

# Current diagnostic approaches to invasive candidiasis in critical care settings

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## Summary

For the specialist, the management of invasive candidiasis infections, from diagnosis to selection of the therapeutic protocol, is often a challenge. Although early diagnosis and treatment are associated with a better prognosis, apart from cases with positive blood cultures or fluid/tissue biopsy, diagnosis is neither sensitive nor specific, relying on many different factors, clinical and laboratory findings but there is certainly a need for the specific markers in this disease. Recently, new serodiagnostic assays as *Candida albicans* germ-tube antibodies or (1,3)- $\beta$ -D-glucan detection and molecular techniques for the detection of fungal-specific DNA have been developed with controversial results in critical care setting. One of the main features in diagnosis is the evaluation of risk factor for infection, which will identify patients in need of preemptive or empirical treatment. Clinical scores were built from those risk factors. For these reasons, an approach to the new diagnosis tools in the clinical mycology laboratory and an analysis of the new prediction rules and its application situations has been made. Currently, the combination of prediction rules and non-culture microbiological tools could be the clue for improving the diagnosis and prognosis of invasive fungal infections in critically ill patients.

**Key words:** Invasive candidiasis, diagnosis, ICU, CAGTA, (1,3)- $\beta$ -D-glucan, *Candida* score.

## Introduction

The incidence of invasive fungal infections (IFIs) has increased greatly in the last few years, with infection by *Candida* spp. being the most common overall (70–87%).<sup>1,2</sup> Approximately, 10.4% of infections in an intensive care unit (ICU) are related to *Candida* species, with the majority being nosocomial.<sup>3,4</sup> However, this rate could be underestimated because of the fact that at least 4% of the critically ill patients who die in an ICU present an unexpected fungal infection during post-mortem examination.<sup>5</sup> ICU patients represent 25–50% of a hospital's cases of candidaemia. Recent ICU studies show that IFIs caused by *Candida* spp. are responsible for over 14% of all microbiologically documented infec-

tions.<sup>2</sup> Furthermore, ICU admission is recognised as being a risk factor in its own right for development of a *Candida* species infection.<sup>6,7</sup> The incidence of non-*Candida albicans* (NCA) isolates has also increased in ICU, together with strains of *Candida* resistant to fluconazole and other antifungal agents; besides, a high geographical variability in the species distribution has been reported.<sup>2</sup>

Invasive candidiasis (IC) is associated with a significant mortality rate, particularly among critically ill patients.<sup>8</sup> The crude mortality rate of these infections has been estimated at 40–75%, and the mortality rate attributable to candidaemia at 25–38%.<sup>6,9–11</sup> A review of matched cohort and case-control studies has confirmed this related mortality.<sup>12</sup>

In recent years, the species of *Candida* that result in candidaemia have shifted from *C. albicans* to NCA and potentially fluconazole-resistant microorganisms (*Candida glabrata* and *Candida krusei*). Approximately half of the reported cases of candidaemia are now caused by NCA species,<sup>6,11,13</sup> and several publications have

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Accepted for publication 11 April 2009

indicated that these cases have a worse prognosis than those caused by *C. albicans*.<sup>14–17</sup> This increase has been attributed to the use of fluconazole prophylaxis.<sup>18</sup> On the other hand, *Candida parapsilosis* episodes have been associated with better prognosis.<sup>19</sup>

New microbiological non-culture-based assays have been developed in the last few years, including detection of (1,3)- $\beta$ -D-glucan antigen, *C. albicans* germ-tube antibodies (CAGTA) and fungal DNA. Some of them have also been applied into critical care setting<sup>20</sup> with controversial results. However, conventional microbiological and histological methods serve as the cornerstone for the definitive diagnosis of mycoses. Careful stratification of patients according to their risks of acquiring fungal infection will improve the usefulness of both new and established diagnostic approaches.

For these reasons, an approach to the new diagnosis tools in the clinical mycology laboratory and an analysis of the new prediction rules and its application situations has been made in this review.

### Conventional microbiological methods

Direct microscopical examination of clinical specimens is a crucial first-line procedure in detecting the presence of fungal elements and is perhaps the most rapid (<1 h), useful, and cost-effective means of diagnosing fungal infections. The use of 10–20% potassium hydroxide with fluorophore calcofluor white (that binds to the chitin in the fungal cell wall and fluoresces blue-white or green) provides a rapid and sensitive means of detecting fungi in clinical material by direct microscopy.<sup>21</sup> However, all methods of direct examination are less sensitive than culture, and negative results never rule out a fungal infection. On the other hand, progress in fungal culture capability has focussed on recovery of fungi from blood. Blood cultures may be negative even when disseminated disease is present; however, detection of fungaemia is useful in diagnosing opportunistic infections caused by yeast. The automatic continuous-monitoring blood culture systems are sensitive methods for the detection of *Candida* species but they are positive in only 50% of IC. The volume of blood cultured is critical because the number of circulating yeast organisms is low (optimum blood volume for each vial 8–10 ml).<sup>22</sup> Identification of yeast recovered from clinical specimens can be challenging because of their slow growth characteristics. Most yeast are identified on the basis of carbohydrate assimilation and/or fermentation and their morphological features after growth on specialised media. CHROMagar Candida (CHROMagar Company, Paris, France) is a culture medium that can

be used for simultaneous isolation and presumptive identification of *C. albicans*, *C. krusei* and *Candida tropicalis*. Use of this medium shortens the time to presumptive identification of the organisms and allows for easier detection of multiple yeast species present in a specimen.<sup>23</sup>

### Need of early diagnosis

Prophylactic use of fluconazole in high-risk ICU patients cannot be generally recommended. A subgroup of patients which might most benefit from prophylaxis in ICU may be patients with upper gastrointestinal perforation,<sup>24,25</sup> patients with high *Candida* colonisation,<sup>26</sup> and patients with severe acute pancreatitis.<sup>27</sup> For these reasons, early diagnosis of IC is mandatory.

As we have described previously, early diagnosis and treatment are associated with a better prognosis. In a Spanish multicentre study involving ICU patients in 28 hospitals, an Acute Physiology and Chronic Health Evaluation II score of >20 with incidence of candidaemia was associated with a higher mortality rate,<sup>10</sup> whereas early treatment with antifungal medication and the removal of central venous catheters were protective against death.<sup>10,11</sup> Furthermore, inadequate empirical antibiotic treatment it is associated with IFIs and a worse prognosis.<sup>28</sup> Two reports have demonstrated a strong association between a delay in the start of antifungal therapy and an increase in hospital mortality rates;<sup>29,30</sup> thus, it is necessary to recognise that time is of utmost importance when considering the therapy of patients who are at risk for IFIs. Garey *et al.* [30] emphasised the importance of the timing of treatment. In this study, mortality rates were lower for patients who began therapy on day 0 (15%) compared with those beginning on day 1 (24%), day 2 (37%) or later (41%). The delay was defined as the difference between blood-drawing and treatment-onset. A comparable result was found by Morell *et al.* [29]; in this study, the authors showed that administration of antifungal treatment 12 h after having the first positive blood sample for culture was an independent marker of hospital mortality. Finally, Kumar *et al.* [31] also demonstrated increased mortality rates in patients with fungal sepsis and shock associated with delays in the initiation of therapy: every hour of delay was associated with a 12% decreased probability of survival.

### Diagnostic approach for preemptive treatment: non-culture-based and culture-based microbiological tools

Early start of antifungal therapy is correlated with improved survival of patients with IFI. The time period

**Table 1** Microbiological tools to diagnosis invasive candidiasis in ICU settings.

Technique	SEN (%)	SPE (%)	PRO (Advantages)	CONTRA (Disadvantages)
(1,3)- $\beta$ -D-Glucan detection	70–100	87–96	Panfungal marker, high sensitivity and PPV, useful in serum and other clinical samples	Limited experience, false-positive results, methodological concerns
Fungal DNA detection	90	100	High specificity, useful in serum and other clinical samples	Few standardised and validated commercial methods
<i>Candida albicans</i> germ-tubes antibodies detection	77–89	91–100	Diagnosis and therapeutic monitoring, high specificity, detect several <i>Candida</i> species	Limited experience
Mannan and anti-mannan antibodies detection	60–89	80–84	Good specificity and sensitivity in combined use	Limited experience
Combination of non-culture methods	87	100	High specificity, sensitivity, PPV, useful for diagnosing and monitoring	High cost and laboratory requirement
Culture methods	50	100	'Gold standard', useful in blood and other clinical samples, allow antifungal susceptibility studies	Low sensibility, time consuming

SEN, sensitivity; SPE, specificity; PPV, positive predictive value.

between the biological onset of a fungal infection and the appearance of clinical signs and symptoms represents a window of opportunity that, if identified through prospective screening, may allow for preemptive therapeutic intervention. In this diagnostic area, progress could come from prospective screening strategies using new serodiagnostic assays such as galactomannan, CAGTA or (1,3)- $\beta$ -D-glucan detection and molecular techniques for the detection of fungal-specific DNA.<sup>32</sup>

Thus, to improve earlier diagnosis and survival of IFIs, new non-culture-based microbiological tools should be used in conjunction with modern imaging techniques in addition to conventional microbiological, histological, and radiological procedures (Table 1).

#### Detection of (1,3)- $\beta$ -D-glucan

Glucans are a cell-wall component of most pathogenic fungi except for zygomycetes and *Cryptococcus* species. (1,3)- $\beta$ -D-glucan can be detected in serum in amounts as low as 1 pg ml<sup>-1</sup> by commercial assays. One of them, Fungitell® (Associates of Cape Cod Inc., East Falmouth, MA, USA), has been approved by the FDA as an adjunct for the diagnosis of IFIs in the USA, based on its evaluation in haematological patients.<sup>33</sup> At a cut-off of 60 pg ml<sup>-1</sup>, the negative predictive value of twice-weekly sampling was 100%, and sensitivity was 100%. Furthermore, the results were not influenced by the use of prophylactic or empirical antifungals. Multicentre clinical trial results have demonstrated that (1,3)- $\beta$ -D-glucan assay can be used in clinical specimens with a high specificity and positive predictive value (PPV) for

subjects with proven or probable IFI when compared with control subjects.<sup>34</sup> (1,3)- $\beta$ -D-glucan is a broad spectrum fungal marker and can detect invasive infections caused by *Aspergillus*, *Candida*, *Fusarium*, *Acremonium*, *Scedosporium*, *Pneumocystis jiroveci*, etc., but after a positive result, the invasive infection must be assessed using radiological and microbiological techniques. To date, overall experience with this test remains limited; furthermore, its methodological concerns (use of endotoxin-free and glucan-free glassware) and false-positive results (resulting from albumin, immunoglobulin, glucan-containing gauze, haemodialysis or Gram-positive bacteraemia) make its use difficult in a clinical setting. However, based on the excellent negative predictive value, detection of (1,3)- $\beta$ -D-glucan seems to be most useful for excluding IFIs.<sup>35</sup>

#### Detection of fungal DNA

In recent years novel molecular methods, notably the amplification of gene sequences unique to fungi by polymerase chain reaction (PCR) assays, have been developed to improve the diagnosis of life-threatening IFIs in high-risk patients. PCR offers the potential for rapid diagnosis. However, because of the absence of a standardised and validated commercial method, the routine use of PCR in the diagnosis of IFI cannot yet be recommended. Real-time techniques combined with automated DNA extraction may, however, allow standardisation and reproducibility between centres, and may broaden the clinical applicability of PCR-based diagnosis in the near future.<sup>36</sup>

A recent study evaluated prospectively, three nested real-time PCR assays for detection of *Candida* species in serum samples from non-neutropenic ICU patients with candidaemia.<sup>37</sup> The results showed a 90.9% sensitivity, and 100% specificity suggesting a future breakthrough by this method, although the 24-h period needed to perform the nested real-time PCR assay acts as a deterrent to readily use this method to guide a pre-emptive treatment.

A retrospective and comparative study of (1,3)- $\beta$ -D-glucan, mannan and anti-mannan antibodies, and *Candida* species-specific semi-nested PCR reinforces the diagnostic value of PCR in patients with candidaemia. Other serological markers evaluated, singly or in combination, could help enhancing sensitivity, but more extensive evaluation in sequentially collected serum samples is required to assess their value in the early diagnosis of candidaemia.<sup>38</sup>

In the last few years, a novel commercial real-time PCR assay, LightCycler SeptiFast<sup>®</sup> (Roche Molecular Systems, Basel, Switzerland) has been designed to detect and identify, directly in 1.5 ml of whole blood, the 25 most important bacterial and fungal species causing bloodstream infections in under 6 h (including *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, *C. krusei* and *Aspergillus fumigatus*). This technique was recently compared with blood culture in the ICU setting.<sup>39</sup> The analysis of concordance evidenced 83% correlation between the two diagnostic approaches, mainly as a result of samples that tested negative by culture but positive by PCR. The molecular technique was more sensitive detecting fastidious organisms such as *A. fumigatus*, and was not affected by the administration of antimicrobial therapy. Then, the LightCycler SeptiFast<sup>®</sup> could be of interest in the development of new algorithms for the diagnosis of sepsis in critical patients.

#### Detection of antibodies against *Candida albicans* germ tubes

Recently, an indirect immunofluorescence assay to detect antibodies, i.e. CAGTA against this antigen has been developed and commercialised (*C. albicans* IFA IgG; Vircell Laboratories, Spain).<sup>40,41</sup> The test has shown an overall sensitivity of 77–89% and a specificity of 91–100% and has been useful in the diagnosis of IC in intravenous heroin users, bone marrow transplant recipients and haematological or intensive care patients.<sup>42</sup> Detection of CAGTA in patients with invasive infections caused by *Candida* species other than *C. albicans* (*C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. dubliniensis*, *C. guilliermondii* and *C. krusei*) may also

be positive. In addition, the detection of CAGTA may be useful for the therapeutic monitoring of patients with IC, as the administration of antifungal therapy usually results in decreasing titres of CAGTA.<sup>41</sup>

In 2006, our group evaluated an immunofluorescence assay for CAGTA detection in a prospective multicentre study of critically ill patients.<sup>43</sup> The rate of CAGTA-positive results was high (41.5%), mainly in surgical patients (60%). Additionally, the intra-ICU mortality rate was significantly lower in CAGTA-positive patients (23% vs. 61.2%;  $P = 0.025$ ) and the presence of this biomarker was the only protective factor independently associated with ICU mortality. These results imply that a strategy based on the early determination of CAGTA expression might reduce the ICU mortality rate of patients with risk factors for the development of IC. However, because of the limited number of studies published on this technique so far and the small number of patients included, the use of this approach is not yet recommendable on a regular basis. More studies are needed to validate this strategy in the critical care setting.<sup>20</sup>

#### Detection of *Candida* mannan and anti-mannan antibodies

Mannan is a major component of the *Candida* cell wall that induces a strong antibody response. Therefore, some authors have suggested that the combined detection of mannan (Platelia Candida Ag; Bio-Rad Laboratories, Marnes-La-Coquette, France) and anti-mannan antibodies (Platelia Candida Ab, Bio-Rad Laboratories) considerably improves the diagnosis of IC. While individual sensitivity of these tests is low (<50%), the combined detection increased the sensitivity (60–89%).<sup>38,44,45</sup>

#### Combinations of non-culture-based microbiological tools

Recent studies have demonstrated improved diagnostic accuracy when combining galactomannan and (1,3)- $\beta$ -D-glucan detection,<sup>46</sup> as well as galactomannan and PCR.<sup>47–49</sup> Additionally, its usefulness for diagnosing and monitoring IC using (1,3)- $\beta$ -D-glucan and CAGTA was evaluated in neutropenic adults at high risk. A combination of both tests improved specificity and positive predictive value to 100%.<sup>50</sup> These studies suggest that a combination of two tests to detect antigen, antibodies, (1,3)- $\beta$ -D-glucan and DNA will be needed to optimise the diagnosis of systemic fungal infections.<sup>51</sup>

### Culture-based microbiological tools

Numerous critically ill patients are colonised by *Candida* species but only a few subsequently develop IC. Screening for *Candida* colonisation assessment is performed routinely in many ICUs. Piarroux *et al.* [26] assessed the efficacy of a preemptive antifungal therapy in preventing proven candidiasis in critically ill surgical patients, using a corrected colonisation index (CCI) (ratio of highly positive samples to the total numbers of samples cultured), previously described by Pittet *et al.* [52], to measure the intensity of *Candida* mucosal colonisation. Patients with a CCI value of  $\geq 0.4$  received early preemptive antifungal therapy with fluconazole, and the incidence of ICU-acquired proven candidiasis decreased significantly from 2.2 to 0%. However, it is possible that the overload of samples sent to the microbiology laboratory could limit the widespread use of this approach.

### Diagnostic approach for empirical therapy: prediction rules, *Candida* score and selection of antifungal therapy

The early identification of risk factors for the development of candidaemia such as peritonitis, abdominal surgery, previous administration of broad-spectrum antibiotics, parenteral nutrition, multiple-lumen catheters, prior *Candida* species colonisation, renal replacement therapy, and mechanical ventilation,<sup>9,53,54</sup> has become the cornerstone of empirical treatment of fungal infections in the ICU setting in order to reduce the high mortality rate associated with these infections.<sup>55,56</sup>

#### The Ostrosky-Zeichner prediction rule

In a multicentre retrospective setting, Ostrosky-Zeichner *et al.* [57] created a prediction rule for IC. The rule was obtained through analysis of a group of 2890 patients, in which incidence of IC was 3% (88 cases). Statistical modelling revealed a particularly high risk for patients under systemic antibiotic treatment (days 1–3) or with indwelling central venous catheter (days 1–3) and at least two of the following factors: total parenteral nutrition (days 1–3), any dialysis (days 1–3), any major surgery (days –7 to 0), pancreatitis (days –7 to 0), any use of steroids (days –7 to 3) or use of other immunosuppressive agents (days –7 to 0). The rule was associated with a sensitivity of 34%, a specificity of 90%, and a PPV and a negative predictive value (NPV) of 1% and 97%, respectively. This rule applies to approximately 10% of patients who stay in the unit

for >4 days, and approximately 10% of patients to whom this rule is applied will develop proven or probable IC. In this study, patients with any combination of diabetes mellitus, new-onset haemodialysis, use of total parenteral nutrition, or receipt of broad-spectrum antibiotics had an IC rate of 16.6%. This compared with a rate of 5.1% in patients who lacked these characteristics ( $P = 0.001$ ). Fifty-two per cent of patients who stayed in the ICU for  $\geq 4$  days met this rule, and the rule captured 78% of patients who eventually developed IC. However, because of its poor sensitivity and high NPV, this predicting rule would be used only as confirmation of no initiation of antifungal therapy.

#### *Candida* score

More recently, a Spanish group (EPCAN Study) reported on the development of a bedside scoring system that allows early antifungal treatment when candidaemia is suspected in non-neutropenic ICU patients.<sup>58</sup> This ‘*Candida* score’ (CS) is based on the predictive value of previously reported risk factors. It is based on a prospective multicentre study with 1699 medical and surgical ICU patients divided into three groups: no colonisation or infection; unifocal or multifocal colonisation; and proven IC. Using a logistic regression analysis and adjusting for possible confounding variables, the authors found several factors to be independently associated with a greater risk for proven candidal infection. The scores for the individual factors were: parenteral nutrition (+0.908), prior surgery (+0.997), multifocal *Candida* colonisation (+1.112), and severe sepsis (+2.038). The authors concluded that a CS of >2.5 could accurately select patients who would benefit from early antifungal treatment (sensitivity 81%, specificity 74%).

The same Spanish group designed a new prospective study (Cava Project) in order to validate prospectively CS. The hypothesis that less than 5% of the patients with ‘*Candida* score’ below 3 points would develop an IC has been finally confirmed in this study and only when CS was >3 did the presence of abdominal surgery significantly increase the risk of IC (30% of the surgical patients with CS > 3 developed IC). For this reason, we think that this predicting rule should be used only as confirmation for not initiating antifungal therapy in non-surgical non-neutropenic critically ill patients but the administration of antifungal treatment in surgical patients should be considered when CS reaches more than 3 points. One of the aims of the ‘Cava Project’ was also to assess prospectively whether CS may assist clinicians in discriminating between colonisation and IC

**Table 2** Antifungal empirical and preemptive therapy strategies in ICU patients.

	Recommended strategy	References
Empirical	Use of 'Candida score' or the Ostrosky-Zeichner prediction rule. Try to combine with non-culture microbiological tools	[57–59]
Preemptive	Based on detection of (1,3)- $\beta$ -D-glucan or <i>Candida albicans</i> germ tube antibodies or PCR	[34,43,66]

as well as the contribution of (1,3)- $\beta$ -D-glucan (BG) alone or combined with CS. Preliminary results have demonstrated that serum level of (1,3)- $\beta$ -D-glucan associated with a CS  $\geq 3$  accurately differentiated *Candida* colonisation from IC in non-neutropenic critically ill patients.<sup>59</sup>

**Empirical antifungal therapy**

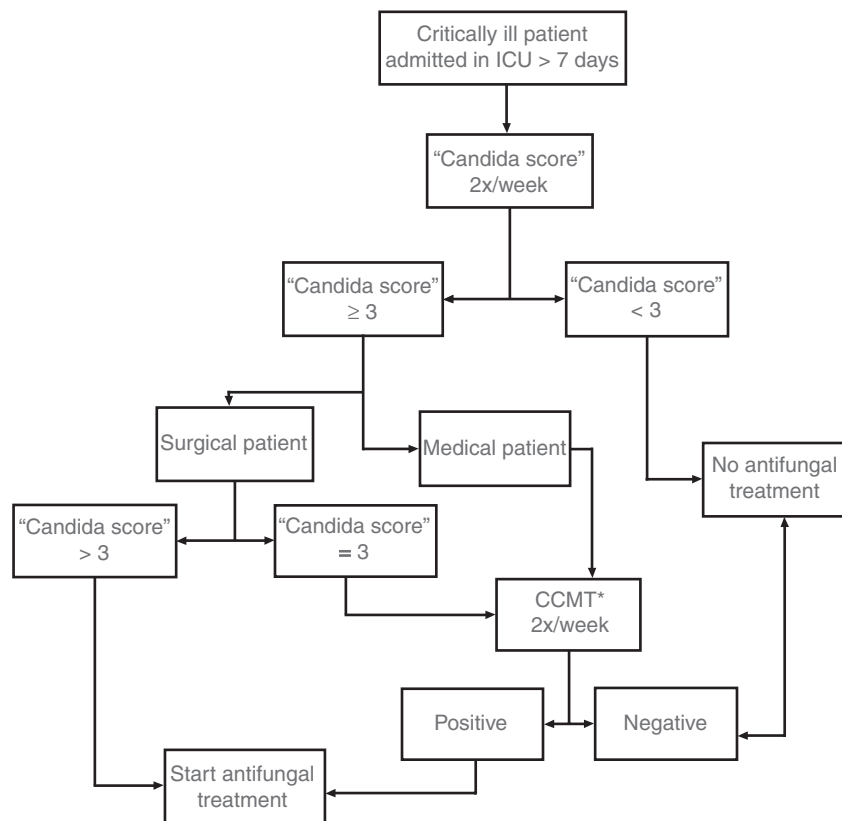
This therapy is defined as the treatment administered to patients who have several risk factors and clinical

features for invasive fungal infections, when species identification or susceptibility data are still not available.

Before establishment of antifungal empirical therapy, several factors must be taken into account, such as: (i) hospital epidemiology; (ii) previous susceptibility data of species isolated in the hospital area; (iii) multicentre surveillance studies to predict the susceptibility patterns of isolates; (iv) the potential risk of emergence of fluconazole resistance in patients receiving fluconazole prophylaxis; and (v) the presence of neutropenia. Furthermore, it must be kept in mind that any individual isolate of any species may become resistant to any antifungal agent. An approach model to antifungal empirical and preemptive therapy strategies in ICU patients is shown in Table 2.

**Diagnostic approach for targeted therapy: culture-based microbiological tools**

Poor outcomes are, in part, associated with difficulties in establishing the microbiological diagnosis at an early stage of infection. Blood cultures are positive in only 50% of invasive *Candida* infections. Furthermore, positive cultures of specimens from non-sterile body



**Figure 1** Algorithm for initiation of empirical/preemptive antifungal treatment in critical care setting. \*NCMT: Non-culture microbiological tools [(1,3)- $\beta$ -D-glucan, *Candida albicans* germ tube antibodies or PCR].

sites may be related to either colonisation or infection, and distinguishing between these can be difficult. However, a positive blood culture or the isolation of *Candida* spp. from a normally sterile site provides the evidence to start a targeted antifungal therapy.

Despite its poor sensitivity, blood culture is the 'gold standard' methodology for candidaemia diagnosis. At present, candidaemia is detected by an automated broth blood culture system in most hospitals. Culture medium is inoculated at the bedside and placed in the automated incubator soon after the specimen reaches the laboratory. Depending on the inoculum, volume of blood cultured, *Candida* species, medium, and detection system, growth is detected in 24–48 h.<sup>60</sup> For yeast species identification, subculture and overnight incubation is needed. The laboratory can then select from a variety of techniques for identifying the yeast colony on subculture, with *C. albicans* being identified the same day and other species up to 3 days later. Designation of the isolate as 'non-*albicans*' is not predictive of fluconazole resistance, because most of these species are as azole-susceptible as *C. albicans*.

In two recent epidemiological studies of candidaemia in critically ill patients carried out in Italy and Turkey, a shift toward an increased rate of infection with NCA isolates, potentially fluconazole-resistant microorganisms (*C. glabrata* and *C. krusei*) was described.<sup>61,62</sup> This novel situation correlated with the increasing use of azoles for prophylaxis or empirical treatment in the ICU setting.

Most institutions use an echinocandin to treat candidaemia until the species is identified, especially when haemodynamic instability is present,<sup>63</sup> but its cost and the higher echinocandin minimal inhibitory concentrations for *C. parapsilosis* makes this choice less suitable for every patient in some countries. On the other hand, the low mortality rates associated to *C. parapsilosis*<sup>19,64</sup> and the low rate of *in vitro* resistance<sup>65</sup> could justify this approach.

As epidemiological data and resistance to antifungal agents depends on characteristics of patients and geographical localisation, it is convenient, in all invasive mycoses, to perform both the identification of all isolates at species level and the antifungal susceptibility tests to identify the local epidemiology so as to apply the most appropriate therapy in each institution.

## Conclusions

*Take-home messages*, ICU patients represent a critical population for the treatment of IC; the vital prognosis is

usually the key of the treatment. To date, diagnosis of IC occurs in the late phase of the evolution of the disease (either a positive blood culture, or a high colonisation index for example), the main challenge that we have for the future is to elaborate diagnosis methods which will give us the opportunity to identify the patients earlier in the course of the disease. The high mortality associated with IC is partly correlated to the diagnostic difficulties, thus, to improve earlier diagnosis and survival of IC, new non-culture-based microbiological tools such as CAGTA and/or PCR techniques for the detection of fungal-specific DNA should be used in conjunction with the recently published 'Candida score' prediction rule. An algorithm based on this approach has been provided to assess early treatment in critically ill patients (Fig. 1). Currently, the combination of prediction rules and non-culture microbiological tools could be the clue for improving the diagnosis and prognosis of IFIs in critically ill patients.

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