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REVIEW

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What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients

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Abstract Invasive candidiasis (IC) is a severe complication in the ICU setting. A high proportion of ICU patients become colonized with *Candida* species, but only 5–30 % develop IC. Progressive colonization and major abdominal surgery are well-known risk factors for *Candida* infection. IC is difficult to predict and early diagnosis remains a major challenge. In addition, microbiological documentation often occurs late in the course of infection. Delays in initiating appropriate treatment have been associated with increased mortality. In an attempt to decrease *Candida*-related mortality, an increasing number of critically ill patients without documented IC receive empirical systemic antifungal therapy, leading to concern for antifungal overuse. Scores/predictive rules permit the stratification and selection of IC high-risk patients who may benefit from early antifungal therapy. However, they have a far better negative predictive value than positive predictive value. New IC biomarkers [mannan, anti-mannan, (1,3)-β-D-glucan, and polymerase chain reaction] are being increasingly used to enable earlier diagnosis and, ideally, to provide prognostic information and/or therapeutic monitoring. Although reasonably sensitive and specific, these techniques remain largely investigational, and their clinical usefulness has yet to be established.

Keywords Critically ill · Invasive candidiasis · *Candida* colonization · Diagnosis · Biomarkers · ICU

Abbreviations

IC	Invasive candidiasis
IAC	Intra-abdominal candidiasis
BG	(1,3)-β-D-Glucan

Introduction

Hospital-acquired bloodstream infection by *Candida* spp. is associated with a large increase in mortality (35–75 %) especially in patients with severe sepsis [1]. Approximately 90–95 % of critically ill patients admitted to mixed (medical–surgical) intensive care units (ICU) are non-neutropenic adults. In these settings, *Candida* accounts for up to 17 % of all ICU-acquired infections and multiple-site *Candida* colonization is found in approximately 50 % of patients [2]. Risk factors for invasive candidiasis (IC) include parenteral nutrition, use of broad-spectrum antimicrobials and prolonged antibiotic therapy, central venous lines, and abdominal surgery; these are also risk factors for *Candida* spp. colonization. There is a link between *Candida* colonization and IC [3], but it is difficult to distinguish between the two. *Candida* colonization scores and indexes have varying predictive value largely depending upon the variables included in the model. Non-culture-based assays of surrogate markers

(detection of antibodies or antigens related to fungal wall components, fungal-related nucleic acids) have been proposed to improve the early diagnosis of IC [4]. Up to 70 % of antifungal therapy in the ICU is pre-emptive/empirical [5, 6] because of the diagnostic difficulties of IC, and the fact that delays in starting appropriate antifungal treatment have been associated with increased mortality in patients with candidemia [7].

This review presents an overview of these challenging clinical scenarios, including epidemiological aspects, the usefulness of culture and non-culture assays in the diagnosis of *Candida* colonization and IC, as well as recent advances in our understanding of the spectrum of the disease.

Background

Candida species are responsible for between 9 and 12 % of all bloodstream infections [8] and are the fourth most common cause of nosocomial bloodstream infections in most US population surveys [8] and the sixth or seventh most common cause in European surveys [9]. The incidence of candidemia has been rising at an alarming rate with as much as a 50 % increase in frequency between 2000 and 2005 [10]. *Candida* bloodstream infections occur at highest rates in the ICU population, with this setting accounting for 33–55 % of all candidemias [8, 11]. In recent point prevalence studies an incidence of 6.9 candidemias per 1,000 ICU patients was seen [12]. In recent studies of North American ICUs, *Candida* species accounted for 18 % of infections overall, and were the third most frequent source of central line-associated bloodstream infection [1]. Although the most common *Candida* species responsible for bloodstream infection remains *C. albicans*, the past two decades has seen a rising proportion of infections caused by non-albicans species [13]. There are geographic differences in both the incidence of candidemia and the prevalence of different *Candida* species. Data from a large surveillance study has shown that the proportion of bloodstream infection due to *C. glabrata* in the USA has risen from 18 % during 1992–2001 to 25 % during 2001–2007 [14]. Recent registry data has reported the following species distribution: *C. albicans* 42 %, *C. glabrata* 27 %, *C. parapsilosis* 16 %, *C. tropicalis* 9 %, *C. krusei* 3 %, with non-albicans species comprising 58 % of the total [15]. In southern European surveys, *C. parapsilosis* is the second most common species and *C. glabrata* is a less common cause [16, 17]. In contrast, in ICUs in France and Denmark, *C. glabrata* has been shown to be the second most common species [18, 19]. The rise in non-albicans *Candida* may have important implications for prevention, treatment, and outcomes.

Patients with candidemia have an overall mortality rate of up to 70 % and estimates of attributable mortality range from 15 to 62 %, with more recent studies indicating lower attributable mortality rates [20–22]. In a Mycoses Study Group prospective observational study the overall mortality 3 months after initial candidemia was 40 % and the attributable mortality was 12 % [13]. IC clearly results in increased cost of hospitalization, and it has been estimated that the additional cost associated with IC is approximately 16,000 euros per episode [23]. A recent review of seven randomized clinical trials for candidemia found a mortality rate of 31 % and noted that the following risk factors were associated with increased mortality from candidemia by logistic regression analysis: increasing age, Acute Physiology and Chronic Health Evaluation II score (APACHE II), use of immunosuppressive therapy, and infection with *C. tropicalis*. Two factors associated with decreased mortality in this study were removal of a central venous catheter and treatment with an echinocandin antifungal [22]. Multivariate analyses from other studies have identified neoplasia, receipt of corticosteroids, infection with *C. albicans* (as compared to non-albicans species), and inadequate antifungal therapy as being associated with higher mortality rate, whereas *C. parapsilosis* was less likely to be fatal [13, 24]. Additionally, several studies have indicated that the time to initiation of appropriate antifungal therapy is associated with mortality [25]. In a recent study of patients with candidemia, which resulted in septic shock, the delay in administration of appropriate antifungal therapy and the lack of adequate source control were associated with higher mortality. In this study each hour of delay in effective therapy during the first 6 h of shock resulted in a 7.6 % reduction in survival [26].

Pathophysiology

There are several distinct pathogenic mechanisms of invasive candidiasis in the ICU. Central venous catheters clearly serve as a portal of entry, and the development of biofilms around catheters is likely important in the pathogenesis of infection [27]. A multicenter study in surgical ICU patients (SICU) showed that rates of candidemia were 0.98/1,000 SICU days in patients without a central venous catheter, compared to 1.42/1,000 SICU days in patients with a central venous catheter [28]. The hands of healthcare workers can be colonized with *Candida* species and reports of clusters of cases provide evidence for the role of nosocomial transmission from healthcare workers or items in the hospital. In some reports using polymerase chain reaction (PCR) fingerprinting analyses of isolates, up to one-third of *Candida* bloodstream infections could be attributable to nosocomial clusters [29]. Transmission from common sources has been demonstrated to occur from contaminated intravenous fluids, hospital food, and medical devices as well as the hands of healthcare workers [30].

Numerous studies have investigated potential risk factors in addition to central venous catheters. In many series, candidemic patients are immunocompromised as a result of a variety of factors including concomitant bacterial infection, the receipt of broad-spectrum antibiotics, diabetes, recent abdominal surgical procedure, parenteral nutrition, hemodialysis, pancreatitis, and neutropenia [13, 15, 28, 31]. The relative importance and interplay of all of these potential risks has not been clearly defined. Additionally, duration of exposure to risk factors is likely important as well, given evidence that the risk of candidemia is associated with the length of stay in the ICU [32].

A subset of ICU patients with a uniquely high risk for invasive candidiasis are those who have had recent intra-abdominal events [33, 34] Patients at highest risk are those with gastroduodenal perforation, anastomotic leak, or acute necrotizing pancreatitis [35]. In contrast, patients with ruptured appendicitis do not appear to be at increased risk [36]. Establishing the pathogenesis has important implications for treatment. In patients with central venous catheter-associated candidemia, removal of the catheter is recommended. For patients with an intra-abdominal process, intravenous catheter removal is not likely to be adequate and source control with drainage is essential [26]. The signs and symptoms of intra-abdominal candidiasis are often non-specific and cultures may be difficult to interpret because specificity is low. Additionally, cultures from intra-abdominal sources or drains are often polymicrobial with both bacteria and yeast present [36, 37], and blood cultures are most often negative in this setting. The specificity of superficial wound cultures, or cultures of material from drainage catheters that were placed more than 24 h prior to culture is known to be poor. In the postsurgical setting, beta-D-glucan may play a role in diagnosis, with reports of a positive predictive value of 72 % and a negative predictive value of 80 % for invasive intra-abdominal candidiasis [38]. More work needs to be done in this area to establish the role of beta-D-glucan in distinguishing between colonization and invasive abdominal candidiasis. *Candida* species obtained from operative sites or abdominal collections, or from freshly placed drains in patients with clinical evidence of infection who have had gastroduodenal perforation, anastomotic leaks, necrotizing pancreatitis, or other acute abdominal events, should be taken as evidence of probable invasive candidiasis.

Colonization with *Candida* species may be a prerequisite for most patients with candidemia, and the number of sites or burden of colonization is likely important as well. A study of 1,699 patients whose were in the ICU for more than 7 days demonstrated that 52 % were colonized with *Candida* and 6 % developed subsequent infection [39]. An earlier study showed that 64 % of ICU patients were colonized with *Candida* species and all those with invasive infection had evidence of prior colonization [40]. However, only a minority of patients colonized with *Candida* develop invasive infection [28, 41]. The role of colonization of catheter tips in the absence of candidemia has not been well defined as a risk factor for subsequent invasive infection. Estimates based on retrospective studies suggest that subsequent candidemia may occur in 4–12 % of patients with catheter tips that grow *Candida* species [42].

Clinical scenario: importance of concepts and definitions

Candida colonization and infection are two closely related and successive events in the natural history of the disease (Fig. 1). On ICU admission, only 5–15 % of patients are colonized by *Candida* spp., a rate that may steadily increase to 50–80 % as exposure to risk factors becomes more prolonged. A continuum exists between *Candida* colonization and IC, although in contrast to bacterial infections, there is a delay of 7–10 days between exposure to colonization and to other risk factors and development of an IC. Also, only 5–30 % of colonized patients will develop IC, which is usually an ICU-acquired infection [43], and may be related to some genetic innate immunity profiles [44].

Multifocal colonization if common in the ICU setting, particularly in patients admitted for more than 7 days, and may range between 56 and 70 %. The most frequently colonized foci are gastric aspirates (45.6 %) followed by oropharyngeal samples (34.3 %), tracheal aspirates (23.4 %), perirectal swabs (21.2 %), and urine (18.7 %); also, these percentages show very small variations over the weeks of ICU stay [2, 45]. In relation to the anatomic site of *Candida* species colonization and risk for IC, a recent study has shown that RR for IC was significantly higher in patients with positive surveillance cultures of feces or rectal swabs than in those with negative cultures (7.5 vs. 3.2 %, $p = 0.019$), as well as in patients with positive

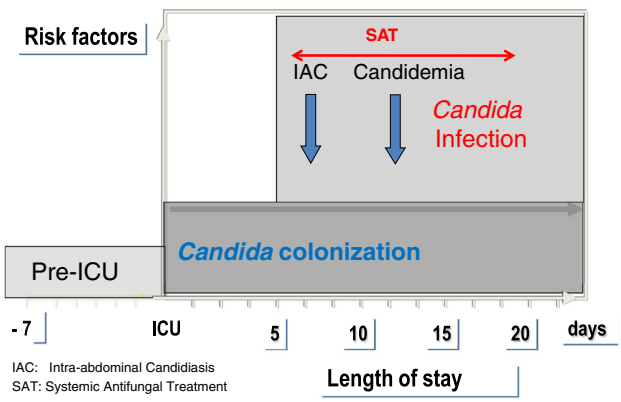

Fig. 1 Invasive candidiasis in ICU. Natural history

urine cultures than in those with negative urine cultures (9.2 vs. 5.2 %, $p = 0.032$). These data support the impact of rectal, urinary, and respiratory cultures, carried out twice a week, to identify patients at risk, although only multifocal colonization was an independent risk factor for IC. Eventually, gastric or pharyngeal aspirates or skin cultures will only be necessary to assess the diagnosis of multifocal colonization in a few patients [2, 45].

Different grades of *Candida* colonization may be considered according to the number of body sites colonized and the duration and intensity of colonization. Therefore, *Candida* colonization may be classified into low grade and high grade. High-grade colonization is usually defined as colonization of at least three body sites on two or more consecutive occasions [46].

Invasive candidiasis in ICU patients includes (1) primary candidemia (PC) defined as the presence of *Candida* spp. in one or more blood cultures obtained from peripheral veins, (2) intra-abdominal candidiasis (IAC) defined on the basis of macroscopic findings and direct examination or positive culture for *Candida* of the peritoneal fluid collected during operation [47] or within 24 h from external drainage [35], and (3) associated forms (PC + IAC). Approximately one-third of patients fall into each group [18, 48]. Most cases of IC although due to different etiopathogenetic mechanisms occur between the first 5–12 days of ICU stay. It is important to differentiate catheter-related candidemia (C-RC), which has a lower morbidity and mortality, from primary or IAC-associated candidemia. C-RC has been defined as isolation of the same *Candida* (genus and species) from the catheter tip (semiquantitative culture, >15 cfu/plate) [49] and at least one blood culture from a peripheral vein. Endophthalmitis, endocarditis, meningitis, and bone/joint candidiasis are other uncommon forms of IC in ICU patients (Table 1).

In all three types of IC in non-neutropenic critically ill patients, different grades of previous *Candida* colonization may be present and pathophysiologically related to IC. In recent years, a direct relationship between *Candida* colonization of the digestive tract and the development of PC (endogenous route) has been established. In C-RC, however, *Candida* spp. colonization is unrelated to the development of this infection because, in this case, systemic candidiasis develops via an exogenous route. In IAC, and according to recent data, the relationship with *Candida* colonization seems improbable. Although peritoneal *Candida* contamination is the main event, the pathophysiological role of *Candida* spp. isolated from the peritoneum remains to be further elucidated [50]. The time of development of IC is another important aspect; whereas PC and C-RC may appear over the course of hours, symptoms of IAC may require several days.

Table 1 Categorization of *Candida* colonization/infection in ICU

1	Neither *Candida* colonization/infection
2	*Candida* colonization
	Candida colonization"low grade"
	Candida colonization"high grade" (heavy)
3	*Candida* infection
	Candidemia
	Primary candidemia
	Catheter-related candidemia
	Deep-seated infection
	Intra-abdominal candidiasis
	Others
	Pleural candidiasis
	Ocular candidiasis
	Candida meningitis
	Candida endocarditis

Symptoms of sepsis and, in many cases, severe sepsis/septic shock are a common clinical presentation of candidemia in critically ill patients [26]. In ICU patients, however, one must frequently consider *Candida* infection in the presence of a severe clinical picture of sepsis/septic shock, with no evidence of bacterial infection that explains the symptoms, with organ (single organ or multiorgan) dysfunction, and multifocal *Candida* colonization. The decision to start antifungal treatment prior to having the results of optional cultures (blood cultures, abdominal exudate, catheter tip, etc.) particularly applies to the suspicion of IC in high-risk patients. These patients have usually undergone gastrointestinal surgery (mainly of the upper gastrointestinal tract) or present necrotizing pancreatitis. In the remaining ICU surgical patients (non-digestive surgery) and medical patients, this therapeutic decision should be discussed and is currently controversial.

Predictive models of IC are useful to stratify patients at high risk of developing IC but decisions regarding the use of antifungal treatment should not be exclusively based on these models. In the last few years, non-culture-based laboratory techniques for the diagnosis of IC have been developed, which may allow the differentiation of *Candida* spp. colonization and infection [43, 51]. It is interesting to assess the reliability of these techniques, not only in cases of low-grade and high-grade colonization but also in candidemia (PC and C-RC) and IAC, considering all variables that may affect the results (Fig. 2). The possible and "ideal" interdependence of microbiologic findings, clinical symptoms, and serologic and molecular biomarkers summarized in Fig. 2 may help clinicians in the stratification of patients and to select more accurately those candidates for an "early" antifungal treatment (Fig. 3).

This requires an operational classification that includes the concept of proven *Candida* infection (candidemia primary, C-RC, and IAC microbiologically documented), and probable *Candida* infection based on the presence of high-risk patients (major abdominal surgery, pancreatitis), prolonged ICU stay, high-grade colonization, clinical condition of severe sepsis/septic shock, and of positive results of specific biomarkers of candidal infection. Looking for a practical clinical

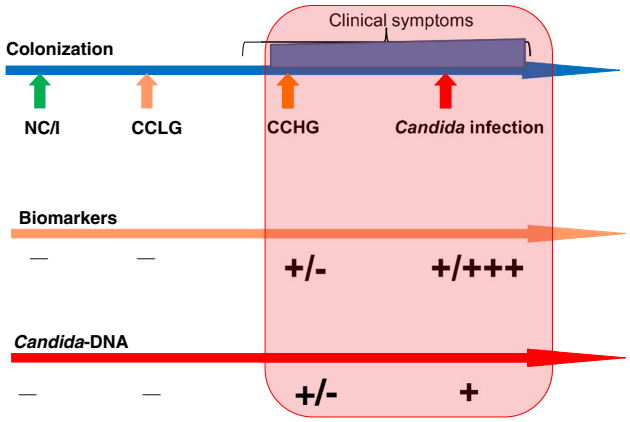

Fig. 2 Interrelation between microbiology, clinical, biomarkers, and *Candida* DNA. *NC/I* no colonized/infected, *CCLG Candida* colonization low grade, *CCHG Candida* colonization high grade

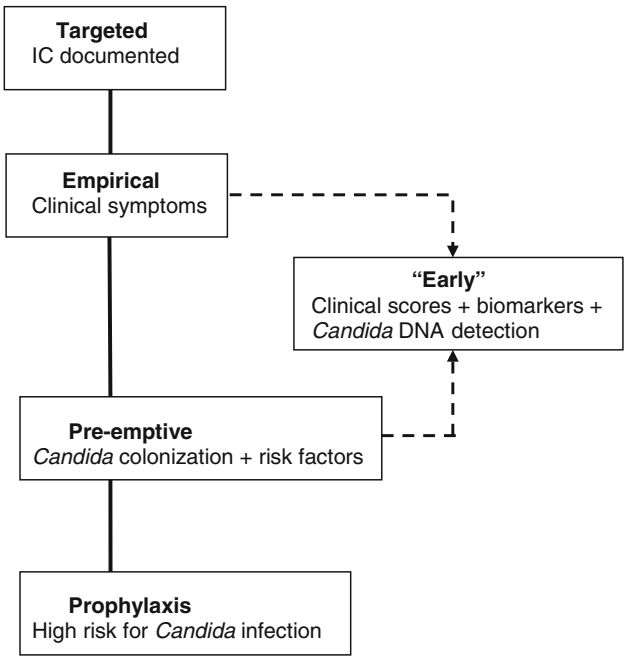

Fig. 3 Antifungal treatment. New proposal in critically ill patients. *IC* invasive candidiasis

application of these concepts, Fig. 4 presents an approach to management of patients with probable *Candida* infection, through the combination of patient types and IC, clinical scores, and biomarkers, although the real clinical impact has to be evaluated.

Identifying high-risk patients: risk factors and prediction rules

The combination of risk factors and clinical data has been the basis for developing predictive models and scoring systems, which allow the identification of critically ill patients at risk for IC [52]. These predictive models should be applied to groups of selected patients with a 10 % (or higher) risk of IC, which in turn may justify antifungal therapy.

Assessment of *Candida* colonization

In a prospective cohort study of critically ill surgical patients, Pittet et al. [46] showed the close relationship between *Candida* colonization and infection and described, for the first time, a *Candida* colonization index. The predictive value of this index has never been examined in a large prospective clinical trial, but different studies suggest that it may be clinically useful [43]. The study by Piarroux et al. [53] using the corrected colonization index showed a significant reduction of IC in a cohort of surgical ICU patients highly colonized with *Candida* and undergoing pre-emptive treatment with fluconazole as compared with the control group of proven candidiasis. Limitations include the design ("before–after") of the study, the low prevalence of candidemia, and its single-center characteristics.

Assessment of clinical scores

Clinical predictive models that combine clinical aspects with *Candida* spp. colonization have been developed.

Dupont et al. [54] developed and validated a predictive score for the likelihood of *Candida* involvement in peritonitis; factors included were female sex, upper gastrointestinal tract origin of peritonitis, perioperative cardiovascular failure, and previous antimicrobial therapy. This score exhibits good sensitivity and overall accuracy to predict yeast isolation in a subpopulation of ICU patients with intra-abdominal sepsis [grade C score: sensitivity 84 %, specificity 50 %, positive predictive value (PPV) 67 %, and negative predictive value (NPV) 72 %].

Also, this approach was recently used by Spanish clinicians to establish a simple model (*Candida* score) incorporating weighted scoring of severe sepsis, major surgery, use of parenteral nutrition (PN), and multifocal *Candida* colonization. This model showed a sensitivity, specificity, and PPV of 81, 74, and 16 %, respectively, in the derivation cohort [39] with similar results in the validation cohort [55].

The group of Ostrosky-Zeichner developed an IC prediction scale based on data of two retrospective multicenter studies. This model requires the combination of one major criterion (diabetes, systemic antibiotic treatment, central venous catheter) and two minor criteria (parenteral nutrition, major surgery, pancreatitis, use of steroids or other immunosuppressants) that should be present for a certain period of time (pre- or intra-ICU). In a

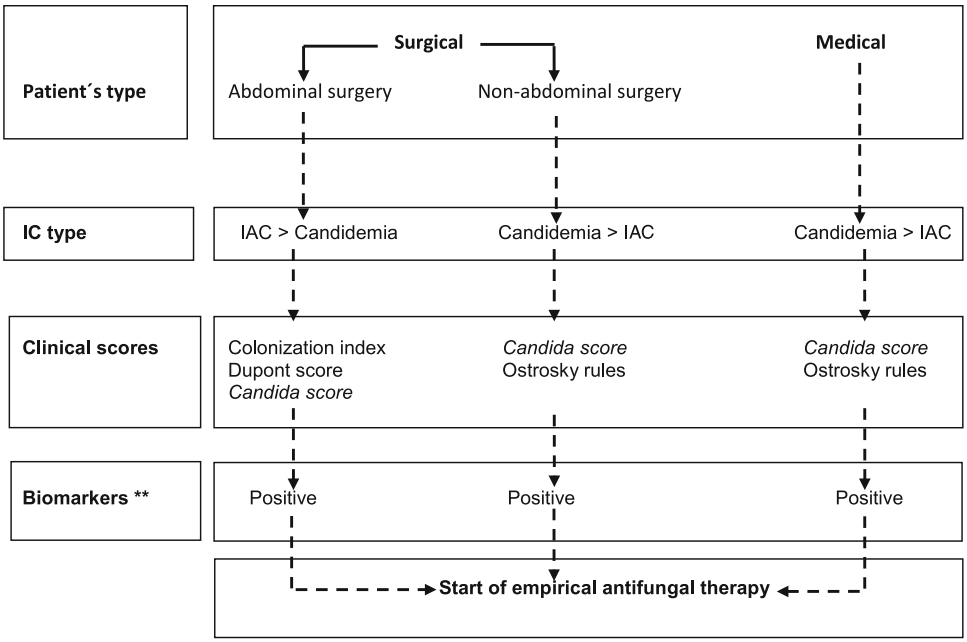

Fig. 4 Approach for management of non-neutropenic critically ill adults patients with probable *Candida* infections *(excluding catheter-related candidemia). **[(1,3)-β-D-glucan (or other biomarker), alone or in combination, two consecutive samples], *IC* invasive candidiasis, *IAC* intra-abdominal candidiasis

further reanalysis of data in which *Candida* colonization was added, the accuracy of the model for predicting IC greatly improved (sensitivity 66 %, specificity 87 %) [56].

Recent studies comparing different clinical scores have demonstrated that the colonization index has greater predictive ability to IAC in a highly selected group [38], whereas the *Candida* score is higher than the latter in a population not selected (medical/surgical) with candidemia [55]. However, although it has been shown that these prediction rules (*Candida* score) could be useful in clinical practice [6, 57], a prospective validation for risk prediction in a prospective and multicenter setting is lacking. Given the very low PPV and the high NPV, many antifungal treatments may be unnecessary (Table 2).

Diagnostic of IC: non-culture-based methods

The diagnosis of invasive infections by *Candida* spp. in ICU patients is hampered by the lack of specific clinical and radiological signs and a delayed clinical course. Diagnostic tests have a low sensitivity (blood culture 50 % and cases of deep-seated candidiasis are not detected) and "gold standard" methods, such as histopathology and cultures of fluids or deep tissues, are aggressive procedures that cannot be used on a routine basis [43]. Therefore, newer surrogate markers of *Candida* infection with improved sensitivity and specificity are needed to enable earlier diagnosis and, ideally, to provide prognostic information and/or to allow therapeutic monitoring.

(1,3)-β-D-Glucan

(1,3)-β-D-Glucan (BG) is a cell wall constituent of *Candida* spp. and other fungi. Several detection assays based upon activation of the coagulation cascade by BG have been developed. The BG Fungitell assay (Associates of Cape Cod, Inc, East Falmouth, MA) is US Food and Drug

Table 2 Comparison of invasive candidiasis prediction rules

Score, year	Patients (*n*) type of study	ICUs	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Threshold
Colonization index, 1994 [46]	29 prospective	1	100	66.6 (43–83)	64.7 (41–83)	100	≥0.5
Dupont score, 2003 [54][a]	57 prospective	1	84	50	67	72	≥3
Candida score, 2006 [39]	1,699 retrospective	73	81 (69–89)	74 (70–77)	24.6 (19–31)	97.4 (95–98)	≥ 3
Candida score, 2009 [55]	1,107 prospective	36	77.6 (65–86)	66.2 (63–69)	13.8 (10–17)	97.7 (96–98)	≥3
Ostrosky rule, 2011 [56]	597 retrospective	6	90 (72–97)	48 (44–52)	6 (4–9)	99 (97–99)	MV + BSA + CVC + other

ICU intensive care unit, *MV* mechanical ventilation, *BSA* broad-spectrum antibiotics, *CVC* central venous catheter

[a] Grade C

Administration (FDA)-approved for the diagnosis of invasive mycoses. The recommended positive cutoff value is 80 pg/mL. A false-positive BG assay may result from glucan-contaminated blood collection tubes and surgical gauze dressings; dialysis with cellulose membranes; bacteremia due to several gram-positive organisms, particularly *Streptococcus pneumoniae*; use of products with cellulose depth filters such as albumin; gut inflammation; and antibiotics such as amoxicillin–clavulanate [51]. In a recent meta-analysis of 11 studies, the sensitivity and specificity of BG for the diagnosis of IC were 57–97 % and 56–93 %, respectively [58]. BG is a valuable adjunct to culture for the diagnosis of IC and is currently recommended in several guidelines from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) [59], European Society of Clinical Microbiology and Infectious Diseases (ESCMDI) (candidemia: level evidence II) [60], Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM) and others (IC: Grade 2 B) [61], and Expert Panel (IAC: BII) [35].

Data in non-neutropenic critically ill patients [38, 62–65] are shown in Table 3. In studies carried out in patients with documented candidemia and/or IAC, most of them were surgical patients (abdominal surgery) and a variable number of samples per patient have been analyzed. The diagnostic accuracy of BG is this particular scenario showed sensitivities and specificities between 51 and 100 %, and 59 and 98.4 %, respectively, although in three studies the NPV exceeded 75 %. In a recent study in patients with IAC, the diagnostic accuracy of BG not only was higher than that of predictive models of IC (*Candida* score and colonization indexes), but also BG positivity diagnosed IAC earlier (5 days) and correlated with severity of illness and outcome [38]. Optimal results are achieved when two consecutive tests are positive [38, 66]. BG pharmacokinetics are poorly understood but a decrease in serial serum BG levels has been associated with success of antifungal treatment [38, 67]. These studies demonstrate a correlation between positive BG testing and confirmed IC.

Mannan antigen and anti-mannan antibodies

Mannan is a polysaccharide component of the *Candida* cell wall that circulates during IC. Latex agglutination and enzyme immunoassay are commercially available methods for mannan detection [51]. The best results have been obtained with a combined mannan antigen/anti-mannan antibody (Mn-Anti-Mn) assay (Platelia, Bio-Rad). In a meta-analysis of 14 studies, seven of which were performed in non-neutropenic critically ill patients, the sensitivity and specificity of Mn and Anti-Mn IgG were 58 and 93 %, and 59 and 83 %, respectively. Values for the combined Mn-Anti-Mn assay were 83 and 86 %, with best performances for *C. albicans*, *C. glabrata*, and *C. tropicalis* infection [68]. On the basis of studies to date, the European Conference on Infections in Leukemia (ECIL) [68] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend the use of this combined diagnostic assay [60, 68]. However, the meta-analysis from the ECIL, on which ESCMID recommendations are based (evidence level II for candidemia), provided guidelines about Mn-Anti-Mn with a low level of evidence (C-II) because eligible studies were mainly retrospective, with heterogeneous populations (both ICU and hematologic patients), different cutoff values, diagnostic criteria (including EORTC which are not relevant in the ICU setting) and controls (such as healthy population or patients with superficial mycoses), as well as sampling and criteria applied for

Table 3 Comparison of BDG test findings in non-neutropenic critically ill adult patients (ICU)

References	Patient type	Number patients/ samples (mean)	IC type (cases)	Cutoff[b]	Sensitivity (%) (95 % CI)	Specificity (%) (95 % CI)	PPV (%) (95 % CI)	NPV (%) (95 % CI)	Proven IC BG[b] (median)
Tissot et al. [38]	Surgical (abdominal) pancreatitis	89/921 [9]	IAC (29)	≥80	65 (46–82)[a]	78 (63–90)[a]	68 (48–84)[a]	77 (61–88)[a]	223
León et al. [65]	SAC	176/766 (4.3)	C, IAC (31)	≥80	51.6 (34–69)	86.9 (78–92)	59.3 (40–75)	83.0 (73–89)	259
Del Bono et al. [64]	Surgical	152/152 (1)	C (53)	≥80	62	98	98.4	57.3	324
Posteraro et al. [63]	Medical/ surgical	95/130 (1.3)	C (13 + 1 M)	≥80	92.9 (66–99)	93.7 (85–90)	72.2 (46–90)	98.7 (92–99)	500
Mohr et al. [62]	Surgical	57/239 (4)	C [3]	≥80	100[a]	59[a]	NDA	NDA	171

CI confidence intervals, *IC* invasive candidiasis, *C* candidemia, *IAC* intra-abdominal candidiasis, *SAC* severe abdominal conditions, *HC* hepatic candidiasis, *M* mediastinitis, *NDA* no data available

[a] Two consecutive BG determinations: maximal BG to time of the IC diagnosis

[b] pg/mL

defining a positive case. Prospective studies are warranted to confirm the advantages of Mn-Anti-Mn testing in everyday clinical practice. Different populations who are at high risk of developing IC, such as patients with hematologic neoplasms, patients admitted to the ICU, or those who have undergone abdominal surgery should be studied separately to draw reliable conclusions about the positive and negative predictive value of a single or multiple positive results.

Antimycelial antibodies (*Candida albicans* germ tube-specific antibody CAGTA)

An immunofluorescence assay (*Candida albicans* IFA IgG, Vircell, Granada, Spain) is commercially available for *C. albicans* germ-tube specific antibody (CAGTA) detection. Limited clinical studies have shown a sensitivity of 77–89 % and a specificity of 91–100 % in a small number of patients with hematologic neoplasms and bone marrow transplantation or in ICU patients [69].

The usefulness of CAGTA in the diagnosis of candidemia associated with deep-seated infection has recently been documented [70].

Detection of *Candida* nucleic acids

Detection of *Candida* DNA is a potentially powerful diagnostic tool. These techniques allow early detection of candidemia in the settings in which they have been extensively tested. Numerous studies of molecular tests for the identification of fungi have been published over the last 5 years. In 2009, Khot and Fredricks [71] reviewed data of PCR-based studies for fungal diagnostics published in the past decade. These techniques allow early detection of candidemia in the setting in which they have been extensively tested. PCR can detect a fraction of an organism especially when multicopy genes are targeted. In addition, if nonviable organisms are present in the circulation, PCR may prove more useful than culture. Different detection platforms, blood fractions, and gene targets have been used. However, in a recent meta-analysis of 54 studies with 4,894 patients, 963 of whom had proven/probable or possible IC, the pooled sensitivity and specificity of PCR for suspected IC were 95 and 92 %, respectively [72]. In cases of probable IC, the sensitivity of PCR and blood culture was 85 and 38 %, respectively. Data in *Candida*-colonized patients were surprisingly limited, although there was a trend towards a lower specificity. There is no doubt that PCR is more sensitive and provides earlier results than blood culture for the diagnosis of IC [73]. Direct molecular detection of *Candida* DNA from human samples is not yet standardized and so far the value of PCR or other molecular methods as early markers of IC remains unclear.

Utility of combinations

A combination of non-culture-based techniques may be needed to optimize the diagnosis of *Candida* infection. In a prospective study of 176 non-neutropenic ICU patients assessing the value of combined positive BG and CAGTA results for differentiating *Candida* colonization from IC in patients with severe abdominal conditions, a 30 % cutoff for IC probability resulted in 90.3 % sensitivity and 54.8 % specificity [65]. In 24 patients with deep-seated candidiasis, the combination of blood culture and BG or PCR had a sensitivity of 79 % and a specificity of 98 % [74]. In a comparison of BG, Mn-A-Mn and Cand-Tec *Candida* antigen in 56 patients with candidemia, the sensitivity and specificity were 89.3 and 63.0 % for Mn-Anti-Mn, and 89.3 and 85.0 % for BDG plus mannan antigen [75]. The combined use of diagnostic tests may be useful to reduce the rate of undiagnosed patients.

General remarks

It is important to assess the results of all these biomarkers (mainly BG) in the differentiation of *Candida* colonization and infection taking into account the following factors: degree of immunocompetence; type of IC (PC, C-RC, IAC); timing of the assay in relation to IC diagnosis and clinical picture (sepsis or severe sepsis/septic shock); presence of antifungal therapy; factors that may interfere with results, etc. Further studies are needed to assess the optimal cutoff in high-risk patients and the efficiency of combining BG with other fungal markers. For all these reasons, although the new diagnostic tests offer advantages over the classical methods, a few hospitals in Europe are currently using them on a routine basis.

Antifungal therapy

Management of IC in the ICU setting has been extensively discussed in international guidelines [76, 77]. The ECIL guidelines reflect the most current information available to date and the Infectious Diseases Society of America (IDSA) guidelines are in the process of being updated and should be released later in 2014. Both European and US guidelines emphasize the need for (1) attempting a prompt diagnosis and (2) early/empirical therapy based on identifying subjects at high risk that may actually benefit from this approach. The ECIL guidelines actually make very specific confirmatory diagnostic recommendations focusing on the blood culture as an essential recommendation and progressive use of biomarkers such as BG and mannan/anti-mannan. Both guidelines recommend using one of the scoring systems

mentioned previously to identify patients who may benefit from empirical antifungal therapy.

The recommendation to treat empirically has to be carefully weighed against over-treating patients. Recent surveys have shown that as many as 7.5 % of patients are on empirical antifungals at any given time in an ICU [6]. Use of antifungals in patients that do not need them is not only associated with potential adverse effects, drug interactions, and increase costs, but with ecological shifts and emergence of resistance [18, 78].

As for what agent should be used for empirical treatment of proven infections, the previous therapeutic approach was based mostly on expert opinion, recommending fluconazole for patients who were mild to moderately ill or who had not been exposed to azoles in the past (thus not having a measurable risk for fluconazole-resistant *Candida* infections) and echinocandins or lipid-based polyenes for moderate to severely ill patients or patients with previous azole exposure [76]. However, recent evidence points to the fact that there may an advantage of initial treatment with echinocandins over azoles [22]; therefore the most recent version of the ECIL guidelines are now recommending initial treatment with echinocandins for all patients and basically all situations. At this time the most progressive approach appears to be treating all patients with echinocandins and reserving azoles for de-escalation in stable patients with isolates showing susceptibility to the agents. Polyenes should be reserved for end-organ infections such as meningitis, endocarditis, or osteomyelitis or for patients where co-infection with other fungal pathogens is documented or possible. There is no significant benefit of combining antifungals for the treatment of IC [79], except for the mostly anecdotal evidence and common practice of using polyenes and 5-FC for severe forms of end-organ disease [76].

Duration of treatment is generally considered to be 14 days from the first negative blood culture in proven cases without abscesses or dissemination and most experts agree that that should be the duration of treatment for patients where antifungals are started for empirical treatment and who have a therapeutic response. Again, it is important to emphasize that this duration of treatment applies only to patients in whom disseminated, abscesses, or end-organ disease has been excluded; therefore it is recommended that all patients with candidemia undergo a dilated eye exam to rule out dissemination. Another important management point is that source control is of paramount importance; therefore all possible central lines should be removed [22] and any identified collection should be drained.

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