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A prospective analysis of invasive candidiasis following cardiac surgery: Severity markers are predictive

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Summary *Aim:* Invasive *Candida* infections (ICI) in intensive care unit (ICU) patients are associated with high mortality. A 2-year prospective study was performed to improve clinical decision making in long-term ICU patients after cardiac surgery.
Methods: Demographic, clinical and physiological data, the incidence of ICI and *Candida* colonisation scores were analysed. To assess severity of illness the new simplified acute physiology score (SAPS II score), the European system for cardiac operative risk evaluation (EuroSCORE) and the sequential organ failure assessment (SOFA) score were calculated. To define independent risk factors univariate and multivariate Cox-regression analyses with time-dependent covariates were calculated.
Results: One hundred and sixty-nine cardiac surgery patients with ICU admittance $\geq$4 days out of 513 admittances were enrolled. Ten patients had proven ICI. In the multivariate analysis the SOFA score (HR = 1.29, $p = 0.009$) was associated with proven ICI. In 71 patients receiving empiric antifungal therapy for presumptive but unproven ICI the SOFA score (HR = 1.18, $p = 0.029$) and corrected *Candida* colonisation index (HR 11.08; $p = 0.030$) were significantly associated to ICI. Neither SAPS II score nor EuroScore were associated with ICI in

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either patient group. The mortality rate of patients receiving empiric antifungal therapy was significantly lower compared to that of patients with proven ICI (36.6% vs. 80%, respectively). *Conclusion:* Time-associated SOFA score assessing acute organ failure was the only independent risk factor for proven ICI. Cardiovascular procedures did not confer risk to develop ICI. Empiric antifungal therapy may be warranted in severely ill cardiac surgery patients.

The incidence of invasive *Candida* infections (ICI) in seriously ill patients requiring long-term admittance at intensive care units (ICU) has substantially increased in the last decade.[1–3] The frequency of ICI may be underestimated because candidaemia is reported to occur in 50% of patients with ICI only.[4] Thus, the start of antifungal therapy may be delayed, and this delay may lead to increased mortality.[5,6] In the absence of rapid diagnostic methods, diagnosis of presumptive ICI and decision to start adequate antifungal therapy is often based on the patient's clinical presentation, the presence of risk factors and *Candida* colonisation.

Risk factors reported to predict ICI in ICU patients without neutropenia are abundant and include severe underlying disease, organ failure, prolonged ICU admittance, major surgery, mechanical ventilation, hemodialysis, severe sepsis, invasive therapeutic procedures, central venous catheters, parenteral nutrition and many others.[2,7,8] As extensive colonisation with *Candida* spp. preceded invasive infection a *Candida* colonisation index was proposed to quantify fungal colonisation in high risk surgical ICU patients.[9] A *Candida* score based on four parameters including severe sepsis, preceding surgery, total parenteral nutrition, and *Candida* colonization was proposed to identify patients with high risk of ICI in a mixed ICU patient population.[10,11] However, cardiac surgery differs from general surgery because of cardiopulmonary bypass, an overall longer duration of surgery and mandatory invasive monitoring. ICI in cardiac surgery patients were investigated in case-control studies and multi-centre studies, but risk factors for ICI differ within these studies.[12–14]

To improve the management of ICI and define patients at risk to receive antifungal therapy we performed a 2-year single-center study in patients admitted to the ICU for at least 4 days after cardiac surgery. The goals were to identify the frequency of ICI, to evaluate the severity scoring systems used in the ICU, *Candida* colonisation scores and other clinical and physiological parameters for risk prediction of ICI in this particular patient population.

Material and methods

Study location and patients

The study was conducted prospectively at the University Hospital of Vienna from December 2006 until December 2008. The study was approved by the Ethics Review Committee of The Medical University of Vienna (EC No. 510/2006). According to the committee's directives informed consent was obtained from all surviving patients enrolled.

Study design and data collection

During the 2-years period overall 513 patients were admitted to the cardiothoracic ICU, 201 patients were admitted for at least 4 days: of these, 169 patients who had undergone cardiac surgery with use of heart–lung machine were consecutively enrolled into the prospective study. Patients' data were collected including basic demographic data, the primary cardiac surgery, the length of this procedure, the number of redo surgeries, days of the ICU stay, use of systemic steroids or other immunosuppressive drugs, parenteral nutrition, mechanical ventilation, presence of persistent or recurrent fever at least four days after any surgical procedure, bacteraemia, continuous venovenous haemofiltration, and ICU mortality. For severity of illness the new simplified acute physiology score (SAPS II score) at the admittance to ICU,[15] the European system for cardiac operative risk evaluation (EuroSCORE) before surgery[16] and initial, maximum and course of the sequential organ failure assessment (SOFA) score during the whole course of the admittance were recorded.[17]

Definitions

Proven invasive candidiasis was defined according to the IFSIG/EORTC criteria. Proven invasive Candida infection was defined as: (1) *Candida species* were isolated in blood cultures, (2) if *Candida* spp. were recovered in culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site and showing clinical or radiological abnormality consistent with an infectious disease process, or (3) detection of *Candida* spp. showing pseudohyphae or true hyphae in histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes).[18]

Candidaemia was defined as isolation of *Candida* spp. plus clinical signs and sepsis. Bacteraemia was defined as isolation of any bacterial pathogen plus clinical signs and sepsis. Severe sepsis was defined according to Bone's sepsis criteria.[19]

Thirty-day mortality was defined as the patient's death within 30 days after admittance to the ICU.

Presumptive ICI was defined in accordance to general perception of the clinical signs and symptoms of ICI in our institution: the presence of clinical sepsis without response to broad spectrum antibiotics treatment and the presence of risk factors suggestive for ICI (central vascular lines, parenteral nutrition, immunosuppression etc.), but without growth of *Candida* spp. in blood cultures or any other relevant material (aspiration of sterile material), the absence