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Article Sub-Title		
Article CopyRight	Springer-Verlag Berlin Heidelberg (This will be the copyright line in the final PDF)	
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Schedule	Received	6 April 2013
	Revised	
	Accepted	4 November 2013

Abstract	Invasive candidiasis (IC) has primarily been studied in intensive care unit (ICU) patients, although, in reality, a vast majority of these infections occur outside of the ICU. The recent publication of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines also deal with the non-ICU population, but many uncertainties remain on the management of IC, particularly in non-critically ill patients. Therefore, the Italian Society of Antimicrobial Therapy, Società Italiana di Terapia Antimicrobica (SITA), produced practical, hospital-wide recommendations on the management of *Candida* infection in non-immunocompromised patients in the hospital ward. Our focus is on patient stratification in terms of risk factors for IC and of clinical severity, emphasising a high index of suspicion to ensure early diagnosis, early treatment and de-escalation when a patient is clinically stable, in order to optimise resource allocation.

Keywords (separated by '-')	Invasive candidiasis - Diagnosis - Management - Risk stratification - Clinical severity - Review - Consensus - Recommendations
Footnote Information	

Infection
DOI 10.1007/s15010-013-0558-0

REVIEW

An Italian consensus for invasive candidiasis management (ITALIC)

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Received: 6 April 2013 / Accepted: 4 November 2013

Abstract Invasive candidiasis (IC) has primarily been studied in intensive care unit (ICU) patients, although, in reality, a vast majority of these infections occur outside of the ICU. The recent publication of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines also deal with the non-ICU population, but many uncertainties remain on the management of IC, particularly in non-critically ill patients. Therefore, the Italian Society of Antimicrobial Therapy, Società Italiana di Terapia Antimicrobica (SITA), produced practical, hospital-wide recommendations on the management of *Candida* infection in non-immunocompromised patients in the hospital ward. Our focus is on patient stratification in terms of risk factors for IC and of clinical severity, emphasising a high index of suspicion to ensure early diagnosis, early treatment and de-escalation when a patient is clinically stable, in order to optimise resource allocation.

Keywords Invasive candidiasis · Diagnosis · Management · Risk stratification · Clinical severity · Review · Consensus · Recommendations

Introduction

The rising incidence of candidaemia and deep-seated infections due to *Candida* (i.e. invasive candidiasis, IC) is parallelling the increasing complexity of surgical procedures and the larger patient populations at risk of infection, as well as changes in patient demographic characteristics. IC, in its various clinical pictures, is burdened by a variable mortality rate ranging from 40 to 75 % [1–5]. While *Candida albicans* has been, for a long time, the species more frequently involved in candidaemia, recently, a shift towards non-*albicans* species has been reported, especially in haematological, transplant and intensive care unit (ICU) patients [6–8]. There is growing evidence that IC is a hospital-wide issue, not confined to specific health care contexts (e.g. the ICU) and it seems, therefore, extremely important to broaden awareness, knowledge and skills for optimal management in the more diverse clinical settings. This is particularly relevant when we consider the evidence that inappropriate initial therapy and/or delay in prescription are associated to worse outcome and to the selection of resistant strains [9–11].

Between 2009 and 2012, both the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) produced a set of guidelines, which, though comprehensive, suggest different therapeutic choices, and, more

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MS Code : INF-D-13-00229 | CP | DISK

relevantly, did not address many uncertainties regarding the practical management of this severe infection, such as actual criteria for empirical therapy and prophylaxis in the daily clinical practice, the management of *Candida* peritonitis and others [12, 13]. In addition, at least the European guidelines address the issue almost only in the ICU patient, forgetting that, in reality, a vast majority of these infections occur outside of the ICU [2]. An additional difficulty is that the vast majority of the literature data is based on candidaemia, while it is increasingly recognised that deep-seated *Candida* disease, though probably underdiagnosed owing to the intrinsic limits of current diagnostic methods, represents a relevant proportion of IC [14].

For these reasons, the Italian Society of Antimicrobial Therapy, Società Italiana di Terapia Antimicrobica (SITA), decided to endorse a national consensus process involving several medical disciplines to review the available evidence and produce practical, hospital-wide recommendations about the management of severe *Candida* infections in non-immunocompromised patients, excluding patients with haematological diseases and those who had undergone solid organ and hematopoietic stem cell transplants. Differently from the above-mentioned international guidelines, the present document takes into consideration a practical approach to antifungal therapy, aiming to give a guideline that is useful for daily clinical practice.

Table 1 ITALIC definition of diagnostic categories of invasive candidiasis (IC)

"Invasive candidiasis (IC)", indicating both deep-seated *Candida* infection and candidaemia
In terms of certainty of diagnosis and consequent therapeutic strategies, the following diagnostic categories (modified from [166]) were used:
Proven IC: cultural evidence of *Candida* or evidence of yeast cells or hyphae or pseudohyphae at histology or at direct examination, in a normally sterile tissue or organ, i.e. excluding urine, sputum, fluids from bronchoalveolar lavage, mucous membrane swabs and specimens from skin sites.
Probable IC: concomitant presence of an underlying disease predisposing to IC, adequate risk factors (see risk stratification), with signs of active infection [26], with at least one positive antigen test (e.g. BDG, mannan/antimannan).
Possible IC: concomitant presence of an underlying disease predisposing to IC, adequate risk factors (see risk stratification), with signs of active infection [26], but without any microbiological confirmation.

Consensus methods

The consensus panel involved 30 infectious disease consultants, surgeons and intensive care physicians, and a clinical epidemiologist, with two external discussants (a microbiologist and a clinical pharmacologist). Five working areas were identified:

- Risk stratification
- Diagnosis and clinical management
- Prophylaxis
- Therapy of possible/probable IC
- Therapy of proven IC

Preliminary consensus on definitions was achieved (Tables 1 and 2).

The consensus strategy was based on a combination of the nominal group technique and the Delphi method (when the EP was involved) [15].

For assessing the quality of evidence and strength of recommendations, we adopted the GRADE profile, since it allows in-depth assessment and description of the available evidence [16–20]. Recommendations were classed following the National Institute for Health and Clinical Excellence (NICE) guidelines, which encompass five categories ("must", "must not", "should", "should not" and "could") [21].

Results

Before delving into the discussion of the five clinical areas of interest, all the "actors" recommend a careful periodical evaluation of the epidemiological situation in each hospital, in terms of new patients at risk, emergence of specific species and resistance patterns. Indeed, local epidemiological surveillance is mandatory, since the antifungal

Table 2 ITALIC definitions of treatment strategies of IC

Treatment strategy	Certainty of diagnosis	RF (including multi-site colonisation)	Clinical signs	Biomarkers	Microbiological diagnosis
Prophylaxis	Not applicable	+	None	Not applicable	Not applicable
Pre-emptive	Probable	+	−	+[a]	−
Empirical	Possible	+	+	−/not available	−/not available
Presumptive	Probable	+/−	+	+	−/not available
Targeted	Proven	+/−	+/−[a]	+/−/not available	+

[a] Unlikely combination

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policy may have an impact on the antifungal resistance of local *Candida* strains [22–24].

Area 1: risk stratification

The major risk factor for IC is the severity of the patient's underlying condition, mainly represented by the APACHE II score. The severity of the underlying disease dictates the occurrence of additional risk factors, such as the use of broad-spectrum antibacterial agents, total parenteral nutrition, indwelling vascular device (central venous catheters, haemodialysis catheters, peripherally inserted central catheters and implanted ports) and major surgery [25].

Important studies were performed with the aim of identifying both a single predicting risk factor or a combination of them for building models able to identify patients more at risk of being affected by IC, and eventually apply the most effective management strategy.

In the *Candida* literature, the term "at risk" is used somewhat inconsistently: in a strictly epidemiological interpretation, a patient "at risk" of IC is a patient without IC who might develop it at a later time, with risk depending on a number of patient characteristics (and possibly deserving a prophylactic approach); however, in many studies on IC, "patient at risk" is a patient likely to actually have IC, based on a number of clinical features and risk factors (thus deserving an empirical treatment approach). Another meaning of "risk" is stratification according to the risk of death, which implies a judgement on the severity of the clinical conditions of the patient (for instance, as we suggest, by adopting the sepsis score) [26].

Some clinical prediction rules have been developed combining different parameters to predict which patient is affected (symptoms of infection are already there) or is likely to later develop an IC (no symptoms, but a situation which might deserve specific prophylaxis). The oldest, purely microbiological, stratification tool was the *Candida* colonisation index (CCI), based on the ratio between the number of distinct body sites colonised with *Candida* and the total number of sites tested. The so-called "corrected CCI (cCCI)", which came later, is the product of the CCI times the ratio of the number of sites showing heavy growth to the total of sites growing *Candida* spp. [27]. Subsequently, based on previous studies [28] in ICU populations, Ostrosky-Zeichner et al. [29] found that the combined presence of previous or concomitant systemic antibiotic therapy and a central venous catheter, plus two or more of the following variables (parenteral nutrition, dialysis, major surgery, pancreatitis and treatment with steroids or other immunosuppressive agents) was able to predict the development of IC with positive and negative predictive values of 10 and 97 %, respectively. The score did not depend on the presence of a clinical situation compatible with infection.

More recently, León et al. derived, from a large population of ICU patients with signs and symptoms of infection, the so-called "*Candida* score" (CS). The final predicting model included parenteral nutrition, surgery, multi-focal colonisation and severe sepsis. Each independent variable was weighted for the strength of its association with the outcome variable, with a score of 1 for the first three variables and a score of 2 for the fourth variable. Subjects with a score >2.5 were almost eight times more likely to later have candidiasis than those with a score <2.5 [30]. The CS has been later validated in a different cohort [31]. The above-mentioned risk factors and clinical prediction rules are certainly useful for stratifying ICU patients according to their risk of IC, but their discriminating ability is still unsatisfactory, so many patients without IC might receive an unnecessary antifungal therapy.

Recommendations

1. Patient stratification:
   - For a correct management of IC and candidaemia, physicians should take into account the individual

Table 3 Risk factors for IC

Hospitalisation in ICU
Acute/chronic organ dysfunction requiring intensive care/invasive procedures (e.g. mechanical ventilation, vasoactive drugs, renal substitution and extracorporeal circulation systems, high-volume fluid or haemocomponents infusions, tracheostomy and others)
Solid organ transplantation (and type)[a]
Onco-haematological diseases (and type) and stem cell transplantation, especially with graft-versus-host disease (GVHD)[a]
Surgery (especially abdominal surgery and surgical revision), trauma and burn patients
Paediatric and neonatal intensive care units[a]
Multiple underlying medical conditions (e.g. elderly patients in medical wards)
Immunosuppressive therapy
Renal failure requiring haemodialysis or haemofiltration
Neutropaenia[a]
APACHE score
Multiple site colonisation
Duration of hospital stay
Previous history of *Candida* infection
Total parenteral nutrition and use of indwelling catheters
Diabetes mellitus
Previous prolonged antibiotic therapy

[a] Will not be discussed because they are not within the scope of the present consensus

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risk profile of each patient. Factors to use to stratify the risk for a patient of being affected by IC are listed in Table 3.

2. Corrected *Candida* colonisation index [27, 31–33]:

   - A corrected *Candida* colonisation index ≥0.4 is an important risk factor for IC, but in many clinical settings, other stratification tools should be preferred owing to their greater simplicity of use.

3. Ostrosky-Zeichner prediction rule [28–31, 34–38]:

   - The Ostrosky-Zeichner prediction rule (based on risk factors in asymptomatic ICU patients) is probably best applied to exclude patients not at risk (rather than to identify those at risk) of developing IC, due to its low positive predictive value and high negative predictive value.

4. *Candida* score [30, 31, 37, 38]:

   - The *Candida* score (based on clinical symptoms and signs of severe sepsis/septic shock) can be used as a tool for predicting the likelihood of actually having IC in symptomatic ICU patients, but it is probably best applied to identify patients without (rather than those with) IC, due to its low positive predictive value and high negative predictive value.

Unresolved issues

A more discriminant stratification tool would be welcome. In addition, existing prediction rules should be validated prospectively in randomised and interventional clinical trials. This would be desirable not only for ICU patients, but also for other settings, such as surgery, internal medicine and geriatrics. It is currently difficult to quantify the impact of previous exposure to antibiotics on the risk of IC. Other settings should be considered in the future, like, for example, the use of biological response modifiers.

Area 2: microbiological diagnosis and clinical management

Blood cultures are currently considered the gold standard for the diagnosis of IC, despite it being shown that blood cultures are negative in roughly 50 % of patients with biopsy-proven disseminated IC and in 30 % of those with single-organ IC [39]. This might be due to the fact that, in deep-seated *Candida* disease following haematogenous spread, viable *Candida* cells are rapidly eliminated from the bloodstream, thus limiting the time window when *Candida* can be successfully detected in blood [14]. Another drawback of blood cultures is that it normally takes 24–72 h to identify a *Candida* strain growing in the blood culture. Hence, waiting for culture results before making a clinical decision determines a delay in the diagnosis and initiation of appropriate antifungal therapy. In conclusion, earlier markers of fungal infection are needed in order to improve diagnosis of IC [14]. Among earlier markers, the detection of galactomannan in blood or other body fluids is generally considered reliable for the diagnosis of invasive aspergillosis. For the diagnosis of IC, two methods have been proposed. The search for mannan antigen and antimannan antibodies separately have low sensitivity and specificity, which improve substantially when the two methods are combined [40–43]. The sensitivity and specificity of these tests have been questioned when used separately, but a number of reports indicate that, when they are used in combination, the performance improves substantially [41, 44]. The beta-D-glucan (BDG) test is a panfungal test which looks for an antigen that is present on many fungal cells [45–47], but not on mammalian and bacterial cells [46]. Thus, its detection in blood or other bodily specimens may represent a marker of a fungal disease. The test has been shown to possess good sensitivity and a very good negative predictive value [48–50] when a proper cut-off value is used. Owing to its high negative predictive value, the BDG test can probably be used better to exclude an invasive fungal infection (IFI) [14]. All these diagnostic tests may diagnose an IC earlier than clinical or culture-based measures [40, 41].

Nucleic acid-based diagnostic techniques are, perhaps, the fastest-growing segment of fungal diagnostics [51]. Generally speaking, molecular-based diagnostic tests can potentially be very sensitive in detecting an IFI and may provide results more rapidly than standard diagnostic procedures, thereby enabling the possibility for earlier diagnosis and more timely initiation of antifungal therapy [46, 47, 51, 52]. Many molecular platforms are currently under investigation [45, 47, 53].

Recommendations

1. Significance of *Candida* isolation from non-sterile body sites [54]:

   - In the asymptomatic patient, the isolation of a *Candida* strain from a non-sterile body site (bronchial aspirate, tracheal aspirate, bronchoalveolar lavage fluid or sputum) should not prompt any antifungal treatment and should be merely considered as colonisation.
   - However, in a patient with signs and symptoms of infection, multiple *Candida* colonisation, including isolation from urine in a patient fitted with a

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bladder catheter, might be suggestive of a *Candida* infection and might prompt antifungal treatment.
- The repeated isolation of *Candida* from fluids obtained from a surgical drainage should not be underestimated and should prompt additional investigations, even in the absence of clinical signs and symptoms.
- The same applies to *Candida* isolation from peritoneal fluids in a patient undergoing peritoneal dialysis.

2. Blood cultures [55–62]:

- As a general rule, at least two blood cultures (each with both aerobes and anaerobes bottles) should be obtained in the presence of signs and symptoms suggestive of infection. One of the two blood cultures should be obtained both from a peripheral vein and from the central catheter, if present. Patients receiving steroid therapy might have low-grade fever only. In these patients, a high level of suspicion should be maintained.

3. Role of BDG [31, 33, 50, 63–76]:

- The BDG test as a diagnostic test in a patient with signs and symptoms of infection might be effective in the early diagnosis or exclusion of IC. However, the results should be interpreted in the setting of the presence of other risk factors and the patient's clinical conditions.
- There is insufficient evidence to recommend the use of the BDG test as a screening tool in patients without symptoms.
- Turnaround time of the results is essential for timely clinical decisions.

4. Role of the mannan antigen/antimannan antibody test [40, 41, 77–79]:

- The mannan/antimannan detection test may be useful for the diagnosis of IC. The separate detection of either mannan or antimannan cannot be recommended.

5. Nucleic acid-based diagnostic techniques [52, 53, 75, 80–82]:

- Diagnostic techniques using biomolecular methods are not yet recommended, because of the heterogeneity of the available results, the lack of reliable reference standards and differences in techniques.

6. Echocardiography [83–86]:

- An echocardiography should be performed in all patients with persistent candidaemia (defined as blood cultures persistently positive after at least 96 h of adequate antifungal treatment and despite removal of the central venous catheter, if originally present), to rule out *Candida* endocarditis.
- These patients should be monitored for at least 6 months, since late *Candida* endocarditis is not uncommon.

7. Fundus oculi examination [87–90]:

- A fundus oculi examination should be performed and possibly repeated in every patient with IC, even in the absence of visual disturbances, to rule out chorioretinitis and endophthalmitis.

Unresolved issues

An agreement should be reached among experts about the optimal methodology for polymerase chain reaction (PCR) and other methods of biomolecular diagnosis [53]. Regarding the BDG antigen detection, open issues are what is the most appropriate cut-off able to maximise the positive and negative predictive values and to discriminate between infection and colonisation. The use of the test in different patient populations should also be explored, as well as its prognostic value and its possible ability to correlate with clinical severity [90]. Other research options include the value of the antigen test as a screening test in asymptomatic high-risk patients [71, 91], the best initial timing and the timing of repeat testing [65, 91, 92] and, finally, the possible benefit of combining BDG antigen and antibody detection [93]. In *Candida* endophthalmitis, the timing of fundus oculi examination should be better defined, as well as the need for and timing of repeated examinations, since small lesions might go initially undetected.

Area 3: prophylaxis

Prophylaxis is the administration of a drug to a patient with risk factors for IC (Table 2) and without clinical signs and symptoms of infection. The administration of an antifungal prophylaxis in a non-immunocompromised patient in the ICU without symptoms is not supported by published evidence. The administration of an antifungal in complicated surgical patients, such as those with anastomotic leakage or recurrent intestinal perforation, reported as an indication for antifungal prophylaxis in other guidelines, should not be defined as prophylaxis but rather as an empirical, presumptive or pre-emptive therapy. We agree that these patients should receive an antifungal but disagree to define this practice as prophylaxis. Indeed, these patients have an infection, often of unknown but probably polymicrobial aetiology, and usually receive antibacterial

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and antifungal treatments. The issue is dealt with in the appropriate section of this article.

Recommendation

1. Antifungal prophylaxis [28, 31, 94–104]:
   - Antifungal prophylaxis should not be administered in non-immunocompromised patients.

Unresolved issues

There might be subgroups of patients, such as, for example, those with obstructive chronic bronchopulmonary disease or those staying for a long time in the ICU, that might deserve antifungal prophylaxis. Future studies should aim to identify these populations and test antifungal prophylaxis in these specific settings. Studies of antifungal prophylaxis in asymptomatic patients at high risk for candidaemia are being performed [105].

Area 4: therapy for possible/probable IC

The administration of antifungal drugs in patients with risk factors for IC and signs and symptoms of infection but no definitive documentation of fungal infection (negative or pending cultures) has been defined in several ways. Some authors call it "empirical therapy", while others call it "pre-emptive" or "presumptive" therapy. As shown in Table 3, in general, empirical therapy means administering an antifungal in the absence of any indication other than fever and compatible symptoms, while the presumptive or pre-emptive approach implies the existence of additional factors increasing the likelihood that a fungal infection is present. However, in a very practical approach (as opposed to research settings), we believe that these are more semantic than practical issues, since the bottom line is that, in such instances, physicians start an antifungal therapy because they think that there are reasons to believe that the patient might have a fungal infection. What differs is the likelihood of the presence of a fungal infection and the risk of treating too early, too late or unnecessarily: what physicians need to know is whom and when to treat.

In 2005, Morrell and coworkers first demonstrated the clinical significance of delaying treatment in patients with IC. In a cohort of 134 patients, the initiation of antifungal therapy more than 12 h after the first positive blood culture was associated with an increased risk of death: the longer the time interval, the higher the mortality [9]. This was later confirmed by Garey and coworkers in a retrospective multi-centre cohort study of 230 patients who were prescribed fluconazole: the time to the initiation of fluconazole therapy was strongly related with outcome [10]. More recently, another retrospective cohort study of adult patients with IC reached the same conclusion, even when echinocandins were used [11]. The logical consequence of these observations prompted some investigators to assess the performance of an empirical antifungal approach in ICU patients with persistent fever not responding to antibacterial therapy, without trying to select patients at higher risk for candidaemia. In a multi-centre, prospective and randomised clinical trial in 270 critically ill ICU patients, Schuster et al. [106] failed to demonstrate any advantage for fluconazole compared to placebo using a composite endpoint for success.

Subsequently, in 2009, the IDSA guidelines for the management of candidiasis introduced the concept of empirical treatment for critically ill patients with risk factors for IC and no other known cause of fever, recommending that the decision should be based on the clinical assessment of risk factors, serologic markers for IC and/or culture data from non-sterile sites [12]. This approach is considered valid by many experts and the general opinion is that the administration of antifungal therapy should be guided by the evaluation of risk factors, use of clinical prediction rules and biological markers.

Recommendations

1. Timing of treatment [1, 9, 10, 31, 33, 41, 65, 67, 69–72, 77, 107–111]:
   - The decision of starting an antifungal therapy in the absence of a positive culture from a normally sterile site should be based on a careful estimation of the individual risk of being affected by a (so far) occult fungal infection. This estimation should preferably be based on criteria or scores stemming from multi-variable analyses and validated prospectively (including multi-site colonisation) (see León's rule).
   - The detection of biological markers for *Candida* (BDG, mannan/antimannan) makes the presence of a fungal infection even more likely and may be an important adjunctive tool, whose results should be evaluated within the overall clinical setting.
   - Patients who underwent multiple laparotomies with intra-abdominal leakage are likely affected by a fungal infection and certainly deserve an antifungal therapeutic intervention.
2. Treatment [111–119]:
   - An echinocandin should be preferred as the first-line therapy because of:
     - Fungicidal activity
     - Activity against strains embedded in biofilms

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- Activity against fluconazole-resistant and non-*albicans* strains that are resistant to fluconazole
- Favourable safety profile
- Low propensity for interactions

- This is particularly true for medical or surgical critically ill patients with prolonged hospital stay (over 1 month), prior prolonged antibiotic therapy and recent fluconazole exposure, all of which are factors potentially able to affect the selection of fluconazole non-susceptible *Candida* strains.
- Significant alternatives, in critically ill patients, are lipid formulations of amphotericin B (especially the liposomal preparation) and, to a lesser extent, voriconazole, but not amphotericin B deoxycholate, in particular when a site other than the blood infection site is suspected (e.g. peritonitis). This is supported by the lack of pharmacokinetic/pharmacodynamic (PK/PD) consideration of echinocandins in peritoneal fluid, although strong evidence is also lacking for amphotericin B.
- Therapy should be reassessed after 72–96 h, based on the patient's clinical conditions and microbiological results.
- Intravenous or oral fluconazole still remains a valid option but should be reserved for second-line or step-down therapy.

Unresolved issues

Large prospective studies are needed in order to validate the classification of therapeutic strategies and its usefulness and applicability both in the clinical practice and in the context of clinical trials. Additionally, optimal duration of empirical therapy is still undefined. The true epidemiological impact of *Candida* spp. in peritonitis is far from being defined and comparative studies are lacking. In this respect, studies about the PK/PD behaviour of echinocandins in the abdominal compartment should be performed.

Area 5: targeted therapy

Several randomised clinical trials have demonstrated the efficacy of echinocandins in the treatment of candidaemia [86, 120–123]. Caspofungin was shown to be as effective as and less toxic than deoxycholate amphotericin B, micafungin was both as effective and less toxic than liposomal amphotericin B in one study, and as effective as caspofungin in another study, while anidulafungin was more effective than fluconazole in a study in which candidaemias due to *C. krusei* were excluded, although the statistical conclusion of superiority was criticised. As a consequence, international guidelines have included echinocandins as the first choice for antifungal therapy in proven *Candida* infections [12, 13, 124]. Recently, a systematic review of all randomised antifungal clinical trials in documented candidaemia and deep-seated *Candida* disease which led to the approval of the three available echinocandins showed that the administration of an echinocandin, as compared with any other antifungal therapy, was significantly associated with survival and success of therapy [120, 121, 123, 125]. Survival is associated with indwelling catheter removal [126]. In a previous analysis, Gafter-Gvili et al. [127] showed a decreased mortality rate in patients with candidaemia and other invasive *Candida* infections treated with an echinocandin in comparison with other antifungal drugs. Which echinocandin should be preferred is an unresolved issue. Firstly, there is no evidence for the superiority of one echinocandin over another. There are differences in fungal minimum inhibitory concentration (MIC) values, liver toxicity, volume of liquids infused and PK/PD parameters, but no clinical study has been performed to analyse whether or not these differences have clinical implications in terms of efficacy or toxicity. The indications are different, with caspofungin having the higher number of indications. All three agents are approved for the treatment of IC in non-neutropaenic adults, although according to the European Medicines Agency (EMA) summary of product characteristics, the efficacy of anidulafungin in patients with deep-seated *Candida* infections or intra-abdominal abscess and peritonitis has not been established. A subsequent phase III exploratory study shows that these indications would also be covered [128]. In addition, caspofungin and micafungin are approved not only for non-neutropaenic but also for neutropaenic patients with candidaemia and for paediatric patients (micafungin for newborns, as well). Other approved indications are, only for caspofungin, salvage therapy in invasive aspergillosis and empirical therapy of febrile neutropaenia and, only for micafungin, prophylaxis of fungal infections in the first month after hematopoietic stem cell transplantation (HSCT). Probably the main downside for all echinocandins is their lack of ocular penetration, which can be an issue, since *Candida* endophthalmitis can seldom be observed as a complication in candidaemia. To reduce direct health care costs and impact on local resistance patterns, de-escalation from echinocandins to fluconazole is advisable, if the isolated *Candida* strain is fluconazole-susceptible and the patient is clinically stable [12, 120, 122, 123]. However, there is no evidence about the timing of such de-escalation. The reduced in vitro susceptibility to echinocandins of certain *Candida* strains, such as *C. parapsilosis* and *C. guilliermondii*, has been shown in several studies, although this finding does not appear to be consistently relevant in clinical practice [86, 129–133]. A large study in French hospitals has shown that, among patients pre-exposed to caspofungin (the

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echinocandin most often used in Europe), the spectrum of subsequent *Candida* infections shows an increasing number of species with higher MICs to echinocandins. The use of micafungin is complicated in Europe because the EMA decided to put a warning related to the possible risk of hepatic toxicity as observed experimentally in animal models, despite the lack of clinical demonstration that this is really an issue in practical terms. For this reason, according to the EMA, the drug should be used only in the absence of any other alternative.

Alternatives to echinocandins and fluconazole are liposomal amphotericin B, which is also fungicidal and active against biofilm, but maintains a certain degree of renal toxicity and is quite expensive, and voriconazole, which is potentially very useful in ocular, central nervous system (CNS) and bone infections, but shows several problems related to possible azole acquired cross-resistance, hepatic and neurological toxicity, and drug interactions [86, 113, 120–123, 134–143]. The PK/PD behaviour of several drugs in bones is suboptimal, particularly unpredictable and even disappointing; it is, therefore, more relevant than in other settings to consider the MIC of the isolated pathogen(s). Itraconazole and posaconazole are not currently indicated, due to the lack of controlled, randomised, large-scale clinical trials [144].

Recommendations

1. First-line therapy [86, 113, 120–123, 134–142]:
   - All patients with isolation of a *Candida* strain from a sterile site deserve antifungal therapy.
   - An echinocandin should be used as the first-line treatment in critically ill patients with IC.
   - There are no data on which echinocandin should be used and the choice should be based on the respective indications of use, possibly PK/PD factors and personal experience regarding use.
   - Acceptable alternatives in critically ill patients are lipid formulations of amphotericin B (especially the liposomal preparation) and, to a lesser extent, voriconazole, but not amphotericin B deoxycholate.
   - In stable patients, fluconazole is an acceptable alternative, although it should be used with great caution, since the drug is not active on strains embedded in biofilms, has only fungistatic activity, is not active against *C. krusei* and is poorly active against *C. glabrata*. In addition, azole resistance in previously sensitive strains is increasing.
   - Itraconazole and posaconazole are not currently indicated.
2. Treatment in case of risk of resistance [22, 120, 125, 145, 146]:
   - In patients with prior relevant exposure to an antifungal agent, a change in class, especially for azoles, should be encouraged.
3. Treatment duration [120, 122, 123]:
   - Patients should be treated for at least 14 days after the last positive blood culture (this requires blood cultures to be performed daily until negativisation).
   - De-escalation from an echinocandin to intravenous or oral fluconazole should be encouraged when the patient is clinically stable and the isolated strain is susceptible to fluconazole. However, the exact timing for shifting to fluconazole is basically unknown and may vary from patient to patient, depending on the patient- and pathogen-related factors.
   - Treatment duration might be much longer in deep-seated infections.
4. *Candida* endocarditis [83, 147]:
   - *Candida* endocarditis should be treated with an echinocandin (mostly caspofungin, because of the largest amount of evidence) or liposomal amphotericin B plus flucytosine.
   - Surgical intervention and removal of intracardiac devices is certainly recommended, whenever possible. When cardiosurgery is impossible, long-term suppressive fluconazole might be an option, once clinical remission has been obtained with first-line therapy and the isolated strain is susceptible to fluconazole.
5. Ocular candidiasis [89, 148–152]:
   - In *Candida* endophthalmitis, the preferred treatment should be voriconazole, because of its ability to concentrate in the eyes, although resistance problems might be considered. Liposomal amphotericin B and fluconazole (for fluconazole-sensitive strains) are valid alternatives. The echinocandins are contraindicated because of their poor ocular penetration.
   - The optimal duration of treatment is unknown, but should certainly be longer (at least until the resolution of ophthalmologic signs) than in uncomplicated IC.
   - In case of vitreitis, vitrectomy and intravitreous infection, deoxycholate amphotericin B should be considered.
6. Management of intravascular catheters in IC [86, 153]:
   - Intravascular catheters should definitely be removed in patients with documented IC. If an intravenous line is indispensable, it should be

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inserted in a different vein. The timing of removal is questionable, although it seems reasonable to proceed to removal as soon as possible.

- In the rare instances in which the catheter cannot be removed (e.g. long-term, tunnelled catheters or in the absence of viable alternatives), an agent active against strains embedded in biofilm (echinocandin or polyene) should be preferred. Lock therapy with the same drug (in addition to intravenous therapy) might be an option, though good evidence is lacking on this issue.

7. Central nervous system [154–158]:

- In CNS *Candida* infections, voriconazole or liposomal amphotericin B plus flucytosine should be first-line agents. Consider a long-term suppressive regimen (i.e. until normalisation of clinical and laboratory signs), usually with fluconazole.

8. Urinary candidiasis [159, 160]:

- A positive culture for *Candida* in urine from a patient without a urinary catheter deserves treatment.
- If the infection is due to a fluconazole-susceptible strain, then fluconazole should be the first choice. With fluconazole-non-susceptible strains, a liposomal preparation of amphotericin B should be used.
- Treatment should be continued for at least 7 days in uncomplicated cystitis, but longer in pyelonephritis.
- Patients fitted with a urinary catheter and with a positive urine culture for *Candida* should be carefully observed for possible systemic infection, especially in the presence of other colonisation sites. Catheter replacement should be considered, upon clinical judgement, and culture repeated.

9. Bone and joint infections [161–164]:

- Treatment of *Candida* bone and joint infections should be based on susceptibility data (if available) and PK/PD considerations.
- Septic arthritis should be treated for at least 6 weeks, while osteomyelitis and prosthetic joint infections should probably require longer treatments (6–12 months).
- In septic arthritis, debridement must be performed, considering the risk of long-term sequelae of untreated arthritis.
- Infected prosthetic devices should be removed, whenever feasible. If removal is not feasible, chronic suppressive therapy is an option.

Unresolved issues

Several areas for research are currently open. For example, there is not enough information available about combination therapy in severe, deep-seated infections (e.g. peritonitis) or in IC with septic shock or endocarditis. Indications about the time to de-escalation to fluconazole is another open issue. No information is available about posaconazole and, to a lesser extent, itraconazole. The role of higher dosages of echinocandins should be investigated, again in the most severe infections, as well as the role of lock therapy with echinocandins, particularly when the central venous catheter cannot be removed; on this issue, some trials have been designed [165]. CNS infections are rare, but little information is available about treatment [89, 148, 149].

Discussion

The diagnosis and management of IC is an extremely complex exercise, especially in settings where the index of suspicion is low. The recently published ESCMID guidelines provide an excellent state-of-the-art of the existing evidence in this field [13]. With this set of guidelines, we offer a different perspective on several issues.

An innovative trait of our work is that we attempted to reconcile discrepancies in the literature by developing a comprehensive set of definitions of diagnostic categories and treatment strategies. In particular, the pre-emptive definition was adopted to account for those (rare) patients with positive biomarkers and no symptoms, in analogy to the cytomegalovirus (CMV) setting, where the definition of pre-emptive is based on the molecular detection of viral DNA in the absence of symptoms and signs of diseases. The presumptive strategy was adopted to stress the growing relevance of biomarkers as opposed to microbiological isolates in the diagnosis of IC. We believe that the adoption of these definitions may help to define inclusion criteria in future studies and improve the comparability of results from current and future studies.

On the other hand, we decided to have a very practical approach and to avoid semantic considerations trying to differentiate in practice between empirical, presumptive and pre-emptive therapy: there is only one therapy for a patient in which the attending physician is convinced (based on clinical and microbiological considerations) that a *Candida* infection is possible/likely or proven.

We aimed to stress candidaemia and IC as a hospital-wide issue, as opposed to an infection limited to ICU and surgical patients, from where most of the literature has been derived. In our view, one of the greatest challenges in the management of IC is to raise awareness

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in internal medicine wards and other situations in which IC was rare in the past. Another important issue it to optimise the use of the new microbiological diagnostic techniques. Once the diagnosis is suspected, further management should be guided by experts in clinical microbiology, infectious diseases and pharmacology, abreast of the latest developments in the field. Risk stratification (in terms of estimating the risk of actually having IC) is extremely important when deciding whether or not to start therapy, allowing better resource allocation (high-cost diagnostics, high-cost drugs); in this setting, a better stratification tool would be welcome. However, stratification in terms of clinical risk also applies to the setting of targeted treatment; for instance, allowing de-escalation to lower-cost drugs (e.g. fluconazole) as soon as the patient becomes clinically stable. We are convinced that the BDG test should be used for the identification of patients deserving early treatment (with the proviso that the local logistics ensures timely results) to improve the likelihood of diagnosis. However, in these times of resource constraints, we realise that not all hospitals can afford the relevant expense for this test. For this reason, we believe that the clinical prediction rules are also useful and can represent a reliable method for making clinical decisions. We feel confident in recommending the administration of echinocandins, but we also believe that a de-escalation approach, when feasible, is safe and cost-saving. The time to de-escalate is controversial and every recommendation is arbitrary, in the absence of specific studies. However, we believe that the 10 days indication in the ESCMID guidelines is excessive and that a 72–96-h limit should be more suitable [120, 122, 123].

PK/PD considerations are important for making therapeutic decisions, especially when published experience is missing or based on small numbers. For this reason, we strongly support the use of voriconazole for patients with CNS or ocular infections, despite the risk of dealing with an azole-resistant strain [143].

We hesitate in recommending an echocardiography (especially transesophageal) in all patients with documented IC and would prefer to limit the indication to patients with persistently positive blood cultures.

Other limitations and difficulties that we encountered in the consensus process mainly stem from the lack of high-quality evidence on many issues related to IC, owing to a number of factors: the relative rarity of the condition, not allowing large generalisable studies; wide variability in diagnostic methods, definitions and inclusion criteria across studies, with, for instance, likely selection bias (patients in wards other than the ICU are less likely to be correctly investigated and diagnosed), limiting between-study comparisons and generalisability; suboptimal performance of the available diagnostic tools for early identification, possibly generating a misclassification bias in many studies, reducing our ability to assess the efficacy of interventions, as in the case of empirical treatment strategy.

Acknowledgements We thank Federico Pea and Maurizio Sanguinetti for their important contributions to the discussion of the recommendations.

Conflict of interest This work, including travel and meeting expenses, was funded by an unrestricted grant by MSD Italia Srl. The sponsor had no role in selecting the participants, reviewing the literature, defining recommendations, drafting or reviewing the paper, or in the decision to submit the manuscript for publication. All views expressed are solely those of the authors. All authors have completed the International Committee of Medical Journal Editors (ICMJE) form, which is available upon request.

Appendix

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continued

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