RESEARCH LETTER

Predicting candidemia in internal medicine departments: are we chasing the Holy Grail?

Filippo Pieralli[1], Anna Maria Azzini[2], Ercole Concia[2], Giuliana Lo Cascio[2], Andrea Tedesco[3], Valentina Benedetti[4], Sabrina Piredda[5], Massimo Giusti[6], Claudio Santini[7], Elisa Zagarrì[8], Andrea Fontanella[9], Dario Manfellotto[10]

1 Internal Medicine Department, Careggi Hospital, Florence, Italy
2 Department of Diagnostic and Public Health, Infectious Disease Section, University of Verona, Verona, Italy
3 Internal Medicine Department, G. Fracastoro Hospital, San Bonifacio, Verona, Italy
4 Internal Medicine Department, Regina Montis Regalis Hospital, Mondovì, Cuneo, Italy
5 Internal Medicine Department, Galliera Hospital, Genoa, Italy
6 Internal Medicine Department, San Giovanni Bosco Hospital, Turin, Italy
7 Internal Medicine Department, Vannini Hospital, Rome, Italy
8 FADOI Study Center, Milan, Italy
9 Internal Medicine Department, Fatebenefratelli Hospital, Naples, Italy
10 Internal Medicine Department, AFaR Division, Fatebenefratelli Foundation, "San Giovanni Calibita" Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy

Introduction Candidemia is a challenging clinical condition with high rates of morbidity and mortality.[1] Key requirements for its prompt management include early identification and timely initiation of appropriate systemic antifungal therapy, consistently reported as a major determinant of survival. However, the diagnosis of candidemia can be challenging and is often delayed as there are no specific clinical signs, blood cultures have low sensitivity, and detection of fungal blood cultures takes a long time. In addition, there is evidence that a significant percentage of such infections occurs in patients admitted to internal medicine departments. This is not particularly surprising given the advanced age of many inpatients at internal medicine departments and multiple complex comorbidities. Moreover, related therapies and healthcare system contacts often involve the use of central venous catheters and other indwelling devices, potentially entailing high risk of candidemia.[2] Therefore, optimization of the diagnostic and therapeutic approach is an important and still unfulfilled need for the management of candidemia in internal medicine departments.

Methods During the period from March to December 2018, the Italian Scientific Society of Hospital Internal Medicine (FADOI) promoted a multicenter nationwide study of candidemia (FADOI-EPICA1, ClinicalTrials.gov identifier, NCT03906916). The aim was twofold: to compare 2 diagnostic tests for candidemia, namely, 1,3-β-D-glucan (BDG) and blood cultures, and to evaluate the efficacy and safety of early treatment with echinocandin micafungin in inpatients of internal medicine departments.

The rationale for combining these aims was based on the rapidity of testing BDG (a cell wall constituent of most medically important fungi) as compared with cultures, together with its high negative predictive value. For the dosage of BDG, we used the Fungitell assay (Associates of Cape Cod Inc, East Falmouth, Massachusetts, United States).

Treatment with micafungin (100 mg/d intravenously, for a maximum of 28 days) can be started as soon as clinical suspicion arises, potentially enabling a better outcome; and, by the same token, it is possible to discontinue the treatment timely in the event of a negative BDG result. To enhance pretest probability, we recruited patients deemed to be at high risk of candidemia.

Inclusion criteria, based on previous findings,[3,4] were as follows:

- Patients with 2 or more of the following criteria defining systemic inflammatory response syndrome: 1) hyperthermia or hypothermia (body temperature >38 °C or <36 °C); 2) tachycardia (heart rate >90 bmp); 3) tachypnea (respiratory rate >20 breaths per minute or partial pressure of carbon dioxide in arterial blood <32 mm Hg); and 4) leukocytosis or leukopenia (white blood cells >12000/mm^3 or <4000/mm^3);
- Patients receiving antibiotic therapy in the previous 4 weeks, with a central venous catheter or peripherally inserted central venous catheter;

Correspondence to:
Elisa Zagarrì, MD, Research Department, FADOI Foundation, Piazzale Cadorna 15, 20123 Milan, phone: +39 02 48005140, email: elisa.zagarri@fadoi.org
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TABLE 1 Distribution of predictive criteria for invasive candidiasis according to a registry promoted by FADOI[7]

Variable		Patients (n = 111)
SIRS defined by the presence of >2 criteria		45 (40.5)
SIRS criteria	Hyperthermia or hypothermia: body temperature >38 °C or <36 °C	55 (49.5)
	Tachycardia: heart rate >90 bpm	44 (39.6)
	Tachypnea: respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg	24 (21.6)
	Leukocytosis or leukopenia: WBC >12000/mm^3 and <4000/mm^3	37 (33.3)
Antibiotic therapy in the previous 4 weeks		75 (67.6)
CVC/PICC		57 (51.4)
Corticosteroid/immunosuppressive therapy		12 (10.8)
Total parenteral nutrition		44 (39.6)
Urinary catheter		64 (57.7)
Anticancer chemotherapy in the previous 3 weeks		25 (22.5)
Major surgery in the previous 3 weeks		15 (13.5)
Acute pancreatitis		0
Diabetes mellitus		19 (17.1)
Liver diseases		1 (0.9)
Dialysis		0

Data are shown as number (percentage) of patients.

Abbreviations: CVC, central venous catheter; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PICC, peripherally inserted central venous catheter; SIRS, systemic inflammatory response syndrome; WBC, white blood cells

- At least 2 of the following: corticosteroid therapy/immunosuppressive agents; total parenteral nutrition; urinary catheter; anticancer chemotherapy or major surgery in the previous 3 weeks; acute pancreatitis; diabetes mellitus; liver diseases; dialysis.

The FADOI-EPICA1 study was approved by institutional review boards of each participating center. It was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki with its later amendments. The study also complied with specific Italian legal and regulatory requirements. Patients provided their written informed consent to participate in the study.

Results A total of 24 Italian clinical centers participated in this study. During the selection of study centers, investigators were asked to report the number of patients with positive blood cultures for *Candida* observed during the previous year (2017): the mean number of patients for each center was 5 (range, 1–17). However, in the 10-month study period, only 14 patients complying with the inclusion criteria were identified and underwent BDG testing and fungal blood cultures. This meant that, despite the promoters' awareness-raising efforts, the envisaged sample of 100 patients remained unachievable, and it was therefore decided to discontinue the study. The disappointingly low enrollment rate was explained by the participating centers on the basis of the inclusion criteria, which had proved to be too selective. Surprisingly, only one of the 14 selected patients with very high pretest probability of candidemia proved positive for BDG. Blood cultures were negative in all cases.

Discussion Despite its early discontinuation and lack of a conclusive outcome, the FADOI-EPICA1 study provided a stimulus for a critical reappraisal of clinical predictors of invasive candidiasis (IC) in internal medicine.

In the same period, FADOI was completing a registry (FADOI-IFI) including 18 Italian centers, aiming to provide real-world data on the incidence, clinical characteristics, management, and outcomes of inpatients with IC at internal medicine departments.[5] A total of 111 patients with an established diagnosis of IC were included in the registry, and we evaluated the distribution of the predictive criteria chosen for enrollment in the EPICA study. The relevant data are reported in TABLE 1.

Overall, only 20 of the 111 patients (18%) in the FADOI-IFI registry presented the inclusion criteria for enrollment in the EPICA study; in other words, more than 80% of the patients with a documented diagnosis of candidemia enrolled in the registry would not have been recognized as high-risk patients by applying the EPICA1 inclusion criteria.

Predictive tools for IC, such as the Candida score and Ostrosky-Zeichner score, have been designed and validated with reference to the risk of candidemia in surgical and medical patients admitted to the intensive care unit.[6,7] On the other hand, these predictors have been neither adequately characterized nor validated in the internal medicine department settings.

The FADOI-EPICA1 study selected a number of variables aimed at identifying patients with high risk of candidemia, on the basis of existing observational data for the Italian internal medicine department setting. However, the figures reported above indicate that these criteria have an low predictive capacity. Recently developed risk assessment models specific to inpatients at internal medicine departments[4,8] have not been prospectively validated. These are certainly useful scientific contributions to the research needed on such a challenging issue, but the identification of a highly effective predictive tool still seems a difficult goal to achieve. Particularly, many risk factors for candidemia have been established, and many of these are included in the scores used in the intensive care setting (ie, Candida and Ostrosky-Zeichner score). An attempt to describe factors associated with an increased risk of candidemia in internal medicine patients has been recently published.[8] In that study, the following factors were associated with an increased risk of candidemia and weighted to build a score: total parenteral nutrition (odds ratio [OR], 2.45; P = 0.008; 1 point); central venous catheter (OR, 2.19; P = 0.031;

1 point); peripherally inserted central catheter (OR, 5.63; P <0.0001; 3 points), antibiotic treatment prior to hospitalization (OR, 2.06; P = 0.059; 1 point) and during hospitalization (OR, 2.38; P = 0.033; 1 point); neurological disability (OR, 2.25; P = 0.01; 1 point); and previous hospitalization within 3 months (OR, 1.56; P = 0.163; 1 point). In the receiver operating characteristic curve analysis, a final score of 4 or more showed 84% sensitivity, 76% specificity, and 80% accuracy in predicting the risk of candidemia.

However, this predicting rule has not been prospectively validated and no predicting criteria are available for reliably establishing an a priori probability of candidemia in internal medicine department patients.

Tellingly, the percentages of patients with proven IC in the FADOI-IFI registry who would have been identified as at high risk of candidemia were 29.7% and 37.8% for the models proposed by Falcone et al[4] and Sozio et al,[8] respectively. Any likelihood of these figures having been underestimated is extremely remote, given the thoroughness of the registry data collection.

Another important consideration is that the study of bloodstream infections by *Candida* is considerably limited by the absence of highly accurate diagnostic methods. Average sensitivity of blood cultures, currently the standard diagnostic tool for candidemia, has been estimated as 50%.[9] This limitation, together with the absence of reliable predictive factors, makes the management of *Candida* infections extremely challenging. It has to be evaluated if a change for the better can be expected with the upcoming availability of accurate and reliable diagnostic methods, such as the T2 magnetic resonance assay.[10]

In conclusion, early recognition of candidemia is a cornerstone of management, enabling timely and appropriate antifungal therapy, and thus improving patients' outcomes. However, in the specific setting of the internal medicine department, which accounts for a large proportion of patients with candidemia, the identification of highly reliable and predictive tools still remains an unfulfilled need. This gap can be possibly filled by targeted research, with large derivation and validation cohorts, while also leveraging the potential of machine learning[11] and bundle strategies to integrate clinical variables with accurate, reliable, and rapid diagnostic tools.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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