Candidaemia after heart valve replacement surgery: recurrence as prosthetic valve endocarditis is an expected over one-year complication

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Sir,

We read with interest the article on risk factors for late recurrent candidaemia by Muñoz *et al.* [1]. The authors conclude that episodes of recurrent candidaemia within the first 3 months could be attributable to an intravascular source of infection as opposed to an intra-abdominal origin for those occurring later.

We noted that the clinical course of patient no. 4 included in Muñoz series refers to a late-onset prosthetic valve endocarditis (PVE) due to *Candida parapsilosis* diagnosed 1-year after prosthetic valve implantation. In particular, the patient was initially treated with 3 weeks of amphotericin B and fluconazole for two episodes of post-operative *C. parapsilosis* candidaemia, and was then discharged without evidence of endocarditis at trans-oesophageal echocardiography. The patient was re-admitted 1 year later with signs and symptoms of septic shock due to a *C. parapsilosis* PVE and died 1 week after admission; importantly, the isolates belonged to the same genotype [1].

In 1974 Seelig *et al.* [2] reported the clinical features of two patients who presented *Candida* bloodstream infection within 1 month from prosthesis implantation and developed a *Candida* PVE, due to the same species, after 13 and 15 months. Interestingly, during recent years we have observed four patients who showed the same clinical characteristics as the cases reported by Seelig *et al.* [2] and Muñoz *et al.* [1]: three were previously reported by our study group [3], and one was presented by one of us (AP) at the National Congress of the Italian Society of Internal Medicine [4]. All of these patients developed an early candidaemia after prosthetic valve implantation without trans-oesophageal echocardiographic evidence of heart valve involvement; in a mean time of approximately 380 days these patients were readmitted to hospital with a diagnosis of PVE due to the same pathogen detected during the first episode of candidaemia.

The risk of developing a late PVE in candidaemic patients with prosthetic heart valves was addressed in a retrospective study by Nasser *et al.* [5]. Overall, *Candida* PVE was documented in 11 of 44 (25%) patients: seven were diagnosed at the same time as candidaemia (group 2), whereas the remaining four (group 3) were diagnosed several months after an episode of early postoperative candidaemia. Reviewing these data, we noted that in both groups, PVE was diagnosed late after valve replacement (after a mean of 270 days in group 2, and after a mean of 232 days in group 3), and this suggests that all the episodes probably had a similar pathogenic mechanism. We can speculate that in the patients of group 2 an early postoperative candidaemia may pass microbiologically undetected, but might lead to colonization of the prosthetic valve with clinical and pathological evidence of PVE only several weeks after the initial episode of candidaemia. Similarly, patients of group 3, who developed a documented early postoperative candidaemia, were diagnosed as having a PVE only several months later, when the endocardial infection was clinically evident. Then, development of *Candida* PVE may be a two-step process comprising a post-operative candidaemia occurring during the hospital stay with probable colonization of the prosthetic valve, and a subsequent biofilm formation with progressive tissue invasion. The clinical syndrome consistent with an endocarditis develops late in the course of the infection, often several months after initial candidaemia, when vegetations reach sizes that allow trans-oesophageal echocardiography visualization and/or septic embolization.

Post-surgery candidaemia is a relatively frequent complication during heart valve replacement, especially in patients who require more than 48 h of mechanical ventilation [6]. In particular, Michalopoulos *et al.* reported that a cardiopulmonary bypass procedure of duration >120 min was associated with an increased risk of candidaemia and candidaemia-related death [7]. Notably, Nasser *et al.* reported a mortality rate of 69% in the first 2 months and of 83% after 1 year in patients who developed a transient post-surgical candidaemia without evidence of early PVE (group 1) [5]; Pasero *et al.* [6]

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confirmed a higher mortality (47%) in patients with post-operative candidaemia 2 months after cardiac surgery, compared with patients who did not develop candidaemia. Probably, we can hypothesize that high rates of mortality in the first months after candidaemia could explain the low incidence of patients developing a late PVE over 1-year after post-surgical candidaemia. Based on the aforementioned, post-surgery candidaemia in patients with prosthetic valve replacement should be considered at high risk of over 1-year recurrence as PVE.

Lefort *et al.* reported 100% sensitivity of the serum (1→3)-β-D-glucan test in patients with *Candida* endocarditis, also in the presence of negative trans-oesophageal echocardiography [8]. We speculate that, after post-surgical candidaemia, detection of persistently high levels of serum (1→3)-β-D-glucan, despite apparent *Candida* clearance from blood under antifungal therapy, should prompt early suspicion of PVE.

In conclusion, candidaemia after heart valve replacement is a strong predictor of late PVE, even >1 year after the first episode of infection: under this circumstance, patients should be strictly monitored with a prolonged follow up.

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Transparency Declaration

The authors have not conflicts of interest to declare.

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