Institutional report - Cardiac general

Candidemia after cardiac surgery in the intensive care unit: an observational study

Daniela Pasero[a],*, Francesco Giuseppe De Rosa[b], Nerlep Kaur Rana[a], Lucina Fossati[c], Alessandra Davi[a], Mauro Rinaldi[d], Giovanni Di Perri[b], V. Marco Ranieri[a]

[a]Department of Anesthesia and Intensive Care Medicine, San Giovanni Battista Hospital, University of Turin, Corso Dogliotti 14, 10126 Turin, Italy
[b]Department of Infectious Diseases, Amedeo di Savoia Hospital, University of Turin, Turin, Italy
[c]Laboratory of Microbiology, San Giovanni Battista Hospital, Turin, Italy
[d]Department of Thoracic and Cardiovascular, San Giovanni Battista Hospital, University of Turin, Turin, Italy

Abstract

Candidemia is a well-recognized complication of hospital stay, especially in critically ill patients. There is not a general consensus that predictors for candidemia in cardiosurgical intensive care unit (cICU) are different from a general ICU and it has been reported that cardiopulmonary bypass time is a specific risk factor in the cICU. We performed a prospective study to evaluate the main predictors for candidemia in patients admitted to the cICU. Included patients were adults admitted between July 2005 and December 2007 with an ICU-length of stay (ICU-LOS) $\geq$48 hours after cardiac surgery. Exclusion criteria were solid organ or bone marrow transplants, previous diagnosis of candidemia or other invasive infections and ICU stay before surgery. A multiple regression analysis was performed to identify the risk factors. Among 1955 patients admitted to the cICU, 345 were enrolled. Only 26 patients (1.3%) had candidemia after an ICU-LOS of 20 days (inter-quartile range, IQR 8–49 days). Total parenteral nutrition [odds ratio (OR)=9.56; confidence interval (CI)=1.741–52.534], severe sepsis (OR=4.20; CI=1.292–13.667), simplified acute physiology score II (OR=1.16; CI=1.052–1.278) and ICU-LOS >20 days (OR=6.38; CI=1.971–20.660) were independent predictors of candidemia. Patients undergoing cardiac surgery developed candidemia late after cICU admission and the independent predictors were similar to the general ICU.
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Keywords: Candidemia; Cardiac surgery; Cardiopulmonary bypass

1. Introduction

The diagnosis of candidemia in the intensive care unit (ICU) has increased five-fold in the last 10 years and it is currently between the fourth and the sixth most common nosocomial bloodstream infection (BSI) both in the USA and European ICU [1]. In European cardiothoracic ICUs *Candida* spp. is the fourth isolate with an incidence of 7.7/1000 admissions with an attributable mortality of 40–50% [2], an extended length of hospital stay [1] and increased costs of medical care [3]. Several risk factors for invasive candidiasis in the adult intensive care settings have been evaluated: ICU-length of stay (LOS) longer than 10 days, diabetes mellitus, renal failure and hemodialysis, broad spectrum antibiotics, central venous catheter, immunosuppressive drugs, cancer and chemotherapy, severe acute pancreatitis, candida colonization at multiple sites, solid organ or bone marrow transplantation [4, 5].

Recently, a bedside candida score have been evaluated [surgery, sepsis, multifocal colonization, total parenteral nutrition (TPN)], in order to select patients eligible for early antifungal treatment [6].

In cardiac surgery ICU (cICU) only ongoing invasive mechanical ventilation (MV) >10 days, BSI caused by bacteria, cardiopulmonary bypass (CPB) $\geq$120 min and diabetes mellitus represented independent predictors of candidemia. Hypoperfusion due to prolonged CPB and subsequent mucosal barrier damage, enhanced by metabolic syndrome and sepsis, may increase intestinal mucosal permeability and promote bacterial translocation [2, 7].

The main objective of this study was to investigate the risk factors for candidemia in a cICU and whether specific risk factors correlated to cardiac surgery were present.

2. Materials and methods

We conducted a prospective observational study between July 2005 and December 2007 in the cICU of San Giovanni Battista-Molinette Hospital in Turin, Italy, a 1200-bed academic primary and secondary referral hospital. An institutional Ethic Committee approved the research protocol and informed consent was not required since the study was observational and mandated no deviations from routine medical practice.

*Corresponding author. Tel.: +39 011 6335513; fax: +39 011 6960448.
E-mail address: daniela.pasero@unito.it (D. Pasero).

2.1. Study population

Included patients were admitted to the cICU for ≥ 48 hours. Exclusion criteria were solid organ or bone marrow transplant, previous diagnosis of candidemia or other invasive infections and ICU stay before surgery. The data recorded for each patient included [2]: age, gender, type of intervention, co-morbidities, coronary artery disease, left ventricular ejection fraction (LVEF) <30%, CPB and aortic cross-clamp time, MV ≥ 10 days, BSI, severe sepsis, administration of ≥ 2 broad spectrum antibiotics, TPN, renal replacement therapy (RRT), ICU-LOS. The amount of antibiotic used was calculated with the daily-defined dose (DDD) for each patient, according to the World Health Organization definition [8].

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) [9] and the Simplified Acute Physiology Score II (SAPS II) [10] were calculated for each patient to assess the operative risk for cardiac intervention and the severity of illness at the ICU admission, respectively.

Diagnosis of candidemia was made with ≥ 1 positive blood culture for *Candida* spp. either from a central venous catheter or a peripheral vein [2]. All patients were treated according to the guidelines, with removal of all intravenous and arterial catheters and administration of antifungal therapy by the attending physician and were followed for 30 days.

The selection of variables, to assess the risk factors for candidemia with the multivariate analysis, were performed based on previous published data [2]: age, hypertension, diabetes mellitus, vascular disease, chronic obstructive pulmonary disease, RRT, low LVEF, re-intervention, CPB, broad spectrum antibiotics, blood stream infections, TPN, MV >10 days, prolonged ICU stay. We excluded central venous line, because all our patients had one until the discharge from the ICU.

2.2. Outcome assessment

Ventilator free days (VFD) were calculated as 28 days less the time on MV and patients who died before were considered as having VFD=0. ICU-LOS was calculated up to 28 days and patients who died before were considered as having the maximum value. We calculated survival rate at 30 and 60 days from cICU admission. We performed a multivariate analysis with a Cox model to evaluate candida-related death. We included all variables that could be responsible for increase risk of death in this kind of patient, according to previous published data [9].

2.3. Statistical analysis

Continuous data were expressed as mean$\pm$S.D. or median and inter-quartile range (IQR). Comparison of continuous and categorical data between groups were performed using the unpaired Student's t-test or Mann–Whitney U and χ^2 or Fisher's exact test, respectively, and were considered significant for $P<0.05$.

To assess independently risk factors of candidemia, a logistic regression model was created and all variables were included into the model when clinically meaningful and a forward stepwise logistic regression analysis was performed to identify the strongest predictors. A significant level for odds ratio estimation was $P\leq0.05$. Model validation was assessed with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Kaplan–Meier survival analysis was done to compare survival between the two groups stratified by candidemia. Curves were compared by means of the log rank test. To estimate the effect of candidemia on mortality after the adjustment for other explanatory variables, a Cox regression model has been created, giving the hazard ratio (HR) of death of each variable (16.0.2, SPSS, Chicago, IL, USA).

3. Results

Among 1955 patients admitted to the cardiac ICU, 349 met the selection criteria (Fig. 1) and 26 (1.3%) developed candidemia. Median time from the ICU admission to the diagnosis was 20 days (IQR 8–49 days). The pathogen isolated more frequently on blood samples was *Candida albicans*, $n=19$ (73%), followed by *C. glabrata*, $n=4$ (15%), *C. krusei*, $n=2$ (8%), and *C. tropicalis*, $n=1$ (4%).

The main results are shown in Table 1. There were no significant differences per gender, co-morbidities, low LVEF and specific cardiac surgery data, such as off-pump surgery, need for re-intervention and CPB time. Patients with candidemia had significantly more renal dysfunction compared to the control group, higher perioperative risk according to EuroSCORE, higher SAPS II, bacteremia, severe sepsis, TPN, RRT, MV ≥ 10 days and ICU-LOS >20 days. There was significantly higher administration of $\geq$ two antibiotics for ≥ 72 hours with statistically significant differences on the daily defense doses (DDDs) of wide spectrum antibiotics, such as meropenem and piperacillin-tazobactam.

A forward logistic regression analysis selected TPN, severe sepsis, SAPS II score and an ICU-LOS ≥ 20 days as independent predictive factors of candidemia. The model was validated with the evaluation of sensitivity, specificity, PPV and NPV tests (Table 2).

3.1. Outcome variables

Patients who developed candidemia had significantly longer MV (VFD: 24 ± 6 vs. 4 ± 9 days, $P<0.001$) and a longer ICU-LOS (21 ± 7 vs. 2 ± 4 days, $P<0.001$) compared to the control group. The mortality rate at 30 days was 31% (8/26), in the Candida group compared to 13% (43/323) in the control group ($P<0.02$) and increased dramatically after 60 days from the cardiac intervention, 47% (12/26) compared to 14% (44/323), in the control group ($P<0.001$). The Kaplan–Meier curve showed a significant higher mortality in the Candida group (Fig. 2).

The Cox regression analysis showed a significant HR for death in the female gender, acute myocardial infarction (AMI) <90 days and dialysis. The hazard ratio (HR) of candidemia was not significant and it was <1, with a 95% confidence interval that included 1 (Table 3).

4. Discussion

The incidence of invasive infections from *Candida* spp. has increased dramatically in the last three decades in the ICU setting with an increased percent of *C. non-albicans*.
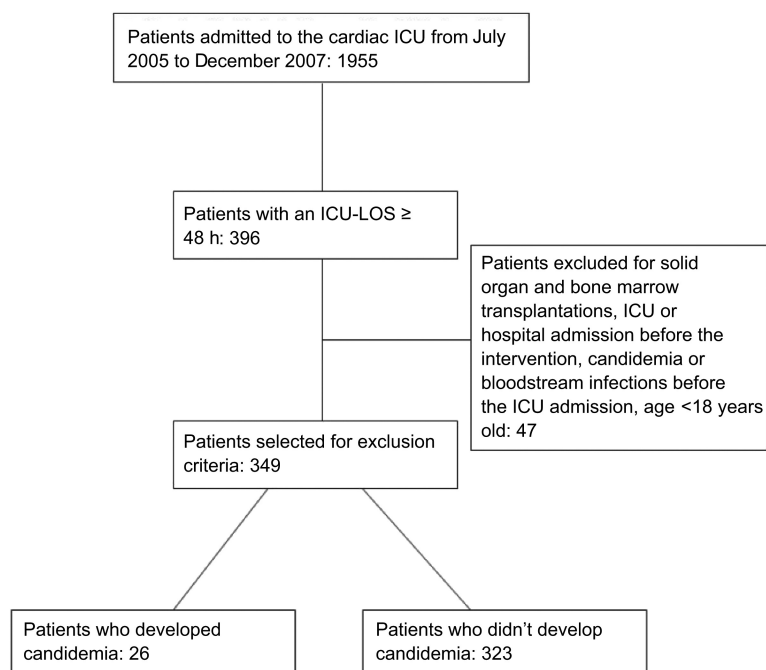
Fig. 1. The flow diagram showed patients admitted to the cardiac ICU and selected for ICU-LOS >48 hours and exclusions criteria. ICU-LOS, intensive care unit-length of stay.

In cICU *C. albicans* is still prevalent (70%), with an overall incidence of candidemia of 7.7/1000 admissions [2]. Our epidemiological data are similar with a prevalence of *C. albicans* of 73% but with a higher incidence of 13/1000 admissions, in a setting with low empiric use of fluconazole.

It has been widely described that prolonged ICU stay represents the single most important risk factor in critically ill patients. Several studies have showed that the incidence of candidemia peaks around day 10, while other studies reported an increase of Candida colonization and invasive

Table 1. Demographic and perioperative data

	Candida group (*n*=26)	Control group (*n*=323)	*P*-value
Age, years, mean±S.D.	60±21	67±16	0.05[a]
Gender, *n*, M/F	16/10	211/112	0.69[b]
EuroSCORE, mean±S.D.	10.5±3.9	7.9±4.1	0.002[a]
SAPS II, mean±S.D.	29.5±12	18.5±4.3	<0.001[a]
Hypertension, *n* (%)	17 (65)	188 (58)	0.47[b]
Smoke, *n* (%)	9 (35)	81 (25)	0.35[b]
Diabetes, *n* (%)	6 (31)	62 (19)	0.18[b]
Coronary heart disease, *n* (%)	12 (63)	133 (41)	0.4[b]
EF <30%, *n* (%)	2 (8)	30 (9)	1.0[b]
Creatinine >2, *n* (%)	9 (35)	46 (14)	0.01[b]
Re-intervention, *n* (%)	4 (15)	59 (18)	0.7[b]
Off-pump surgery, *n* (%)	0	13 (4)	0.6[b]
CPB >120 min, *n* (%)	19 (79)	201 (63)	0.2[b]
CPB, min, mean±S.D.	178±100	149±76	0.08[a]
AC, min, mean±S.D.	106±68	91±45	0.12[a]
RRT, *n* (%)	17 (65)	60 (18)	<0.001[b]
Batteremia, *n* (%)	23 (88)	56 (17)	<0.001[b]
Severe sepsis, *n* (%)	18 (69)	8 (6)	<0.001[b]
TPN, *n* (%)	23 (88)	112 (35)	<0.001[b]
>2 ATB, 72 h, *n* (%)	23 (88)	65 (20)	<0.001[b]
Meropenem, DDD, median (IQR)	5 (0–19)	0 (0–23)	<0.001[c]
Piperacillin/tazobactam DDD, median (IQR)	3.65 (0–25)	1 (0–16)	0.02[c]
Vancomycin, DDD, median (IQR)	0.25 (0–14)	0 (0–8)	<0.001[c]
ICU-LOS >20 days, *n* (%)	20 (77)	26 (8)	<0.001[b]
Mechanical ventilation >10 days, *n* (%)	22 (85)	41 (13)	<0.001[b]

[a]Unpaired *t*-test; [b]χ² or Fisher's exact test; [c]Mann–Whitney test. S.D., standard deviation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; SAPS II, Simplified Acute Physiology Score II; EF, ejection fraction; CPB, cardiopulmonary bypass; AC, aortic clamping; RRT, renal replacement therapy; TPN, total parenteral nutrition; ATB, antibiotics; DDD, daily-defined dose; IQR, inter-quartile range; ICU-LOS, intensive care unit-length of stay; *n*, number.

Table 2. Logistic regression analysis and validation of the independent predictive factors with sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV)

	OR (95% CI)	*P*-value	Sensibility	Specificity	PPV	NPV
ICU-LOS >20 days	6.38 (1.971–20.660)	0.002	77	92	43	98
TPN	9.565 (1.741–52.534)	0.009	88	65	17	98
Severe sepsis	4.201 (1.292–13.667)	0.017	69	94	49	97
SAPS II	1.159 (1.052–1.278)	0.003				

OR, odds ratio; CI, confidence interval; ICU-LOS, intensive care unit-length of stay; TPN, total parenteral nutrition; SAPS II, Simplified Acute Physiology Score II.

disease after eight days [11, 12]. Recent data did not confirm these results in a cICU, where an ICU stay >9 days was significantly higher in patients with candidemia without representing a risk factor [2].

Our data showed that after cardiac surgery patients developed candidemia later during the cICU stay, around day 20, compared to other available data for a general ICU [11, 12], while a shorter LOS dramatically reduced the diagnosis of candidemia, confirming that probably only the most severe and complicated patients are at risk of invasive candidemia [13]. The question is whether specific risk factors of cardiosurgery may be highlighted as Michalopoulos et al. reported that CPB >120 min was significantly associated with the development of candidemia [2].

Our results do not support these findings and do not confirm that a higher CPB time is associated with candidemia but strongly suggest the role of general and well-known ICU risk factors. We should mention, however, that in our study only patients with an ICU stay ≥48 hours were included while Michalopoulos et al. studied all patients undergoing cardiac surgery [2].

A delay in the antifungal treatment dramatically increases mortality in patients with candidemia [14]. Therefore, a recent bedside scoring system has been developed for the early identification of non-neutropenic critically ill patients with the weighted scoring of severe sepsis, major surgery, TPN and Candida colonization [6]. Although we could not use the colonization index we found that severe sepsis and TPN were strong predictors of candidemia and avoiding

TPN, as demonstrated by the high NPV and the low PPV, is highly protective.

Several authors showed a dramatic increase of mortality in critically ill patients with candidemia, ranging from 31 to 57% [13–15]. In the present study the absolute mortality in the Candida group was 31% and 47% after 30 and 60 days from cICU admission, respectively, and this was significantly higher compared to the control group.

Even though the survival rate, at 60 days after cardiac intervention, was significantly reduced in the Candida group, candidemia did not represent a variable that increases the risk of mortality in our cICU after cardiac surgery, while being a male and avoiding recent AMI and dialysis reduces the risk of mortality after 60 days from cardiac surgery. These variables are a confirmation that EuroSCORE still remains the strongest method to predict mortality in cardiac surgery patients.

These results could suggest that candidemia is not a frequent event in this kind of population, but it is expression of severity of these ICU patients and it is not a variable that increases the risk of death.

Table 3. Multivariate analysis of 60-day survival by a Cox regression model

	HR	95% CI	*P*-value
Gender (M/F)	0.252	0.134–0.474	<0.001
Age, years	0.994	0.977–1.012	0.537
Co-morbidities			
Hypertension	1.001	0.549–1.825	0.997
Diabetes	1.452	0.650–3.240	0.363
Cerebrovascular diseases	1.546	0.342–6.982	0.571
Vascular diseases	0.615	0.288–1.315	0.210
COPD	0.849	0.393–1.836	0.678
Creatinine >2 mg/dl	1.040	0.484–2.233	0.920
Cardiac function variables			
AMI <90 days	0.333	0.125–0.890	0.028
EF <30%	1.177	0.376–3.686	0.779
IABP	0.885	0.340–2.303	0.802
Intraoperative variables			
CPB >120 min	0.937	0.495–1.771	0.841
Re-intervention	1.548	0.605–3.964	0.362
Postoperative variables			
Dialysis	0.142	0.071–0.283	<0.001
ICU-LOS >20 days	1.974	0.754–5.172	0.166
MV >10 days	0.455	0.166–1.247	0.126
Candidemia	0.611	0.227–1.641	0.328
Severe sepsis	1.266	0.450–3.565	0.655
TPN	1.585	0.781–3.216	0.202
>2 ATB, 72 h	0.909	0.371–2.227	0.835

HR, hazard ratio; 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass; ICU-LOS, intensive care unit-length of stay; MV, mechanical ventilation; TPN, total parenteral nutrition; ATB, antibiotics.
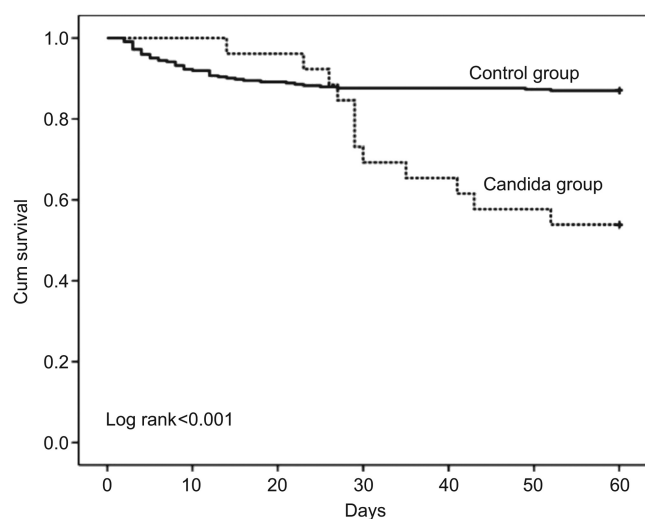

Fig. 2. The Kaplan–Meier curve showed a significant higher mortality in the Candida group. Control group is the black continuous line; Candida group is the black dotted line.

In conclusion, patients undergoing cardiac surgery developed candidemia late after cICU admission and the independent predictors were similar to the general ICU population.

We may need lager multicenter trials to confirm these results and rule out any effect from cardiac surgery factors.

Acknowledgements

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