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Clinical Research Study

Candidemia in patient with body temperature below 37°C and admitted to Internal Medicine Wards: assessment of risk factors

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Key words: Candidemia; Fever; Internal medicine wards; Risk factors.

Running title: afebrile candidemia in internal medicine wards.

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Abstract

Background: An increasing number of candidemia has been reported in patients cared for in Internal Medicine Wards. These usually older and frail patients may not be suspected as having candidemia because they lack fever at the onset of the episode. To identify the risk factors associated with the lack of fever at the onset of candidemia (i.e. the collection of the first positive blood culture for *Candida* spp.) in patients cared for in internal medicine wards, we compared two group of patients with or without fever.

Methods: We retrospectively review data charts from three tertiary care, University Hospitals in Italy, comparing patients with or without fever at onset of candidemia. Consecutive candidemic episodes in afebrile patients and matched febrile controls were enrolled during the three years study period. Patient baseline characteristics and several infection-related variables were examined. Random Forest analysis was used given the number of predictors to be considered and the potential complexity of their relations with the onset of fever.

Results: We identified 147 candidemic episodes without fever at onset and 147 febrile candidemia. Factors associated with the lack of fever at onset of candidemia were: diabetes, *C. difficile* infection and a shorter delta time from internal medicine wards admission to the onset of candidemia. The only variable associated with fever was the use of intravascular devices. Quite unexpectedly, antifungal therapy was administered more frequently to patients without fever and no differences on 30-day mortality rate were documented in the two study group.

Conclusions: Clinicians should be aware that an increasing number of patients with invasive candidiasis cared for in internal medicine wards may lack fever at onset, especially those with diabetes and *C. difficile* infection. Candidemia should be suspected in patients with afebrile systemic inflammatory response syndrome or in worsening clinical condition: blood cultures should be taken and a timely and appropriate antifungal therapy should be considered.

Introduction

Candidemia is frequently documented in hospitalized patients with severe underlying diseases or underwent abdominal surgery. An increased rate of candidemia either as absolute rate or rate for 10.000 days of hospital stay, has recently been reported in patients cared for in internal medicine wards [1-2]. Patients in internal medicine wards are usually older, suffer for several co-morbidities and are treated with multiple therapies. Previous studies underlined that many patients with candidemia in internal medicine wards do not receive a timely antifungal treatment [1-2]. Furthemore, Morrell et al already observed that patients with candidemia have an increased mortality if they are afebrile at the onset [3].

To identify risk factors associated with the lack of fever at the onset of candidemia, we compared two group of internal medicine wards patients with and without fever observed in 3 different hospitals in Italy.

Materials and methods

Patient population and study design: This retrospective multicenter cohort study was conducted in 3 large teaching italian hospitals, in a 3-year period (January 2012 – December 2014). Hospitals participating to this study were: Nuovo Santa Chiara Hospital in Pisa, Umberto I Hospital in Rome, Santa Maria della Misericordia in Udine.

Patient baseline characteristics and infection-related variables were collected from the hospital charts and microbiology and pharmacy database of the participating centres. The baseline characteristics included age, gender, comorbidities (including Charlson Co-morbidity index), use of immunosuppressive therapy, length of hospital stay, time from the admission to the onset of candidemia (Δ Time Admission to Candidemia), previous antibiotic therapy and antifungal therapy (more than 7 days in the previous 30 days), antifungal therapy administered during episode of candidemia, surgery in the previous 30 days, previous hospital admission (90 days before the onset of candidemia), total parenteral nutrition, chemotherapy and/or radiotherapy, diabetes mellitus, concomitant *Clostridium difficile* infection, ICU admission, severe sepsis or septic shock, systemic inflammatory response syndrome (SIRS) criteria [4], presence of intravascular device (Central Venous Catheter - CVC or Peripherally Inserted Central Catheter - PICC), white blood counts. The mortality rate at 30 days from the microbiological diagnosis of candidemia was registered.

Definitions, study groups and endpoints: Bloodstream infection was defined according to the standard definitions of the Centers for Disease Control and Prevention (CDC) [5]. Candidemia was defined as the isolation of microorganism in one or more separate blood culture [6]. Fever was defined as tympanic temperature more than 37℃. Patients with temperatu re below 37℃ for at least two measurement in the day in which blood culture that became then positive for Candida, was drawn; were included in the group without fever. No patient with body temperature below 35℃ was detected.

For every patient with documented candidemia and no detection of fever at time of candidemia (group NO Fever: cases) one patient hospitalized in internal medicine wards with confirmed diagnosis of candidemia and detection of fever at the time of *Candida* infection (group Fever YES: controls) was chosen with a case/control ratio 1:1. Controls were matched for age, sex, time of admission and comorbidities.

The goal of our study was the assessment of factors associated with lack of fever at the onset of candidemia and the evaluation of 30-day mortality rates in both groups.

Statistical analysis: Variables are described as means ± standard deviation, median and interquartile range or proportion (depending on distribution). To compare categorical variables, we used two-tailed paired test, Mann-Whitney U test and Chi-square test. Chi-square test was used through Yates continuity correction or Fisher test, as required by the specific case. Normality of the variables was assessed with non-parametric Kolmogorov-Smirnov test. Given the number of predictors to be considered and the potential complexity of their relations with the onset of fever, we don't use a multivariate analysis but a survival forest of 1000 trees was computed. Random forest is a non-parametric approach, frequently used for personalized medicine [7]. Along with an unbiased estimation of prediction accuracy, a ranking of variable importance and a measure of similarity between any couple of patients were produced. The similarity measure was used for risk stratification, following a model-based clustering approach. Multiple comparisons were adjusted with the Bonferroni's method. We used the statistical software R for all statistical analyses and we considered a p-value less than 0.05 statistically significant.

Results

Overall, 294 patients with documented candidemia hospitalized in internal medicine wards were included in the study: 147 patients without fever at the onset and 147 patients with fever at the time of the first

blood culture positive for *Candida* spp. One hundred-twenty (40.8%) cases of candidemia were enrolled in Rome, 92 (31.3%) in Pisa, and 82 (27.9%) in Udine. Patients without fever represent the 40% of the overall candidemia cases in internal medicine wards in the three hospitals in the study time period.

In patients without fever, the temperature remained below 37℃ for a mean of 48 hours after the starting point for candidemia.

Demographics, main clinical characteristics, antifungal therapy during candidemia and outcome of study population are summarized in Table 1. No statistically significant differences were reported on the incidence of sever sepsis or septic shock, admission to ICU, immunosoppressive therapy, previous antibiotic or antifungal therapy, Charlson co-morbidities score, probability of SIRS, *Candida* spp distribution and length of hospital stay. The frequency of renal failure was 26/147 (18%) in the febrile and 47/147 (32%) in afebrile patients (p = 0,007).

Compared to patients with fever, patients without fever showed a lower Δ time admission to candidemia (5 *vs.* 10 days, p<0.001), and more frequently suffered for diabetes (72% *vs.* 28%, p<0.001), and *Clostridium difficile* infection (29% *vs.* 6%, p<0.001).

Total parenteral nutrition (59% *vs.* 31%, p<0.001), and the use of any central (CVC and PICC) intravascular device (77% *vs.* 24%, p<0.001), were more frequently documented in patients with fever.

Antifungal therapy was administered more frequently to patients without fever and no antifungal therapy was more frequently documented in patients with fever.

No differences was documented on 30-day mortality among the two study groups.

Variables statistically significant at the univariate analysis were analysed using a Random Forest model, with an accuracy of 84% in prediction of the event fever.

Five variables were associated with absence of fever: presence of intravascular device, diabetes mellitus, antifungal therapies during episode of candidemia, Δ Time Admission to candidemia, and concomitant *Clostridium difficile* infection. Using the proximity map created by the Random Forest analysis, a bayesian analysis was applied and three different group of patients with different risk of fever at the time of candidemia were detected (see Figure 1): group 1, fever in 9.4% of cases (95% confidence interval: 3.3%-20%); group 2, fever in 47.0% of cases (95% confidence interval: 38.1%-55%); group 3: fever in 80.6% of cases (95% confidence interval: 70.3%-87.2%). The differences between the three groups were

statistically significant (p<0.001).

Table 2 report the comparison of the three study groups with multivariate analysis: diabetes mellitus, Δ time admission to candidemia, and *Clostridium difficile* infection were associated with the absence of fever at the onset of candidemia, the presence of any intravascular device was associated with fever.

Discussion

Elderly patients and those with co-morbidities may have blunted inflammatory and febrile response due to impaired immune function as a direct consequence of advanced age (immune-aging) [8, 9]. Other SIRS components may also be lacking, including tachycardia due to beta-blockers use, tachypnea due to muscle atrophy and hypocapnia due to chronic respiratory failure.

In the most recent decade, the number of hospitalizations in internal medicine wards of patients over the age of 65 years has increased, and a particular attention has been directed to the 'frail elderly patient' [10-13]. Elderly patients with poor functional status are characterized by a higher risk of developing invasive infections, frequently due to multidrug resistant pathogens, by the concomitant presence of underlying respiratory and cardiac diseases, alteration of mental status, immunosuppression, renal impairment and/or hepatic failure, with the need of specific dose adjustment of antimicrobial therapy. Infections may be clinically silent, with no fever due to anergy or immuno-paralysis. A significant proportion (20-30%) of elderly patients with serious infections have absent or blunted febrile response [14-16]. Although the presence of fever may often indicate infection, the absence of fever does not reliably exclude serious illness. All these observation led to a difficult to obtain early diagnosis of invasive candidiasis [17].

We identified diabetes and concomitant *Clostridium difficile* infection as factors associated with the absence of fever at the onset of candidemia. Delta time from admission to candidemia, seems also play a role, and the presence of any intravascular device seems already to be related with febrile candidemia.

A factor strongly associated with absence of fever was diabetes. Hyperglycaemia might lead to a state of low-level, persistent activation in polymorphonuclear leukocytes. This observation has been evidenced by an increased neutrophil activity and an increased rate of oxygen consumption among un-stimulated PMNs in patients with diabetes mellitus [18]. This hyper-excited state leads to spontaneous activation of the oxidative burst and release of myeloperoxidase, elastase, and other neutrophil granule components. This

process may, in turn, lead to cytokines increase (e.g., TNF-a, IL-6 and IL-8) in individuals with diabetes, but on stimulation, the cells produce less IL-1 and IL-6 than do similar cells in control subjects. In addition, abnormalities in monocyte and macrophage chemotaxis and phagocytosis have been reported [19].

Although, in the multivariate random forest analysis, renal failure was not selected as important predictor for absence of fever, it may play a significant role in lacking fever in Candidemia when associated to diabetes, explaining why in diabetic patients there were less fever.

The relationship between concomitant *C. difficile* infection and the lack of fever may be explained by influence on cytokines production. *C. difficile* might up-stimulate production of immune-suppressive cytokines such as IL-10, and different *C. difficile* toxins or different amount of the same toxin may elicit variable cytokine production [20, 21]. Wu et al demonstrated the primary role of toxin A in altering T cell migration and chemotaxis, suggesting possible implications for *C. difficile* toxin mediated adaptive immune responses and therefore a reduction of general inflammatory response in case in *C. difficile* infection [22].

Furthermore, *Candida* spp. can coexist with the bacterial microbiome and grow during antibiotic perturbations of the microbiome, colonizing the inflamed mucosa and disseminate into bloodstream. Most individuals are asymptomatically colonized with *Candida*, especially *C. albicans*, which can synergize or antagonize with other members of the microbiome. When environmental conditions permit the outgrowth of *C. albicans*, colonization can lead to infection and invasion of host tissues [23]. Many studies [24-25] have suggested as a prolonged damage of the intestinal mucosa might be directly correlated to *Candida* translocation. Therefore the pathogenic potential of *Candida* spp is due to the ability to adapt, survive, and grow in constantly changing environments.

The reduction of time from the admission to onset of candidemia, in patients without fever, may be due to a more severe condition of these patients that probably were admitted several time to internal medicine wards in Italy, as described already by Tascini et al in patients with candidemia [26].

CVC might be associated more frequently with fever because an higher *Candida* spp bloodstream inoculum might elicit a more potent inflammatory response [27]. Furthermore, CVC- or PICC-related infections are associated with a continuous dissemination of *Candida* from a mature biofilm into the blood by sessile cells.

Patients included in the present study have been studied by physicians that are trained to recognize candidemia in the internal medicine wards [2, 26, 28]. Therefore it may be possible that doctors in internal medicine wards ask for an “Infectious Disease” consultation in case of patients without fever but with risk factors for candidemia and/or SIRS without signs of bacterial sepsis; this latter fact may explain because a high rate of candidemic patients without fever received an antifungal therapy.

For all these reasons clinicians should include candidemia as a possible cause of clinical worsening in patients hospitalized in internal medicine wards, identifying those who have potential risk factors and predisposing underlying diseases (diabetes, renal insufficiency, immunosuppressive therapy). Only the increased awareness of possible candidemia will prompt an immediate diagnostic effort and timely administration of an appropriate antifungal treatment that may reduce consistently mortality [28].

Conclusion

In conclusion, candidemia is frequently not associated to fever in patients residing in internal medicine wards, therefore it may be more difficult to recognize in this setting. A delayed diagnosis of candidemia in these cases may complicate management of this infection.

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Figure Legend

Figure 1. Random Forest based similarity map and clustering in 3 groups. Group 1: probability of fever in 9.4% of cases (95% confidence interval: 3.3% - 20%). Group 2: probability of fever fever in 47.0% of cases (95% confidence interval: 38.1% - 55%). Group 3: probability of fever in 80.6% of cases (95% confidence interval: 70.3% - 87.2%).

Tables:

Tables 1: Clinical characteristics, therapy and outcomes of study population divided in three group of probability of fever

Variables	Fever YES (n= 147)	Fever NO (n= 147)	*p*
Median age, years ± SD	73 ± 15	73 ± 12	0.891
Male	73 (50%)	81 (55%)	0.414
Charlson Comorbidity index	7 [6 – 9]	7 [6 - 9]	1.0
Candida albicans spp.	77 (52%)	70 (48%)	0.484
Diabetes mellitus	41 (28%)	106 (72%)	< 0.001
Δ Time admission to candidemia (days)	10 [2 - 21]	5 [1 - 10]	< 0.001
Total parenteral nutrition	87 (59%)	46 (31%)	< 0.001
Chronic Kidney Failure	26 (18%)	47 (32%)	0.007
C. difficile infection	9 (6%)	42 (29%)	< 0.001
SIRS	119 (81%)	116 (79%)	0.771
Intravascular device (CVC/PICC)	113 (77%)	36 (24%)	< 0.001
No antifungal therapy	33 (23%)	11 (7%)	0.001
Severe sepsis or septic shock	64 (44%)	61 (41%)	0.813
Hospital stay (days)	28 [12 - 45]	32 [19 - 36]	0.457
30-day mortality	72 (49%)	61 (41%)	0.410

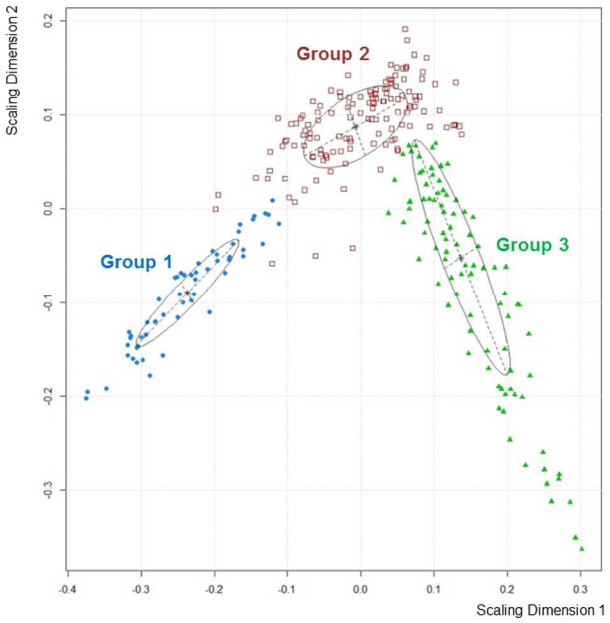
Legend. SD: standard deviation; SIRS: systemic inflammatory response syndrome; CVC: central venous catheter; PICC: peripherally inserted central catheter.

Table 2. Descriptive analysis among the 3 study groups (low, intermediate and high probability of fever) according to Random Forest analysis.

Variables	**Group 1 (n = 64) Low probability of fever**	**Group 2 (n = 132) Intermediate probability of fever**	**Group 3 (n = 98) High probability of fever**	***P***
Intravascular device (CVC/PICC)	0 (0%) *, §	70 (53%) #	89 (91%)	< 0.001
Diabetes mellitus	59 (92%) *, §	70 (53%) #	18 (18%)	< 0.001
Δ Time admission to candidemia	5 [2 - 8] °, §	2 [1 – 6] #	18 [12 - 31]	< 0.001
C. difficile infection	20 (31%) §	26 (20%) #	5 (5%)	< 0.001

Legend. CVC: central venous catheter; PICC: peripherally inserted central catheter.

* Group 1 *vs.* Group 2 (p<0.001); § Group 1 *vs.* Group 3 (p<0.001); # Group 2 *vs.* Group 3 (p<0.001); ° Group 1 *vs*. Group 2 (0.001 < p < 0.05)



Highlights

- An increasing number of candidemia has been reported in patients cared for IMWs
- Increasing number of invasive candidiasis may lack fever at onset
- Diabetes and C. difficile infection are associated with afebrile candidemia in IMWs
- A delayed diagnosis of candidemia may complicate management of this infection