Management of Invasive Candidiasis and Candidemia in critically ill adults – Expert opinion of the European Society of Anaesthesia (ESA) Intensive Care scientific subcommittee

Ruth-Aoibheann OLeary, Sharon Einav, Marc Leone, Krisztina Madách, Claude Martin, Ignacio Martin-Loeches

PII: S0195-6701(17)30647-3
DOI: 10.1016/j.jhin.2017.11.020
Reference: YJHIN 5290

To appear in: Journal of Hospital Infection

Received Date: 14 September 2017
Accepted Date: 29 November 2017


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Management of Invasive Candidiasis and Candidemia in critically ill adults – Expert opinion of the European Society of Anaesthesia (ESA) Intensive Care scientific subcommittee

Ruth-Aoibheann OLeary (1) Sharon Einav (2). Marc Leone (3), Krisztina Madách (4), Claude Martin (3), Ignacio Martin-Loeches (1),

Institutional Affiliations:
1. Multidisciplinary Intensive Care, St James's University Hospital, Department of Clinical Medicine, Trinity College, Welcome Trust-HRB Clinical Research Facility, St James Hospital, Dublin, Ireland.
2. General Intensive Care unit, Shaare Zedek Medical Centre and Hebrew University Faculty of Medicine, Jerusalem, Israel.
3. Aix Marseille University, Anaesthesia and intensive care unit and trauma centre, Nord Hospital, Assistance Publique Hôpitaux de Marseille, APHM, Marseille, France.
4. Department of Anaesthesiology and Intensive Therapy, Semmelweis University, Budapest, Hungary

Word Count: 5766

Assistance with the study: none.
Financial support and sponsorship: none.
Conflict of interest: none.

Correspondence to:
Ignacio Martin-Loeches. St James's University Hospital, Dublin 8, Ireland. Phone: (01) 410 3000
E-mail: drmartinloeches@gmail.com

Keywords: candida, intensive care, critical care, invasive candidiasis, management, diagnosis

1
ABSTRACT

OBJECTIVE: The global burden of invasive fungal disease is increasing. Candida albicans remains the leading cause of fungal blood stream infections although non-albicans Candidal infections are emerging. Areas of controversy regarding diagnosis and management are hampering our ability to respond effectively to this evolving threat. The purpose of this narrative review is to address current controversies and provide recommendations to supplement guidelines.

DIAGNOSIS OF INVASIVE CANDIDIASIS: Diagnosis of invasive candidiasis requires a combination of diagnostic tests and patient risk factors. Beta-D Glucan and Candida albicans germ tube antibody are both used as biomarkers adjuncts to diagnosis although direct culture remains the gold standard. Scoring systems are available to help distinguish between colonisation and invasive disease.

TREATMENT OF INVASIVE CANDIDIASIS: Echinocandins are recommended as first line therapy in candidemia with de-escalation to fluconazole when clinical stability is achieved. Empirical therapy is highly recommended in high-risk patients but a more targeted preemptive approach is now being favoured. The evidence for prophylactic therapy remains weak.

SUMMARY: Mortality attributable to invasive candidiasis may be as high as 70%. Prompt diagnosis and treatment, in conjunction with source control, are the key to improving outcomes.
INTRODUCTION

The global burden of Invasive Fungal Disease (IFD) is increasing. There is an urgent need to implement antifungal stewardship programs in critically ill patients (1) due to an overuse of antifungal agents in up to 74% of cases (2). There are many areas of controversy regarding diagnosis and management of invasive Candida infection. Firstly, isolation of Candida from microbiological samples does not clearly correlate with the burden of the disease. Therefore, with the exception of patients with positive blood cultures, there is no direct evidence showing that antifungal administration reduces mortality rates. In intra-abdominal infections an association has been found between the presence of Candida species in sampling and subsequent mortality rates (3,4) but the use of antifungals did not affect patient outcome. Secondly, the timing and choice of antifungal therapy remains a matter for debate, with convincing evidence that delayed treatment of candidemia is an important determinant of patient outcome. However, septic shock attributed to Candida infection and its determinants of outcome remains an evolving area of research (4,5). We have published this narrative review with the aim of addressing these controversies and providing some recommendations to supplement existing guidelines.

EPIDEMIOLOGY AND RISK FACTORS OF INVASIVE FUNGAL DISEASE

Traditionally, IFD has been associated with immunocompromised states, particularly involving patients with malignancies, chronic inflammatory diseases and chronic immunosuppressive conditions. Thus, the number of patients at risk is rising in intensive care units (ICUs) (6). Candida species are the most common fungal pathogens associated with health-care infections of the bloodstream in ICU (7). The leading cause of fungal bloodstream infections among patients admitted to an ICU remains Candida albicans, but non-
Candida albicans Candida infections are also an emerging problem (8). Attributable mortality associated with invasive candidiasis (IC) remains unacceptably high, ranging 5-71% depending on clinical manifestations and timing of therapy administered (9,10).

Candida species are part of the human microbiota, colonising the skin, the gastrointestinal and genitourinary tracts (11). IC is generally caused by a change in the concentration and distribution of normal flora combined with an alteration of the barrier function of the mucous membranes. Critical illness and critical care therapies lead to dysbiosis and disruption of the normal barrier mechanisms, resulting in translocation of flora, including Candida (12). Prolonged ICU stay and the use of broad-spectrum antibiotics are associated with IC. Other risk factors include indwelling central venous catheters (CVC), particularly those used for total parenteral nutrition; haemodialysis; recent major gastrointestinal surgery; necrotizing pancreatitis; diabetes and any pre-existing cause for immunosuppression (13). Moreover, the pathogenicity of Candida is enhanced by its ability to adhere to prosthetic surfaces and form biofilms (14). The formation of biofilms plays an important role in antifungal, especially azole, resistance (15).

The pathogenesis of IC involves all elements of the immune system. Lymphocytes are essential for cell-mediated immunity to Candida and for the prevention of increased colonization. Neutrophils and monocytes interfere with the reproduction of Candida by damaging pseudohyphae and blastospores. Thus, patients with neutrophil dysfunction or leukopenia are at risk for IC. This may lead to acute disseminated candidiasis (ADC), characterised by a diffuse haemorrhagic and papular rash and small vessel vasculitis, with multiple organ involvement (e.g. lungs, GI tract, liver, spleen, kidneys). ADC is associated
with a high mortality and is often seen at autopsy (16). Patients recovering from chemotherapy-induced neutropaenia may present with chronic disseminated candidiasis. The reappearance of functional neutrophils leads to the formation of multiple parenchymal lesions in the splanchnic organs, detectable on imaging. These patients often present with right upper quadrant abdominal pain, pyrexia and elevated alkaline phosphatase and biopsies are usually needed for diagnosis (17). Finally, complement and immunoglobulins play an important role in opsonisation and intracellular killing of pathogens so deficiencies in these elements may lead to refractory infection (18).

Table 1 summarizes the major risk factors for IC.

**DIAGNOSIS OF INVASIVE CANDIDIASIS**

The diagnosis of IC involves the interpretation of fungal diagnostic tests in the context of patient risk factors and clinical and radiological assessment (Table 2). The clinical manifestations of IC are largely dependent on the site involved. Candidemia is the most commonly diagnosed form of IC. However, IC has a wide range of manifestations.

Ocular involvement, manifesting as endophthalmitis, chorioretinitis or vitritis can occur in up to 20% of cases, so ophthalmological examination is recommended in IC in ICU patients (19). In neutropenic patients, a further ophthalmological examination should be performed after neutrophil recovery(20). Involvement of bones and vertebral discs, in the form of osteomyelitis and discitis, is an increasing problem mainly associated with untreated IC (21).
The incidence of Candida endocarditis has risen in parallel with the general increase in Candida infections. Candida endocarditis is characterised by persistent pyrexia and candidemia in blood cultures, new heart murmurs, often with worsening cardiac function and embolic phenomena. It may be associated with recent cardiac surgery, prolonged CVC use, chemotherapy or intravenous drug abuse (22). Critical care patients have a high risk of central nervous system (CNS) involvement, often manifesting as meningitis, as a complication of candidemia or as a complication of IC in presence of CNS prosthetic devices (23). This occurs more frequently in severely immunosuppressed hosts.

The gold standard IC diagnostic test remains morphologic/phenotypic assessment, requiring culture from sterile sites such as blood, pleural or peritoneal fluid or histopathology. Direct tissue samples are desirable but it may not be feasible to obtain these in many clinical situations. Pure cultures remain essential for antifungal susceptibility testing. This gives an estimate of the in vitro potency of an antifungal agent against the cultured pathogen and is very valuable as elevated minimum inhibitory concentration (MIC) is associated with breakthrough infection and worse outcome (24). Antifungal susceptibility testing is particularly relevant now that fluconazole resistance is detected in up to 50% of non-albicans Candida infections (25). It also plays a role in de-escalation strategies (e.g. from echinocandins to fluconazole), thus reducing treatment costs and antifungal pressure.

Several laboratory tests have been proposed as adjuncts for diagnosing the presence of IC (Table 2). Assays of surrogate markers (i.e. antigens or antibodies related to fungal wall components, fungal-related nucleic acids) have also been proposed to improve early diagnosis of IC. Martin-Mazuelos et al conducted a prospective study in critically ill patients
and found that (1,3)-ß-D-glucan (BDG) levels were higher in patients with IC and high-grade candida colonization (26). Two consecutive BDG levels ≥ 80 pg/mL allowed discrimination between IC and high-grade colonization, but the area under the receiver operating curve for both BDG and Candida albicans germ tube antibody (CAGTA) was low (0.67 and 0.55 respectively), indicating that this test cannot be used without supportive clinical correlates (24). Similarly, more commonly used markers such as mannan and anti-mannan could be useful as diagnostic tests. It is important to highlight that mannan tests have a very low specificity (27). In the future, biomarker kinetics may be used to determine the presence of fungal infection with greater precision, thereby ensuring appropriate recommendations for early antifungal treatment.

Molecular methods, which are being gradually implemented in fungal diagnostics, may open up a new dimension in the near future. However, at present they still have serious limitations. PCR assays lack standardization regarding DNA isolation and choice of primers, and contamination with fungi ubiquitous in the environment can happen at any stage of fungal PCR. Due to these issues no single test was found to be accurate enough to be incorporated in guidelines (28). Other molecular methods such as matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometer (TOF) - a postculture technique requiring growth of the organism using matrix assisted laser desorption ionization time-of-flight mass spectrometry and fluorescent in situ hybridization (FISH) performed on positive blood cultures - may shorten species identification (29,30).

One of the major difficulties in the diagnostics of IC is differentiating between infection, colonization and contamination. Two methods can be helpful in this situation:
1) **Definitions** created by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) for invasive fungal diseases (IFD), which were created for research purposes. They apply to immunocompromised patients but not necessarily to critically ill patients (31).

2) **Scores** assessing the severity of Candida colonization, which correlate with the occurrence of IC (32), and are meant to assess immunocompetent patients.

The EORTC/MSG definitions create a usable framework for defining proven, probable, possible and unlikely presence of IFDs (31). These diagnostic criteria have proven to be useful in research and practice in severely immunocompromised patients but not in intensive care unit (ICU) patients. According to these definitions the presence of IFD can be considered proven when the pathogen is found in normally sterile tissue/blood – either by microscopic analysis or by positive cultures. Cases of probable IFD require a host factor, clinical features including imaging findings, and mycological evidence – either direct tests like cytology, microscopy, culture; or indirect tests like mannan or β-D-glucan. IFD is possible with appropriate host factors and with sufficient clinical evidence but without mycological support.

The rate of invasive fungal infections described in the literature is highly variable - often because these definitions of IFD are still not being adhered to. Estimates may thus vary widely even within regions of the same country and over time in the same region (33,34). For example, the Extended Prevalence of Infection in Intensive Care II (EPIC II) study reported a 19% prevalence of fungal infection based on positive isolates taken from ICU patients. The authors noted that the presence of Candida in any isolate type was not
Colonisation with Candida is associated with the occurrence of invasive candidiasis (32). Therefore clinical risk-assessment tools have been proposed by several authors to determine the likelihood of invasive candidiasis compared with colonization in non-neutropaenic critically ill patients. These include the Candida Colonization Index (CI), the Corrected Colonization Index (CCI) and the Candida Score (CS). The CI is the ratio of the number of distinct non-blood body sites colonized by Candida species to the total number of body sites cultured. Samples may include oropharyngeal swabs, tracheal secretions, gastric fluid, perineal swabs, stool samples, urine samples, surgical wound swabs, abdominal drain fluids...
and catheter insertion sites. Only strains of Candida species with identical electrophoretic karyotypes are included (38). The CS was developed in 2006 is comprised of the sum of the following risk factors associated with invasive candidiasis: use of total parenteral nutrition (TPN) (1 point), surgical patient (1 point), multifocal Candida colonization (1 point) and current presence of severe sepsis (2 points). When using this score, a value ≥ 2.5 suggests antifungal treatment might be required. The sensitivity of this score for proven (i.e. microscopically seen or culture positive) infection rates is >0.8, with a specificity of 0.74 and there have been studies demonstrating that the use of the CS may promote timely initiation of antifungal treatment in cases of true fungal infection (39). In further studies, such as the validation of the CS from Leon et al in 2009 (40) and a more recent study from Leroy et al in 2011 (41), the diagnostic CS value used was 3 and we consider that this threshold would have a better predictive value. Different Candida colonization scores have different predictive values for the likelihood of developing an invasive fungal infection, largely dependent on the variables included in each score. At present, careful consideration of past medical history and fungal diagnostic tests combined with clinical and radiological assessment and clinical scores remain the best method for diagnosing the presence of IC in our ICU patients.

TREATMENT OF INVASIVE CANDIDIASIS

In the critical care setting, the treatment of infection due to Candida remains a challenge. Systemic antifungal therapy is widely used, in up to 7.5% of intensive care patients (42), despite the fact that two-thirds of these patients have no documented IFD. Prophylactic and empirical approaches to therapy may lead to overtreatment of patients with an increase in resistant organisms whereas delay in treatment may increase mortality (5). Thus, a balance
must be found between timely and targeted treatment. The recommendations below are based on clinical guidelines (20,43) and expert opinion.

Increases in resistance patterns locally and internationally have influenced the recommended initial therapy for systemic candidiasis (see Table 3, 4). Echinocandins are strongly recommended as the initial therapy for candidemia (20,43). Patients may subsequently be switched to fluconazole after 5-7 days if clinical stability is achieved and blood cultures remain negative (20). In view of this, blood cultures should be repeated regularly until they are negative. Blood cultures could be repeated with a 1-day interval rather than every day in the presence of fever. If a central venous catheter is suspected to be the source of candidemia it is strongly recommended that the device should be removed (20,43). Treatment should be continued for two weeks after blood cultures are negative and clinical symptoms are resolved. Combination therapy is not recommended for candidiasis.

Empirical antifungal therapy is most broadly defined as administration of antifungals in patients with refractory pyrexia and other risk factors for IFD (44). Empirical antifungal therapy is strongly recommended in cases of suspected invasive candidiasis in non-neutropenic patients in the presence of clinical risk factors (table 1)(20) and positive surrogate markers, such as beta-D glucan, and pyrexia with no other cause. In patients with septic shock and suspected candidiasis, empirical treatment should be started as soon as possible and continued for the same duration as recommended for candidemia. If there is no response to empirical treatment after 4-5 days and no evidence of invasive candidiasis, clinicians should consider stopping treatment.
Current guidelines recommend empiric antifungal therapy (20), however this often fails to provide any benefit in ICU patients (45,46) and may result in significant over-treatment. Given the low efficacy of this approach, clinicians should rely more on a combination of risk factors and biomarkers. (1→3)-β-D-glucan (BG) and mannan, both fungal cell wall components, are candidate biomarkers for fungal infection. On the one hand mannan is a highly immunogenic antigen polysaccharide, immunologically more active than β-glucan and positive results may be obtained 2-15 days before positive blood cultures. On the other hand, (1→3)-β-D-glucan is an exo-antigen that can be detected in serum, BAL or CSF and present in most Aspergillus (47). Thus, both may be of use in guiding therapy but mannan is more relevant for Candidal infections. Of note, combined mannan antigen and antimannan antibody testing is more sensitive than either test by itself (48). This more targeted approach is referred to as the pre-emptive approach (49).

The pre-emptive approach is defined as administration of antifungals in patients with a prolonged ICU stay; previous broad-spectrum antibiotic therapy; other clinical risk factors and microbiological evidence of Candida infection, including multifocal colonisation or a positive β-D glucan (50). The knowledge of epidemiological data, clinical risk factors and, above all, the analysis of local epidemiology of candidemia in ICU allows one to determine whether a patient is at low or high risk of developing this infection. There are currently no validated definitions to define high versus low risk other than clinical assessment based on different criteria. From expert opinion expressed in reviews and guidelines (20), therefore, a high rate of invasive candidiasis is defined when there is >10% risk, as compared with the normal rates of 1-2%. The pre-emptive approach is an attractive approach as it still allows prompt treatment of high-risk patients while limiting the use of antifungals in low-risk
patients. However, scientific evidence is lacking to support its wider introduction so prospective trials are needed for validation (45,51). When pre-emptive therapy is considered, β-D glucan concentration should be ≥ 60 pg/mL or Candida score should be ≥3 (52,53).

Prophylactic therapy is defined as the administration of antifungals according to protocol in patients with no definite evidence of infection. There is only moderate-quality evidence giving a weak recommendation to use fluconazole or an echinocandin to prevent invasive candidiasis in ICU patients. Potential benefits in terms of reduction in candidaemia rates are balanced by risks of toxicity and increased resistance patterns. A Cochrane analysis noted that the number needed to treat varied from 9 in high-risk patients to 188 in low-risk patients (45). In view of this, antifungal prophylaxis is only recommended in high risk patients in ICUs with a high incidence of invasive candidiasis (20,37).

With regard to suspected abdominal candidiasis, empirical therapy (see table 3) should be considered for patients with intra-abdominal infection and significant clinical risk factors, such as recent abdominal surgery, anastomotic leaks and necrotising pancreatitis (20). The presence of Candida on direct examination of peritoneal fluid in the setting of intraabdominal infection is significant and is associated with increased mortality (3). In the presence of three of the four following criteria - haemodynamic failure, upper digestive tract perforation, female gender, and antibiotic treatment within the previous 48 h – the probability of identifying Candida in the peritoneal fluid is 71%, encouraging the empiric use of antifungals. However, the scientific evidence is weak with studies of poor quality (54).
The interpretation of the significance of Candida isolates from non-sterile sites can be difficult. For most, if not all, non-immunocompromised patients growth of Candida from respiratory secretions indicates colonisation rather than pneumonia due to Candida. As a result, the decision to treat should never be made on the basis of respiratory samples alone (55). Similarly, in cases of asymptomatic candiduria treatment is not recommended unless the patient is neutropenic or undergoing urological procedures (20). For symptomatic pyelonephritis fluconazole is recommended (14 days) or amphotericin B deoxycholate if resistance to fluconazole is suspected (1 to 7 days)(20).

In the setting of oesophageal candidiasis systemic therapy is always recommended in HIV patients (56), based on current published guidelines (20). A diagnostic trial of antifungal therapy (14 to 21 days) is reasonable before performing endoscopy (57) and oral or intravenous fluconazole, or an echinocandin are the treatment options. In ICU patients, there is no evidence at the present to treat with systemic antifungal therapy.

Candida endocarditis requires aggressive treatment and a high index of suspicion (58). High-dose echinocandin is recommended as initial therapy, although the evidence for this is weak (20,59): caspofungin 150mg daily, micafungin 150mg daily, or anidulafungin 200 mg daily. Liposomal amphotericin B, 3-5 mg/kg daily, with or without flucytosine, 25 mg/kg 4 times daily, is an alternative(60). Step-down therapy to fluconazole, 400-800 mg (6-12 mg/kg) daily is recommended when susceptible isolates and negative blood cultures are obtained.
Whenever possible, valve replacement should be performed and treatment continued for at least six weeks after surgery.

In Candida meningitis a combination of liposomal amphotericin B, 5 mg/kg daily, with oral flucytosine, 25 mg/kg 4 times daily, is recommended, although evidence for this is weak (20). Amphotericin B can also be used alone. Fluconazole, 400-800 mg (6-12 mg/kg) daily is recommended for step-down therapy. This can be considered after the patient has responded to initial therapy. The duration of treatment is not known: therapy is continued until all signs, symptoms, cerebro-spinal fluid and radiological abnormalities have resolved. If a central nervous system device is in place it should be removed if possible.

In figure 1 an algorithm is presented based on clinical evaluation, Candida scores and biomarkers. Measurement of drug concentrations in the plasma should be performed when treating with voriconazole and flucytosine. This is not routinely recommended for other agents (61). This is particularly important in patients requiring renal replacement therapy.
CONCLUSION

The mortality of invasive candidiasis can be as low as 5%, but may be as high as 70% (9,10).

Early diagnosis and development of newer diagnostic technologies with higher sensitivity and specificity is of crucial importance. Prophylactic therapy needs to be better evaluated and is supported only by weak evidence. Empirical treatment is still a matter of controversy but generally involves the use of an echinocandin and, when possible, a step-down therapy with fluconazole. Source control is an important part of treatment - particularly in the case of candidemia related to intravascular catheters. Diagnostic parameters must be consistently adhered to in order to guide treatment and future research.
REFERENCES


15. Lafleur MD, Kumamoto CA, Lewis K. Candida albicans Biofilms Produce Antifungal-


National Institute of Allergy and Infectious Diseases Mycoses Study Group
(EORTC/MSG) C. Clin Infect Dis [Internet]. 2008;46(12):1813.
33. Pfaffer MA, Diekema DJ. Epidemiology of Invasive Candidiasis: a Persistent Public
35. Vincent J, Rello J, Marshall J. International study of the prevalence and outcomes of
Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A Multi-
Clinical Practice Guidelines for the Management Candidiasis: 2009 Update by the
38. Eggimann P, Pittet D. Candida colonization index and subsequent infection in critically
A bedside scoring system ("Candida score") for early antifungal treatment in
the "Candida score" for discriminating between Candida colonization and invasive
Crit Care Med [Internet]. 2009;37(5).
of “Candida score” in critically ill patients: a prospective, multicenter, observational,
antifungal therapy in critically ill patients without invasive fungal infection*. Crit Care
ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-
44. Playford E, Lipman J, Sorrell T. Prophylaxis, empirical and preemptive treatment of
Antifungal agents for preventing fungal infections in non-neutropenic critically ill
Empirical Systemic Antifungal Therapy in Mechanically Ventilated Critically Ill Patients.
47. Bassetti M, Bouza E. Invasive mould infections in the ICU setting: Complexities and
antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis:
recommendations from the Third European Conference on Infections in Leukemia.


Table 1. Main risk factors of invasive candidiasis

High APACHE II score
Diabetes mellitus
Neutropenia
Renal insufficiency
Surgery, mainly abdominal
Pancreatitis
Use of broad-spectrum antibiotics
Parenteral nutrition
Hemodialysis
Mechanical ventilation
Presence of central venous catheters
Immunosuppressive agents
Table 2. The most relevant diagnostic tests for invasive *Candida* infections (IC)

BDG: (1,3)-β-D-glucan assay; CAGTA: *Candida albicans* germ tube antibody; IVIG: intravenous immunoglobulin

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>• Gold standard</td>
<td>• Results take time</td>
</tr>
<tr>
<td></td>
<td>• Required for antifungal susceptibility testing</td>
<td>• Some infecting organisms do not grow on cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Insensitive, may identify only ~50% of all patients with IC (61)</td>
</tr>
<tr>
<td>Histology</td>
<td>• Gold standard</td>
<td>• Invasive procedure</td>
</tr>
<tr>
<td></td>
<td>• Broad categories of potential pathogens can be differentiated</td>
<td>• Sensitivity depends on proper sample collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It has limited specificity to identify genus and species level</td>
</tr>
<tr>
<td>Antigen detection: (1,3)-β-D-glucan assay (serum)</td>
<td>• Serial surveillance of at-risk patients may help early identification of IC and start preemptive therapy (except for hematologic)</td>
<td>• Nonspecific, panfungal screening test. BDG is a cell-wall constituent of <em>Candida</em> spp, <em>Aspergillus</em> spp, <em>Pneumocystis jirovecii</em> and several other fungi.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Repeated positive results are</td>
</tr>
</tbody>
</table>
malignancy patients in whom false positive results are common (62))

- May be used for monitoring response to therapy

---

### Antibody detection: CAGTA assay (serum)

- Helps to identify previous exposures and at-risk patients, may indicate antifungal prophylaxis prior to immunosuppressive therapy
- Not affected by *Candida* colonization or antifungal treatment

### Does not differentiate between previous and active disease

- Sensitivity of an antibody test is limited for immunocompromised patients, who often can not produce antibodies against *Candida* spp.
| Nucleic acid detection | • Rapid results  
• Sensitivity and specificity can be high with certain specimens | • Lack of standardized methodologies  
• It cannot differentiate between infection, colonization or contamination  
• Contamination can be a frequent problem  
• Most assays require special equipment and expertise  
• Can be expensive |

[30]
### Table 3. Treatment of candidemia

**Treatment for Candidemia (Based on 2016 IDSA recommendations)**

<table>
<thead>
<tr>
<th>Non neutropaenic patient</th>
<th>Neutropaenic patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) An echinocandin as initial therapy</td>
<td></td>
</tr>
<tr>
<td>- Caspofungin: 70 mg then 50 mg daily</td>
<td></td>
</tr>
<tr>
<td>- Micafungin: 100 mg daily</td>
<td></td>
</tr>
<tr>
<td>- Anidulafungin: 200 mg then 100 mg daily</td>
<td></td>
</tr>
<tr>
<td>2) Fluconazole: 12 mg/kg then 6 mg/kg daily, not in critically ill and only when resistance is unlikely. Recommended as step-down therapy when susceptibility is established (5-7 days). Negative repeated blood cultures must be documented. For <em>C. glabrata</em> use 12 mg/kg daily*.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neutropaenic patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) An echinocandin as initial therapy (see non neutropaenic patients).</td>
</tr>
<tr>
<td>2) Lipid formulation amphotericin B (3-5 mg/kg) is a less attractive alternative.</td>
</tr>
<tr>
<td>3) Lipid formulation amphotericin B (3-5 mg/kg) is an alternative in case of intolerance or resistance to other agents.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>4) Voriconazole 6 mg/kg for 2 doses and then 3-4 mg/kg, can be used as step-down therapy.</td>
</tr>
</tbody>
</table>

a For fluconazole-resistant C. glabrata, AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days OR oral flucytosine, 25 mg/ kg 4 times daily for 7–10 days is recommended.

<table>
<thead>
<tr>
<th></th>
<th>Polymyxins</th>
<th>FC</th>
<th>Triazoles</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMB*</td>
<td>5FC*</td>
<td>FLU*</td>
<td>ITR</td>
</tr>
<tr>
<td>Y Candida albicans</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Y Candida glabrata</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Y Candida parapsilosis</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Y Candida tropicalis</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Y Candida krusei</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Y Candida lusitaniae</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Y Cryptococcus neoformans</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>M Aspergillus fumigatus</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>M Mucorales</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>M Fusarium spp</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>M Scedosporium</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>D Blastomyces dermatitidis</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>D Coccidioides immitis</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>D Histoplasma capsulatum</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

*good penetration in CNS, eye

5FC: flucytosine; AMB: amphotericin B; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ISA: isavuconazole; ITR: itraconazole; MICA: micafungin; POS: posaconazole; VOR: voriconazole; D: dimorphic fungus; M: mold; Y: yeast; green background: potent antifungal activity; orange background: increasing fungal resistance; red background definitive fungal resistance; CNS: central nervous system
ICU patients with signs of sepsis (CI: colonization index, CS: Candida score). A high rate of invasive candidiasis is defined when there is >10% risk, as compared with the normal rates of 1-2%.

### Candida scores

<table>
<thead>
<tr>
<th>CI ≥ 0.5 or CS ≥ 3</th>
<th>CI &lt; 0.5 or CS &lt; 3</th>
</tr>
</thead>
</table>

- **Risk assessment**
  - high or low
  - high
  - low

- **Follow up**

- **Start treatment**
  - Continue if positive mannan/antimannan
  - Stop if negative biomarker

- **Consider treatment**
  - If started, stop if mannan/antimannan negative

- **Consider treatment if mannan/antimannan positive**