Clinical Score of Candidemia in medical non-neutropenic, non-ICU Patients.

Hospital Universitario San Cecilio

P-774

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ABSTRACT

Background: Candida species are the leading cause of invasive fungal infections in hospitalized patients and are the fourth most common isolates recovered from patients with bloodstream infection. Few data exist on risk factors for candidemia in non-ICU patients, so we performed a population based case-control study of patients with candidemia to evaluate the main predictors for candidemia in non-ICU patients.

Methods: This retrospective, multicenter study included all non-neutropenic, non-surgical and non-ICU adult patients with candidemia between January 2006 and January 2011. Cases and controls were identified using laboratory records. Patient with positive, non-candidal blood culture obtained at the same day were selected as controls. Patients were matched according to hospital ward, age and clinical characteristics. A multiple regression analysis was performed to identify the risk factors

Results: We identified 60 patients with candidemia. Median age was 67 years (25-90). Most patients were male (35; 58%). *Candida albicans* was the most frequent specie (29 cases; 48%) followed by *C. parapsilosis* (13 cases; 22%). Time to positivity was significantly shorter in patients with bacteraemia tan in those with candidemia (10,2±14 days vs 17,6±14,1 days; p=0,043). Mortality rate was significantly higher for patients with candidemia than that for patients with bacteraemia [22/60, (37%) vs. 12/60 (18%); p=0,04. OR 2,57 (95%CI 1,11-5,96)].

Univariated analysis identified prior use of antibiotics (p<0,001; OR 9,34 95%CI 3,6-23,8), total parenteral nutrition (p=0,014; OR 3,37 95%CI, 1,29-8,77), central venous catheter (p=0,033; OR 2,4 95%CI 1,09-5,29) and subcutaneous implantable devices, (p=0,025; OR 4,58 95%CI 1,22-17,2). In multivariate analysis factors independently associated with candidemia included were prior use of antibiotics [p<0,001; Exp(B): 9,26; (95%CI 3,52-24,39)], central venous catheter [p=0,032; Exp(B): 2,36; (95%CI 1,22-16,83)] and presence of subcutaneous implantable devices [p=0,045; Exp(B): 4,52; (95%CI 1,12-19,6)]. Predicted probability of having various combinations of the aforementioned factors ranged from 12% to 45%.

Conclusion: Crude mortality was 37% highlighting the need for prompt identification and initiation of therapy in these patients. We identify a set of easily determinable independent predictors of the occurrence of candidemia in non-ICU patients. Our results provide a rationale for initiating early antifungal treatment in high-risk non-ICU patients.

INTRODUCTION

- The incidence of candidemia has increased significantly in the preceding 10-20 years, and *Candida* spp has become the fourth most common pathogen isolated in blood cultures in US **(1)** and one of the ten most frequently isolated pathogenesis in Europe **(2)**.
- Candidemia is a life-threatening infection with crude mortality rates above 40% in most studies **(3)**. In addition, delayed treatment is associated with an increased of mortality as high as two-fold increase with only 24 hours delay **(4)**. Despite this well known characteristics, up to 70% of patients with candidemia do not receive empirical antifungal therapy within 24h of the time the blood sample is obtained for culture **(5)**.
- Because of the increase frequency and mortality among non-neutropenic patients with invasive candidiasis several authors have developed predictive scores to identify patients at higher risk. Particularly useful is the candida score **(6)**, however no predictive scores exists for non-neutropenic, non-ICU patients who are at risk for invasive candidiasis, so we aimed to identify some factors that could aid in the early identification of such patients at risk for candidiasis.

PATIENTS AND METHODS

Study population and design

- This was a retrospective, case-control, multicenter study. Data were obtained through retrospective study of patients charts. Data were recorded using case-report forms designed specifically for this study.
- All medical non-ICU, non-neutropenic patients aged 18 years or older with diagnosis of candidemia during the period January 2006-January 2012 were included.
- Patients with positive non candidal blood culture obtained the same day (±2 days) served as controls for risk factor identification. Patients were matched according to hospital demographic characteristics.

Statistical analysis

- Univariate analysis were used to asses the relationship between the presence and absence of each individual factor and subsequent development of candidemia.
- Statistically significant variables in the univariate analysis were included in the model, and through a stepwise elimination process a score was obtained. The crude odds ratio (OR) for each risk factor associated with candidemia was estimated and was weighed to fit in the model.

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RESULTS

- Seventy medical non-ICU non-neutropenic patients with candidemia were identified and matched against 70 controls (medical non-neutropenic non-ICU patients with bacteraemia).
- Although *Candida albicans* was the most frequent species isolated (47%; 33/70) non-abicans species taken altogether were more frequent in our cohort (37 vs 33 isolates). Among non-albicans, *C. parapsilosis* (22,8%; 16/70) and *C. glabrata* (18,5%; 13/70) were 2nd and 3rd most frequent isolates recovered. We did not have any *C. krusei* candidemia.
- Crude mortality was significantly higher in patients with candidemia than in those with bacteraemia, [35,7% (25/70) vs 20% (14/70; 20%), p=0,038; OR: 1,78 CI95% 1,12-2,45].
- Final model identified total parenteral nutrition, central venous catheter, prior antibiotic therapy and presence of candiduria as independent predictors of candidemia, being previous antibiotic therapy the strongest predictor.
- Probability of having candidemia ranged from 11% with only one risk factor to 52% with 4 risk factors. A weighed score is currently under development and validation

Table 1. Demographic characteristics of patients

	Cases n=70	Controls n=70	Univariate analysis	
			OR (95 CI)	p
Sex (male)	42 (60)	38 (54,2)	--	ns
Age (mean, SD)	63,2 (2,1)	67,6 (2,2)		ns
Diabetes	14 (20)	23 (32,8)	--	ns
Renal failure	18 (25)	15 (21,4)	--	ns
Steroids	21 (30)	16 (22,8)	--	ns
Cancer	30 (42,8)	27 (38,5)	--	ns
HIV	6 (8,5)	5 (7,1)	--	ns
Immune suppression	4 (5,7)	3 (4,2)	--	ns
TTP (mean, SD)	**17,6 (1,8)**	**12,2 (1,7)**		**0,04**
Prior ATBs	**62 (88,5)**	**30 (42,8)**	**1,97 (1,46-2,66)**	**<0,001**
Prior antifungal	10 (14,2)	5 (7,1)	--	ns
TPN	**22 (31,2)**	**8 (11,4)**	**2,62 (1,19-5,76)**	**0,014**
CVC	**30 (42,8)**	**16 (22,8)**	**1,79 (1,04-3,08)**	**0,033**
sc vascular device	**14 (20)**	**4 (5,7)**	**3,86 (1,15-13)**	**0,025**
NGT	18 (25)	17 (24,2)	--	ns
Vesical catheter	39 (55,7)	28 (40)	--	ns
Abdominal surgery	6(8,5)	4 (5,7)	--	ns
Candiduria	**19 (27,1)**	**3 (4,2)**	**5,55 (1,3-23,6)**	**0,01**
CRP (mean, SD)	6,4 (1,6)	5,8 (1,9)	--	ns
Leukocytes (mean, SD)	**8,499 (724)**	**11,262 (1,037)**		**0,032**
Mortality	**25 (35,7)**	**14 (20)**	**1,78 (1,12-2,45)**	**0,038**

Results are expressed as **number (%)**, unless otherwise indicated.
Steroids: > 10 mg/day or > 200 mg prior month. **TTP**: Time to positivity of blood culture. **TPN**: Total parenteral nutrition. **CVC**: central venous catheter. **sc vascular device**: totally implantable central venous access device. **NGT**: naso-gastric tube. **CRP**: C-reactive protein

Table 2. Predictors of candidemia in medical non-neutropenic, non-ICU patients

	Univariate analysis		Multivariate analysis	
	OR (95 CI)	p	OR (95 CI)	p
Time to positivity		0,04	--	--
Prior antibiotic therapy	1,97 (1,46-2,66)	<0,001	**8,33 (1,84-38,4)**	**<0,001**
TPN	2,62 (1,19-5,76)	0,014	**3,82 (1,02-9,12)**	**0,049**
CVC	1,79 (1,04-3,08)	0,033	**3,92 (1,11-7,56)**	**0,048**
sc vascular device	3,86 (1,15-13)	0,025	--	--
Candiduria	5,55 (1,3-23,6)	0,01	**5,95 (1,51-28,3)**	**0,015**
Leukocytes		0,032	--	--

TPN: Total parenteral nutrition. **CVC**: central venous catheter. **sc vascular device:** totally implantable central venous access device.

CONCLUSIONS

- Crude 30-days mortality was 35,7% highlighting the need for prompt identification and initiation of therapy in these patients.
- We identify a set of easily determinable independent predictors of the occurrence of candidemia in medical non-ICU, non-neutropenic patients.
- Our results provide a rationale for initiating early antifungal treatment in high-risk medical non-ICU non-neutropenic patients.