Alternatives include an echinocandin[b]or AmB-d (0.5–1.0 mg/kg) for several weeks followed by fluconazole to completion. Surgical debridement is recommended in all cases.

a Echinocandin dosages for endocarditis: anidulafungin 200 mg loading dose, 100–200 mg/day; caspofungin 70 mg loading dose, 50–150 mg/day; micafungin 100–150 mg/day.

b Echinocandin dosages for endophthalmitis and osteoarticular infection: anidulafungin 200 mg loading dose, 100 mg/day; caspofungin 70 mg loading dose, 50 mg/day; micafungin 100 mg/day.

AmB-d = amphotericin B deoxycholate; **CSF** = cerebrospinal fluid; **LFAmB** = lipid formulation of amphotericin B; **NVE** = native valve endocarditis; **PVE** = prosthetic valve endocarditis; **q12h** = every 12 hours; **qid** = four times daily.

bers of patients at risk, there is a need for agents with potent efficacy against *Candida* biofilms. Echinocandins represent a potential therapeutic option in this setting. Antifungal agents may also be of use in the treatment of complications in patients with ocular candidiasis, osteoarticular or CNS infections.

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