# Diagnosis, management and outcome of *Candida* endocarditis

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## Abstract

Limited data exist on *Candida* endocarditis (CE) outcome in the era of new antifungals. As early diagnosis of CE remains difficult, non-culture-based tools need to be evaluated. Through the French prospective MYCENDO study (2005–2007), the overall characteristics and risk factors for death from CE were analysed. The contribution of antigen detection (mannan/anti-mannan antibodies and (1,3)-$\beta$-D-glucans) and molecular tools was evaluated. Among 30 CE cases, 19 were caused by non-*albicans* species. Sixteen patients (53%) had a predisposing cardiac disease, which was a valvular prosthesis in ten (33%). Nine patients (30%) were intravenous drug users; none of them had right-sided CE. Among the 21 patients who were not intravenous drug users, 18 (86%) had healthcare-associated CE. Initial therapy consisted of a combination of antifungals in 12 of 30 patients (40%). Thirteen patients (43%) underwent valve replacement. The median follow-up was 1 year after discharge from hospital (range, 5 months to 4 years) and hospital mortality was 37%. On univariate analysis, patients aged ≥60 years had a higher mortality risk (OR 11, 95% CI 1.2–103.9; p 0.024), whereas intravenous drug use was associated with a lower risk of death (OR 0.12, 95% CI 0.02–0.7; p 0.03). Among 18 patients screened for both serum mannan/anti-mannan antibodies and (1,3)-$\beta$-D-glucans, all had a positive result with at least one of either test at CE diagnosis. Real-time PCR was performed on blood (SeptiFast) in 12 of 18, and this confirmed the blood culture results. In conclusion, CE prognosis remains poor, with a better outcome among younger patients and intravenous drug users. Detection of serum antigens and molecular tools may contribute to earlier CE diagnosis.

**Keywords:** antibody detection, antigen detection, *Candida*, endocarditis, molecular tools
**Original Submission:** 2 October 2011; **Revised Submission:** 3 December 2011; **Accepted:** 3 January 2012
Editor: D. Raoult
**Article published online:** 7 January 2012
*Clin Microbiol Infect* 2012; **18:** E99–E109
10.1111/j.1469-0691.2012.03764.x

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Previous presentation: This work was presented in part at the 49th International Conference on Antimicrobial Agents and Chemotherapy, Clinical Mycology Oral Session, San Francisco, CA, USA, 14 September 2009, presentation number M-1249, and at the 50th International Conference on Antimicrobial Agents and Chemotherapy, Clinical Mycology Poster Session, Boston, MA, USA, 13 September 2010, presentation number M-1073.

## Introduction

*Candida* endocarditis (CE) is rare, accounting for <2% of all infective endocarditis cases [1–3], and complicates candidaemia in up to 17.7% of patients when transoesophageal echocardiography (TEE) is systematically performed (Fernandez Cruz *et al.*, 50th ICAAC, 2010, Abstract K-2172). Previously observed predominantly in intravenous drug users, it now occurs in the healthcare-associated setting, affecting patients at risk for invasive fungal infections [1,2,4–7]. Recent hospital mortality rates are still as high as 30–47% [1,2]. The

most recent guidelines for the treatment of CE recommend an amphotericin B-based or echinocandin-based regimen, with or without flucytosine, followed by fluconazole for susceptible organisms, in combination with valve replacement. If surgery is contraindicated, chronic antifungal suppression is recommended. However, data on the long-term outcome of CE are very scarce, as no large prospective study focusing specifically on CE has yet been conducted. Therefore, the guidelines are mainly based on anecdotal case reports, case series, and clinical experience [8]. We conducted a 27-month prospective study in France to determine the current characteristics, risk factors for death and long-term prognosis of CE, in addition to the diagnostic contribution of fungal antigen detection and molecular tools.

## Materials and Methods

### Clinical sample and data collection

The prospective MYCENDO study on fungal endocarditis was conducted in France between 1 January 2005 and 31 March 2007. Infectious disease, cardiology, internal medicine, intensive-care and paediatric specialists, cardiovascular surgeons and microbiologists of all university and general hospitals were informed about the study by their scientific societies. Anonymous data were collected in centres and then validated by the MYCENDO scientific committee. Diagnostic and therapeutic management of individual cases was performed in each participating hospital according to local recommendations. In addition, all fungal isolates were analysed at the French National Reference Centre for Mycoses and Antifungals (Institut Pasteur, Paris); serum samples were sequentially collected for detection of fungal antigens at the University of Lille, blood samples were collected for detection of fungal DNA at University of East Paris Créteil, and valvular samples were sent to Georges Pompidou Hospital, Paris. Control sera were collected from six patients with definite bacterial endocarditis. The study was approved by the Comité de Protection des Personnes, Hôpital Necker, Paris; #04-10-05, and promoted by the Institut Pasteur.

### Definitions

All patients who met the criteria for definite or possible CE were enrolled [9]. In accordance with previously published criteria [9,10], CE was definite if culture and/or histology of cardiac material or embolic tissue demonstrated *Candida* species, or if there was the combination of persistently positive blood cultures for *Candida* species and evidence of endocardial involvement on echocardiogram; CE was possible in cases where there were positive blood cultures for *Candida* species and a predisposing heart condition, but no evidence of endocardial involvement on the echocardiogram.

The date of CE diagnosis was defined as the day of the first echocardiogram suggestive of endocarditis ($n$ = 29) or the first day of blood culture positivity in a patient with ventricular assist device infection. Median time to diagnosis was the number of days elapsed between the first clinical symptoms of CE and diagnosis.

Cases of CE were classified as either healthcare-associated or community-associated, according to previously defined criteria [11]. The indications for surgery were classified as 'infectious', 'cardiac', or 'embolic' [12].

The portal of entry was determined on the basis of compatible clinical, microbiological and/or radiographic features and the isolation of the same *Candida* species from this presumed source of infection, except for skin, which was considered as the portal of entry in intravenous drug users when no alternative source of infection was found after careful examination. If the clinical data were ambiguous, the portal of entry was categorized as 'undetermined'. Myocardial abscess and pacemaker lead infection were defined as previously reported [13,14].

At the time of death, CE was considered to be 'ongoing' in the presence of otherwise unexplained fever of ≥38°C, persistent positive blood cultures for *Candida* species, new vascular phenomena [9], and/or the persistence of other major criteria [9]. Otherwise, it was considered to be 'controlled'.

### Mycological methods

*Species identification and antifungal susceptibility determination.* All isolates were identified to the species level by the use of carbon assimilation profiles (ID32C; Biomérieux, Marcy-l'Etoile, France). *In vitro* susceptibility testing was performed according to EUCAST procedures [15]. Fluconazole, voriconazole, flucytosine, caspofungin [16] and amphotericin B were tested as previously described [17,18]. The thresholds defined by EUCAST were used for fluconazole [19] and voriconazole [20]. MICs ≥8 mg/L were considered to be high for flucytosine [21].

*Detection of serum (1,3)-β-D-glucans.* Serum samples were diluted in glucan-free reagent-grade water (Fungitell assay; Associates of Cape Cod, Falmouth, MA, USA). Interpretation of (1,3)-β-D-glucan values was as follows: <60 pg/mL, negative; 60–79 pg/mL, indeterminate; >80 pg/mL, positive.

*Detection of serum mannan and anti-mannan antibodies.* Mannan and anti-mannan antibodies were measured with commercialized tests (Platelia Candida Ag and Ab; Bio-Rad, Marne-la-Coquette, France) [22]. The cut-offs were those