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SEVEN-DAY PROFILE PUBLICATION

ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients

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Abstract

Introduction: The term invasive candidiasis (IC) refers to both bloodstream and deep-seated invasive infections, such as peritonitis, caused by Candida species. Several guidelines on the management of candidemia and invasive infection due to Candida species have recently been published, but none of them focuses specifically on critically ill patients admitted to intensive care units (ICUs).

Material and Methods: In the absence of available scientific evidence, the resulting recommendations are based solely on epidemiological and clinical evidence in conjunction with expert opinion. The task force used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to evaluate the recommendations and assign levels of evidence. The recommendations and their strength were decided by consensus and, if necessary, by vote (modified Delphi process). Descriptive statistics were used to analyze the results of the Delphi process. Statements obtaining > 80% agreement were considered to have achieved consensus.

Conclusions: The heterogeneity of this patient population necessitated the creation of a mixed working group comprising experts in clinical microbiology, infectious diseases and intensive care medicine, all chosen on the basis of their expertise in the management of IC and/or research methodology. The working group's main goal was to provide clinicians with clear and practical recommendations to optimize microbiological diagnosis and treatment of IC. The Systemic Inflammation and Sepsis and Infection sections of the European Society of Intensive Care Medicine (ESICM) and the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) therefore decided to develop a set of recommendations for application in non-immunocompromised critically ill patients.

Keywords: Sepsis, Fungal, Antifungal, Echinocandin, Fluconazole, Shock

Introduction

Invasive candidiasis (IC) includes both bloodstream and deep-seated invasive infections caused by *Candida* species [1]. Over the past few decades, the incidence of IC has either progressively increased or remained stable in most regions of the world [2–5]. This is probably due to the increasing complexity of surgical procedures and the growth of patient populations at higher risk of infection (i.e. with more severe acute physiological derangements and a greater burden of comorbidity). At the same time, the increasing prevalence of multidrug-resistant organisms encourages the use of broad-spectrum

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antibiotics, which ultimately leads to selection of fungal infections [6]. Even though IC has become a challenge in many intensive care units (ICUs) worldwide, with a mortality rate approaching 40% in most series [7, 8], antifungal treatment recommendations remain largely based on randomized control trials (RCTs) that were not restricted to critically ill patients admitted to ICUs [9].

Delays in initiating adequate antifungal therapy have been associated with increased mortality [10, 11], a finding that has prompted the exploration of early risk management strategies such as prophylactic antifungal therapy, biomarker-based pre-emptive therapy and risk-based empirical therapy [12]. Several guidelines on the management of candidemia and invasive infection due to *Candida* species have recently been published [1, 5, 13–16], but none of them focus specifically on ICU patients. The Systemic Inflammation and Sepsis and Infection sections of the European Society of Intensive Care Medicine (ESICM) and the Critically Ill Patients Study Group of European Society of Clinical Microbiology and Infectious Diseases (ESCMID) therefore decided to develop a set of recommendations for application in non-immunocompromised critically ill patients.

Methodology

The heterogeneity of critically ill patients admitted to ICUs necessitated the establishment of a mixed working group comprising experts in microbiology, infectious diseases and intensive care medicine, all chosen on the basis of their expertise in the management of IC and/or research methodology. The experts were initially approached in January 2017 by the coordinators of this project (IM-L and MB) on behalf of the ESCMID and ESICM, and invited to participate. All those approached accepted the invitation. The main goal of the working group was to provide clinicians with clear and practical recommendations to optimize the diagnosis and treatment of IC.

The study coordinators (IM-L and MB) generated an initial list of topics and clinically relevant questions for consideration, which was distributed among the experts. From an initial document covering quite a broad range of items, it was decided by consensus (see below) to focus on the nine questions.

Medical Subject Headings (MeSH) terms and keywords were used for the main search, which covered the concepts underlying each question. Articles in all languages and all publication years were included. In the period from August to November 2016, initial searches were created and confirmed with input from the guideline committee chairs and group leaders. The searches were finalized and delivered between late November 2017 and June 2018. Once the literature searches had been performed, the authors continued to review the literature, adding any relevant articles.

In addition, the bibliographies of articles extracted in full were manually reviewed for additional potentially relevant publications. This was done using the keywords: "candidemia", "invasive candidiasis", "fungal diagnostics", "azoles", "echinocandins", "amphotericin b", "antifungal agents", "candidiasis", "fluconazole", "infection candidemia", "invasive candida".

The recommendations made were classified as strong or weak on the basis of the quality of the evidence, the balance of desirable and undesirable consequences of the management options compared, the assumptions about the relative importance of outcomes, the implications for resource utilization, and the acceptability and feasibility of their implementation.

The taskforce followed the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) [17] scheme of levels of evidence and recommendation grades. GRADE has four levels of evidence: high, moderate, low and very low. A consensus process determined the content of the recommendations and their strength. When required, a modified Delphi process was used in accordance with ESCMID guidelines [18–21]. Descriptive statistics were used to analyze the results of each round of votes in the Delphi process. For topics on which there was insufficient quality evidence, a "best practice statement" was formulated in order to at least furnish clinicians dealing with critically ill patients with a set of patient-centered management strategies based on recommendations from an expert working group.

Statements achieving >80% agreement were considered to have achieved consensus and included in the final document. Those with less than 80% agreement had to be revised and submitted to a further round of votes. Only the topic of pre-emptive therapy actually had to be discussed a second time and submitted to an additional round of votes. The reformulated statements on this topic reached the necessary 80% threshold of agreement. Therefore, at the end of the process, the working group had a complete set of statements, all of which had achieved consensus.

The working group writing committee (JDW, JGM, PM and MCE) drafted the first version of this paper, which was sent to the other group members for their critical review. The authors then amended the paper as required by the group. The final recommendations presented here are based on epidemiological and clinical studies together with, in the absence of available scientific evidence, expert opinion.

Table 1 Recent publications analysing pre-emptive therapy in non-neutropenic patients

Authors	Pre-emptive agent	Inclusion criteria	Proportion of invasive candidiasis
De Waele [121]	Fluconazole 400 mg daily (no duration mentioned)	Candida colonization: Candida species in ≥ 1 of the routine surveillance cultures (performed 3 times per week) of tracheal aspirate samples, oropharynx samples, urine samples, wound specimens, and perineal samples without signs or symptoms of infection	
Piarroux [76]	Fluconazole 800 mg loading dose then 400 mg daily for 2 weeks	Evidence of substantial colonization in the presence of multiple risk factors for candida infection Recent abdominal surgery or recurrent gastrointestinal perforations or anastomotic leakages Broad-spectrum antimicrobials Other risk factors, such as candida colonization, high APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, and use of parenteral nutrition	Cases of proven candidiasis Retrospective cohort: 32/455 (7%) Prospective cohort: 18/478 (3.8%)
Shan [22]	Fluconazole 400 mg daily	Persistent fever Prolonged ileus (> 7 days after the operation) No other source of fever Broad-spectrum antibiotics recently used Surgery has been performed, especially surgery transecting the gut wall	
Tsuruta [122]	Fluconazole 200-400 mg daily for 2 weeks	Patients with clinically documented candida infection (> 2 sites of colonization and positive β-D-glucan test (cut-off not mentioned) Patients with possible invasive candida infection (> 2 sites of colonization and positive β-D-glucan test)	Proven candida infection: 3/1000 admissions (6/1900 patients) Clinically documented candida infection: 13/1000 admissions (25 patients) Possible candida infection: 55/1000 admissions (104 patients)
Hanson [123]	Anidulafungin 100 mg daily for 14 days	Surgical ICU patients β-D-glucan testing at baseline and twice weekly (cut-off ≥ 60 pg/mL) during ICU stay	Probable invasive candidiasis: 3/45 (6.6%) patients
Ostrosky-Zeichner [124]	Caspofungin 70 mg loading dose then 50 mg daily until ICU discharge or a maximum of 28 days	Mechanical ventilation on any of days 1 through 3 of ICU admission AND use of a central venous catheter on any of days 1 through 3 of ICU stay AND use of any broad-spectrum antibiotic (i.e., one with activity against ≥ 2 bacterial classes) on any of days 1 through 3 of ICU stay AND at least 1 of the following risk factors: use of parenteral nutrition on any of days 1 through 3 of ICU stay, any type of dialysis on any of days 1 through 3 of ICU stay, any major surgery within 7 days prior to or on ICU admission, diagnosis of pancreatitis (by computed tomography or lipase level > 1000 U/L) within 7 days prior to or on ICU admission, use of systemic steroids (> 1 dose of prednisone equivalent to ≥ 20 mg/day) within 7 days prior to or on ICU admission, or use of any other immunosuppressive agent (> 1 dose) within 7 days prior to or on ICU admission	Placebo arm: 10/84 (12%) probable invasive candidiasis 4/84 (5%) proven invasive candidiasis Caspofungin arm: 9/102 (9%) probable invasive candidiasis 1/102 (1%) proven invasive candidiasis
Prattes [125]		Clinical/mycological/radiological findings Positive β-D-glucan results (> 120 pg/mL) In case of intermediate β-D-glucan results (between 60 and 120 pg/ml) β-D-glucan testing was repeated	Suspected invasive candidiasis 8/66 (12%) patients Proven invasive candidiasis 1/66 (1.5%) patients Probable invasive aspergillosis: 4/66 (6%) patients
Knitsch [126]	Micafungin 100 mg daily for 6 weeks	Community-acquired (CAI) or nosocomially acquired (NAI) intra-abdominal infection requiring surgery and ICU stay and appearing within 48 h (NAI) or 72–120 h (CAI) of surgery expected minimum ICU stay of 48 h	According to the analysis of the independent data review board Placebo arm: 11/124 (8.9%); micafungin arm: 13/117 (11.1%)

Table 1 (continued)

Authors	Pre-emptive agent	Inclusion criteria	Proportion of invasive candidiasis
Pang [73]	Simulation analysis	Two sequential positive β-D-glucan tests with one of the following signs/symptoms: (1) fever or hypothermia; (2) hypotension; (3) elevated white blood cell count	Not applicable

Treatment definitions

Different studies define treatments using different terminology, thereby precluding cross–study comparisons (Fig. 1). It is inherently difficult to compile a clear classification of what is, in reality, a continuum in IC. This is particularly true of prophylaxis vs pre-emptive and pre-emptive vs empirical treatments. Therefore, in the present document, the proposed treatment definitions are not mutually exclusive. The panel agreed on the following terms and definitions (Fig. 1):

- *Prophylaxis therapies* are antifungal therapies for critically ill patients with a high risk of developing IC because of intrinsic or patient-specific risk factors (such as immunosuppression) and/or risk factors linked to the reason for their admission (septic shock, abdominal surgery, long ICU stay, broad-spectrum antibiotic therapy, etc.) [15].
- *Pre-emptive therapies* are antifungal treatments administered to patients at risk of IC, with a diagnosis based on fungal biomarkers. The ESCMID guidelines define pre-emptive therapy as "therapy triggered by microbiological evidence without proof of invasive infection due to *Candida* species" [13]. The best tools are still to be clearly defined but the use of fungal biomarkers has been universally suggested, particularly (1,3)-β-D-glucan (BDG), *Candida* antibody and mannan antigen assay. Some authors refer to "presumptive" therapy, meaning that which is initiated in settings suggestive of a high *Candida* "load" [22].
- *Empirical therapy* refers to the administration of antifungal agents in patients with signs and symptoms of infection along with specific risk factors for IC, irrespective of biomarkers [23].
- *Directed/targeted therapies* are treatments based on microbiological confirmation of an invasive infection due to *Candida* species (e.g. a positive blood culture for *Candida* species) [24].

Specific topics discussed by the expert workgroup

The following section of the paper summarizes the recommendations on each topic (question) discussed by the experts.

Question 1 Can we recommend the use of risk prediction models in daily clinical practice?

Risk prediction models can be used to select high-risk patients for further microbiological work-up and biomarker sampling [25]. However, as these models are often specific to the hospitals and patients where they

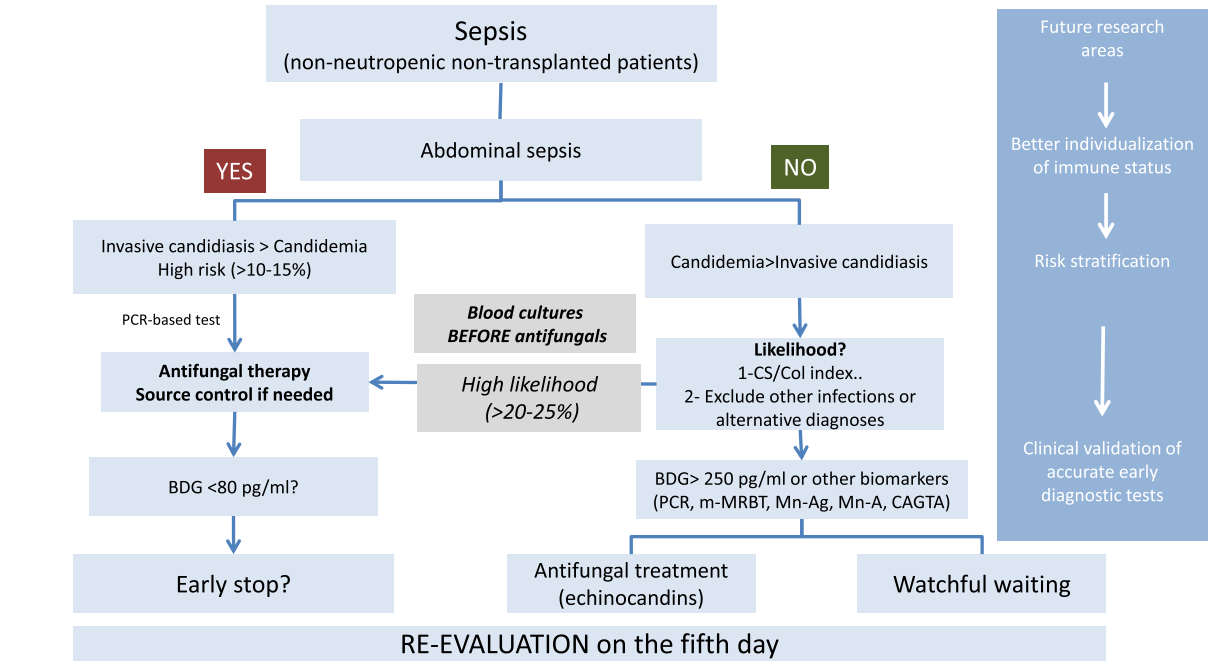

Fig. 1 Proposed algorithm for sepsis in non neutropenic non transplanted ICU patients at risk for Candidemia and/or IC. BDG, 1-3 β-D-glucan; CS, Candida score; m-MRBT, miniaturized-magnetic resonance-based technology; Mn-Ag, mannan antigen; Mn-Ab, anti-mannan antibody; CAGTA, *Candida* species germ tube antibody; Col index, colonization index; PCR, polymerase chain reaction; Abdominal sepsis: refers to anastomosis leak, postoperative abscess, repeated surgery for recurrent abdominal sepsis or infected pancreatitis

were developed, their reproducibility in other hospitals/countries might need to be evaluated and validated. Risk prediction models can be useful not only for determining a low likelihood of IC but also for selecting those candidates most likely to benefit from further biomarker assessment (i.e. to improve the positive predictive value of such testing).

Several authors have proposed scoring systems that combine clinical variables and, in some cases, microbiological information about the colonization status, and use a mathematical approach to determine the cut-off value that differentiates *Candida* species colonization from IC (mainly candidemia) [26–32]. Used appropriately, these risk prediction models may assist in the identification and treatment of patients with or at risk of IC, thereby directly reducing the mortality rates associated with this infection [32–35].

These risk prediction models commonly give high negative predictive values and modest or low positive predictive ones. They can therefore be used for ruling out the presence of IC in specific high-risk patients. Their usefulness for targeting empirical antifungal treatment, i.e. for restricting it to those at greatest risk, is limited. Nor have they been designed to monitor the response to antifungal treatment, with a view to reducing the duration of the therapy [23].

Recommendations

- Risk prediction models, because of their simplicity and high negative predictive values, should be used for identifying high-risk patients (Strong recommendation, low-quality evidence).

Question 2 What conventional and non-culture-based microbiological techniques are available for diagnosing IC?

The sensitivity of blood cultures is limited and they have a slow turn-around time for diagnosing IC [36]. Moreover, in the absence of a gold standard reference test, their true sensitivity for detecting candidemia remains uncertain and probably varies according to the type of IC (i.e. intravascular or deep-seated, with or without secondary candidemia) and the type of *Candida* species (e.g. lower for *C. glabrata*)[37, 38].

Standard automated blood culture systems are capable of detecting yeasts. Specific blood culture bottles, such as

the BACTEC Myco/F Lytic or Mycosis IC/F bottles (Becton–Dickinson Diagnostic Systems, Sparks, MD) or the BACT/ALERT FAN aerobic bottles (BioMérieux, Durham, NC) have been suggested to enhance the likelihood of recovering yeasts in blood cultures. However, these bottles have not been proven superior to conventional blood cultures in terms of either yield or cost-effectiveness [39–41].

The major limitation of blood cultures is the delay in obtaining definitive identification of the species in question. Typically the incubation time until detection of growth is 24–72 h, followed by an additional 24–48 h for species identification. The advent of mass spectrometry (MALDI-TOF) has significantly reduced the time required to identify *Candida* species in subcultures, without affecting the excellent diagnostic accuracy. However, the yield of blood culture bottles for yeasts remains low, and this method has not been fully validated [42]. Fluorescence in situ hybridization (PNA-FISH Yeast Traffic Light assay) differentiates between *C. albicans*, *C. parapsilosis* and *C. tropicalis* and the intrinsically azole-resistant *C. glabrata*/*C. krusei* within 1 h of blood culture positivity [43]. Molecular classification of *Candida* species by DNA target sequencing can also be clinically useful in some cases [44].

The non-culture-based microbiological techniques available for the diagnosis of IC include polymerase chain reaction (PCR)-based tests, miniaturized-magnetic resonance-based technology, and serological tests.

- *PCR-based tests* DNA detection by PCR is an alternative approach for rapid detection of yeasts. Multiple in-house *Candida* species PCRs have been developed. Meta-analyses suggest that most perform excellently, allowing direct detection of *Candida* species in blood [45]. However, the lack of standardization remains a major limitation of this method. Some PCR panel tests for detection of bacteria and fungi are commercially available. For example the LightCycler SeptiFast and the IRIDICA BAC BSI assay. The latter combines PCR and electrospray ionization mass spectrometry. The performance of these tests for detecting yeasts seems promising, but they require validation in large patient cohorts [46, 47]. The role of direct PCR testing of serum or blood samples in patients without candidemia also requires further investigation [48, 49].
- *Miniaturized-magnetic resonance-based technology* This fully automated, FDA-approved technique combines PCR technology with nanoparticle-based hybridization. The pathogen DNA is amplified and then identified by agglomeration of super-magnetic particles. Thus, the presence of pathogens can be established even in patients with a low fungal load (1–3 CFU per ml). The platform allows identification of the five predominant *Candida* species (*C. albicans, C. tropicalis, C. parapsilosis, C. krusei and C. glabrata*) within 3–5 h and without the need for prior incubation. When compared with blood cultures, the sensitivity and specificity of this technique were each found to be nearly 100% for all tested species [50, 51]. The ability of a miniaturized-magnetic resonance-based technology to detect *Candida* species in blood-culture negative IC (including deep-seated IC) remains to be investigated.

Several biomarkers are commercially available for the detection of fungi in the serum. These include, for example, the mannan antigen (Mn–Ag) and anti-mannan antibody (Mn–Ab), 1,3-beta-D-glucan (BDG) and the *Candida* species germ tube antibody (CAGTA), all of which have been proposed for early detection of IC. These tests have been used for guiding pre-emptive therapeutic strategies, especially in patients with suspected deep-seated IC without candidemia. However, Mn–Ag and Mn–Ab, used alone or in combination, exhibit suboptimal performance for diagnosis of IC, and CAGTA, too, has been associated with low sensitivity and specificity [48, 52].

The biomarker most commonly used for detecting fungi in critically ill patients is the BDG test. *Candida* species biomarkers (especially BDG) are now increasingly being used to enable earlier diagnosis of IC [53]. Thus, the BDG assay makes it easier to identify patients at risk of invasive infection due to *Candida* species and may inform the decision to start antifungal therapy in these patients. The performance of BDG antigenemia is superior to that of risk prediction models and colonization indexes for predicting blood culture-negative IC [54]. This test is included among the EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycosis Study Group) diagnostic criteria for invasive fungal infections [55]. The ESCMID also recommends the BDG test for ruling out candidemia or IC in adult patients at risk of infection [13]. However, reports on the diagnostic accuracy of BDG are very heterogeneous in terms of underlying conditions, risk factors, type of IC (candidemia or deep-seated *Candida* species infections) and the cut-off value used to determine positivity. This test probably performs best when used in high-risk patient populations; its sensitivity and specificity have been reported as 70–80% and 55–60% respectively [56]. The specificity of this test can be further increased with moderate loss of sensitivity by using higher cut-off values (200 pg/ml or higher, instead of 80 pg/ml) or by requiring

two consecutive positive tests for a definitive diagnosis [48, 54, 57]. The BDG test shows an excellent negative predictive value, and its utility is optimized when it is used in combination with risk prediction models or other fungal biomarkers (Mn–Ag, Mn–Ab or CAGTA), allowing either avoidance or early discontinuation of antifungal therapy in a significant proportion of patients [48, 53, 57, 58]. BDG can also be positive in critically ill patients affected by invasive pulmonary aspergillosis [59].

Consensus statements

- The panel suggests that when IC is suspected, cultures and microscopic examination should be performed on blood and other body fluids taken from all normally sterile sites (best practice statement).
- The panel recommends incorporating conventional and non-culture-based techniques as part of the diagnostic strategy for IC (best practice statement):
- Conventional culture-based tests (best practice statement).
- PCR-based tests (weak recommendation, low quality of evidence).
- Miniaturized-magnetic resonance-based technology (weak recommendation, low quality of evidence)
- Serological tests:
- BDG (weak recommendation, moderate quality of evidence)
- Mn-Ag and Mn-Ab (weak recommendation, low quality of evidence)
- CAGTA (weak recommendation, low quality of evidence).
- The panel agrees that PCR-based tests and miniaturized-magnetic resonance-based technology perform well. However, the lack of standardization and of large-scale validation precludes their clinical use without ancillary testing (weak recommendation, low quality of evidence)
- The panel agrees that the combined use of Mn-Ag and Mn-Ab, BDG quantification and CAGTA provides added value and that these tests are therefore of clinical utility (weak recommendation, low quality of evidence)
- The panel agrees that quantification of BDG has an excellent negative predictive value, and should therefore be used to rule out IC (weak recommendation, low quality of evidence)
- The panel recommends that the utility of quantitative detection of fungal biomarkers for identifying IC should be further assessed in large-scale clinical trials (best practice statement).

Question 3 Should antifungal prophylaxis be used in critically ill patients?

Early empirical therapy is the standard of care for critically ill patients with a high likelihood of the presence of a severe infection [60]. Early empirical treatment against infectious pathogens has been associated with lower mortality rates in a variety of studies and in different types of infection [61]. *Candida* species are no exception to this rule; early empirical antifungal therapy in high-risk populations (associated with source control if necessary) is a determinant of survival in critically ill patients with IC [62, 63].

However, unacceptably high mortality rates associated with IC, especially in immunocompromised and critically ill patients, are driving research into alternative treatment strategies [64]; so, too, is the fact that, in the context of few and non-specific clinical symptoms accompanied by low sensitivity and specificity of microbiological cultures and biomarkers, the diagnosis of the condition remains challenging. This situation is exacerbated by the lack of standardization of terminology across different studies as noted above (see Sect. 3).

The use of prophylactic antifungal therapies in critically ill adults has been evaluated in several studies that, despite their clinical and methodological heterogeneity, consistently report reductions in IC. However, the impact of these therapies on mortality remains controversial. Four meta-analyses combining the results of trials using azoles have been published. Prophylaxis with fluconazole or ketoconazole was shown to reduce invasive infection due to *Candida* species in critically ill surgical patients [65]. However, two analyses showed no impact on mortality rates [66, 67], while two others reported significant reductions [68, 69]. Resistance to fluconazole and the emergence of non-albicans isolates are unwanted side effects that are often associated with the use of azoles for prophylaxis [70].

Consensus statements

- The panel recommends against the routine and universal administration of antifungal prophylaxis in critically ill patients (weak recommendation, moderate quality of evidence).

Question 4 Should pre-emptive therapy be used in critically ill patients?

Patients with risk factors for IC are usually assessed for the presence of fungal biomarkers. Pre-emptive therapy was mentioned in the empirical treatment section of the 2009 Infectious Diseases Society of America (IDSA) guidelines [71]. However, the IDSA panel noted that the criteria for starting empirical antifungal therapy in non-neutropenic patients were poorly defined in these guidelines. Pre-emptive therapy subsequently disappeared

from the recently revised 2016 IDSA guidelines [5]. In addition, the relevant Canadian guidelines did not recommend pre-emptive treatment in non-neutropenic patients [72].

Several indications for pre-emptive therapy have been described, and some of the most relevant are presented in Table 1. However, in many studies, the criteria for initiating pre-emptive therapy remain unclear. As noted above, the high negative predictive value of BDG testing could be exploited for excluding IC in ICU settings; Pang et al. proposed surveillance with BDG to determine whether pre-emptive therapy should be initiated [73] and evaluated the potential cost-effectiveness of active BDG surveillance in patients admitted to adult ICUs. However, the BDG biomarker is often unavailable, which limits the applicability of this proposed approach. The accuracy of biomarker diagnosis of IC has been evaluated in subsets of ICU patients in whom the risk of IC reached 15% or more. Similarly, fungal colonization could be considered a marker of likely recourse to antifungal "pre-emptive" therapy, as well as a risk factor.

Overuse of antifungal therapy is a cause for concern from the cost perspective, but also from that of the emergence of antifungal resistance [74], and it is a particularly important aspect when considering the role of pre-emptive therapy. An observational study conducted in ICUs in Spain and Germany found that 32% of the patients with available microbiological results had invasive infections due to *Candida* species categorized as potentially resistant to intravenous fluconazole [75]. Similar results were described by Azoulay et al. [74] of 2047 patients across 169 ICUs in Belgium and France, 7.5% received systemic antifungal therapy, two-thirds of whom had no documented invasive fungal infections. These observations consistently suggest excessive unnecessary use of pre-emptive antifungal therapy.

Very few clinical studies examining the impact of pre-emptive treatment have demonstrated obvious efficacy. One study, using the corrected colonization index to assess the intensity of *Candida* species mucosal colonization, showed that pre-emptive therapy with fluconazole in selected colonized surgical ICU patients was associated with a reduced incidence of proven candidiasis [76].

Consensus statements

- The panel does not recommend the use of pre-emptive antifungal therapy in critically ill patients (weak recommendation, low-quality evidence).

Table 2 Inclusion criteria in recent publications analyzing empirical therapy in non-neutropenic patients and rates of invasive candidiasis in the study populations

Author	Inclusion criteria	Rates of invasive candidiasis
Golan [79]	Diagnosis after 3 days in the ICU Antibacterial therapy for 3 days Persistent fever, hypothermia or hypotension	
Schuster [80]	ICU stay of at least 96 consecutive hours, APACHE II score within 24 h of randomization ≥ 16 4 days of fever (defined as temperature > 38.3 °C on 3 separate occasions at least 12 h apart within 72 h before study entry, with at least 1 temperature spike within 12 h of study entry) Broad-spectrum antibiotics (both Gram-positive and Gram-negative coverage) for at least 4 of the preceding 6 days Presence of a central venous catheter for at least 24 h before study entry	Study population Fluconazole 6/122 (5%); placebo 11/127 (9%) Subgroup of patients with candida colonization at baseline Fluconazole 5/32 (15%); placebo 9/36 (26%)
Kollef [127]	Septic shock attributed to Candida infection if vasopressors were initiated within 24 h of the blood culture collection date and time that subsequently yielded a Candida species and no other infection potentially accounting for septic shock was present.	
Hanson [123]	β-D-Glucan testing at baseline and twice weekly (cut-off 60 pg/mL) during ICU stay Antifungal treatment decisions based on clinical judgment	Empirical therapy population 3/17 (17.6%) (1 probable invasive Candidiasis, 1 proven invasive candidiasis and 1 probable invasive aspergillosis)
Timsit [81]	Mechanically ventilated ≥ 5 days At least 1 colonization site (other than rectal swab or stool) positive for Candida species using traditional Culture methods At least 1 additional organ dysfunction Previous treatment > 4 days using broad-spectrum Antibacterial agents within the last 7 days Arterial or central vein catheter New finding of ICU-acquired sepsis of unknown origin	Study population Micafungin 4/128 (3%); placebo 15/123 (12%)

- The panel agrees that more studies are needed to define the critically ill patient profile that would benefit most from pre-emptive antifungal therapy and whether the widespread use of antifungal agents influences fungal ecology (best practice statement).

Consensus was not achieved on the question of whether pre-emptive antifungal therapy decreases the risk of subsequent invasive candidiasis in critically ill patients. Whilst the panel agreed that more studies are needed to determine the exact role of pre-emptive therapy in these patients, there was no agreement on the biomarkers whose performance might be the focus of future research, or on how many of them should be used when starting antifungal treatment.

Question 5 Which patients should receive empirical antifungal treatment?

Empirical antifungal therapy is commonly used in ICU patients. Examining the data collected from five French ICUs, Bailly et al. [77] observed that 6.7% of patients ventilated for more than 5 days received systemic antifungal therapy due to suspected infection. Another prospective study on the indications for systemic antifungal therapy in ICU patients with suspected or proven IC found that 65% of prescriptions (544/835) were ordered empirically. IC was secondarily confirmed in only 21% of these cases (112/544) [78]. Similar findings were reported in another multicenter, longitudinal, observational study in which empirical antifungal therapy accounted for 46% of all fluconazole prescriptions [75].

The key to maximizing the efficacy of empirical therapy lies in selection of the target cohort. Golan et al. [79] demonstrated that when empirical therapy in ICU patients was initiated on the basis of clinical suspicion alone (i.e. regardless of the presence of candidemia), IC was confirmed in only 20% of the cases. Strictly restricting the cohort to cases with candidemia increased the rate of diagnosis to 42%. The diagnostic rates of IC in various populations are presented in Table 2. As noted above, the use of additional criteria such as biomarkers might result in more accurate selection of the correct target population; however, treatment based on such selection can no longer be defined empirical.

The potential benefit of empirical antifungal therapy in ICU patients with sepsis and risk factors of fungal infection is debatable. In 2008, a study conducted in ICU patients at risk of IC with unexplained fever, empirical fluconazole (800 mg daily for 14 days) was not associated with better outcomes, compared with placebo [80]. Similarly, in patients with septic shock attributable to invasive infection due to *Candida* species, Micek et al. [62] observed similar in-hospital mortality rates with empirical therapy and treatment of the documented infection. The same observation was recently made in a retrospective cohort of patients with *Candida* species peritonitis. An exception to this rule might be constituted by low severity cases in which antifungal treatment can be delayed due to uncertainty: in such cases, delayed therapy has been associated with worse prognosis [35]. In short, multiple studies with different endpoints have failed to prove the efficacy of an empirical approach to antifungal therapy [62, 80, 81].

Consensus statement

- The panel suggests that empirical antifungal therapy might be considered only in patients with septic shock and multi-organ failure (MOF) who have more than 1 extra-digestive site (i.e. urine, mouth, throat, upper and lower respiratory tracts, skin folds, drains, operative site) with proven Candida species colonization (strong recommendation, low quality of evidence).
- The panel recommends not starting empirical antifungal therapy in patients without septic shock and MOF (strong recommendation, low quality of evidence).
- Candida isolation from respiratory samples should be considered as one site of colonization among others and isolation of Candida from the respiratory tract alone should not prompt initiation of treatment. However, this suggestion does not apply to patients with a clear diagnosis of pneumonia despite the presence of fungal colonization in a non-digestive site (best practice statement).
- The panel recommends the promotion of antifungal stewardship programs in order to limit the use of empirical therapy. The current practice of indiscriminate use of antifungals may lead to the emergence of resistant strains (best practice statement).

Question 6 What is the preferred first-line empirical therapy in a non-neutropenic critically ill patient with invasive candidiasis?

Fluconazole is a well-known and well-tolerated antifungal agent with a concentration- and time-dependent antifungal activity and a prolonged post-antifungal effect. It is significantly less costly than echinocandins and has value in clinically stable patients with no recent exposure to azoles in the setting of fluconazole-sensitive pathogens (best practice statement). The ratio of the free drug area under the concentration–time curve from 0 to 24 h to the minimum inhibitory concentration (fAUC0–24/MIC) is considered the pharmacokinetic/pharmacodynamic (PK/

PD) index of choice. A fAUC0–24/MIC of at least 100 is associated with optimal outcomes in the treatment of invasive infection due to *Candida* species.

As with antibiotics, there are important differences in the pharmacokinetics of antifungal drugs in critically ill patients compared with healthy volunteers [82]. Important determinants include the volume of distribution, fluid therapy and, in particular, kidney function, as fluconazole is primarily eliminated from the body via the kidneys. ICU patients consistently show considerable inter-individual variability in fluconazole concentrations. A one-dose-fits-all approach appears to result in variable concentrations and therefore variable target attainment [83]. Robust data on the possible impact of this variability on clinical outcomes are currently lacking.

All three echinocandins (caspofungin, micafungin and anidulafungin) are fungicidal and exhibit broad-spectrum activity. Acquired resistance to echinocandins is rare [84]. Furthermore, the minimal inhibitory concentration (MIC90) of echinocandins against *C. parapsilosis* is higher than that observed against most common *Candida* species [85]. This is also reported in observational studies [86].

Micafungin, caspofungin and anidulafungin have different volumes of distribution and plasma concentrations. Pharmacokinetic studies conducted in the ICU setting have yielded controversial pharmacokinetic results. Some studies suggest that caspofungin [87] and micafungin [88] have limited intra-individual and moderate inter-individual variability. Others have observed that the trough plasma concentrations of all three echinocandins may be highly variable and could be quite low in ICU patients [83, 89]. More recent data suggest that the pharmacokinetic parameters of anidulafungin in critically ill ICU patients with complicated intra-abdominal infections are similar to those of non-critically ill patients, even though an increased volume of distribution and a longer half-life are observed [90].

The safety profile of echinocandins has been evaluated in registered trials and has been compared with that of other antifungal agents. Fluconazole is a well-known and well-tolerated antifungal agent. It is significantly less costly than echinocandins and has value in clinically stable patients with no recent exposure to azoles in the setting of fluconazole-sensitive pathogens [91]. The toxicity of amphotericin B, both deoxycholate and liposomal formulations, is significantly higher than that of echinocandins [92, 93].

Although published guidelines no longer consider fluconazole the drug of choice for IC, especially in moderately to severely ill patients [5, 13, 72, 94], it is still recommended as the first-line agent for the treatment of candidemia and other forms of IC in non-critically ill patients who have not been exposed to this drug [11]. These recommendations are based mainly on the only existing head-to-head comparison of fluconazole with an echinocandin (anidulafungin), which, overall, demonstrated echinocandin non-inferiority [13]. However, in this same study, post hoc analysis was performed only in patients who were considered critically ill (i.e. those diagnosed with sepsis and admitted to the ICU with a high probability of death). Among these patients, even though the global response at day 14 was significantly better in the anidulafungin group, mortality at day 28 was comparable (20.2% vs 24.3%, $p=0.57$) [95]. Some have raised concerns regarding differences in the duration of intravenous therapy and in catheter removal strategies in this study [96]. Nevertheless, echinocandins are currently considered the first line of therapy in critically ill patients. Other arguments in favor of echinocandins include their wider spectrum of activity (that also includes *C. krusei* and *C. glabrata*), given the increasing incidence of invasive infection due to non-albicans *Candida* species, and their favourable safety and drug-interaction profile. One quantitative review of RCTs (1915 patients, 7 studies) showed that treatment with echinocandins led to decreased mortality [odds ratio (OR) 0.65; 95% confidence interval (CI) 0.45, 0.94] and increased treatment success (OR 2.33; 95% CI 1.27, 4.35) [97]. Conversely, two recent prospective studies showed no correlation between the type of antifungal treatment administered and patient prognosis [87, 98]. One meta-analysis reported favorable outcomes for micafungin [99], while another concluded that echinocandins are as effective and safe as triazoles for the treatment (and prophylaxis) of patients with fungal infections [100]. The authors of both these meta-analyses noted that the heterogeneity of the patient populations studied limited their ability to draw meaningful conclusions, and that none focused on critically ill patients. More recently, a propensity score-adjusted multivariable analysis of critically ill patients with proven candidemia showed that empirical therapy with echinocandins instead of fluconazole led to lower 30-day (OR 0.32; 95% CI 0.16, 0.66; $p=0.002$) and 90-day mortality (OR 0.50; 95% CI 0.27, 0.93; $p=0.014$) [101].

Current guidelines recommend that if treatment with fluconazole is selected, an initial fluconazole-loading dose of 800 mg (12 mg/kg) should be followed by a maintenance dose of 400 mg (6 mg/kg). The guidelines do not address whether the dose should be fixed or weight-based. However, there appears to be a clear correlation between dosing expressed in mg/kg and target attainment. In a small set of patients, the Defining Antibiotic Levels in Intensive care unit (DALI) study found that at least 5 mg/kg should be administered to reach the PK/PD target [83]. When converted to a weight-based dose,

the currently recommended fluconazole dose of 400 mg often falls below the 6 mg/kg recommendation. Although the fixed dose may be adequate for 70 kg patients, many patients with higher bodyweights are currently being treated with an inadequate dose. Suboptimal dosing with fixed-dose fluconazole appears to be common; up to 40% of patients are treated with fixed doses that correspond to less than 6 mg/kg [102].

With regard to echinocandins, recent PK/PD data suggest that the probability of reaching the target is not similar across the available echinocandins. Yang et al. [103] found that caspofungin was more optimal than anidulafungin and micafungin, owing to its higher probability of a successful outcome against IC. On the other hand, patients with *C. parapsilosis* need a higher caspofungin dose (100 mg q24 h). In patients with hepatic impairment, a suitable drug should be selected on the basis of their disease severity, pathogenic species and drug toxicity. Gustot et al. found that patients undergoing caspofungin dose reduction adjusted for liver failure show sub-therapeutic exposure [104].

Consensus statement

- The panel recommends that echinocandins should be used as the first treatment option in critically ill patients with septic shock and MOF with IC (weak recommendation, low quality of evidence).
- The panel recommends that fluconazole should be considered the first treatment option for critically ill patients with low severity of disease (i.e. without septic shock and/or MOF) in settings with low fluconazole resistance (strong recommendation, low quality of evidence).
- The panel recommends that critically ill patients treated with fluconazole should receive a loading dose. A weight-based dosing scheme is recommended (loading dose 12 mg/kg; maintenance dose 6 mg/kg) (strong recommendation, low quality of evidence).

Consensus was not achieved on the question of whether the favorable characteristics of echinocandins (i.e. their fungicidal and anti-biofilm activity, broader coverage and better safety profile compared with other antifungals) justify their use as first-line agents in patients with septic shock attributable to Candida species despite the finding that their use was not associated with higher survival rates.

Question 7 What is the role of polyenes in critically ill patients?

Amphotericin B deoxycholate (AmB-d) has several important pharmacological characteristics, including broad-spectrum coverage, a rapid time-kill rate, and its post-antifungal effect and efficacy, which are directly related to concentration (i.e. increase in parallel) [105]. The major disadvantages of AmB-d include infusion-related side effects (chills and fever), and other adverse events and toxicity (mainly to the kidneys) [106]. Lipid formulations of amphotericin B (LF-AmB) have the same efficacy as AmB-d, but a more acceptable safety profile [107]. However, to date there is no evidence that LF-AmB provides any therapeutic advantage over AmB-d (provided appropriate pre-medication is administered), and the cost of LF-AmB treatment constitutes a major limitation to its routine use. According to the conclusions of a recent meta-analysis, there is no evidence in the existing literature that choosing between echinocandins, voriconazole or amphotericin B formulations as first-line therapy for critically ill adults with invasive infection due to *Candida* species is associated with a therapeutic or survival benefit [108].

Candida species biofilm infections (commonly associated with central venous catheters) are often resistant to antifungals [109]. Removal of the catheter is warranted in such cases but this is not always possible (antifungal lock therapy in high dose concentrations to sterilize the catheter may be beneficial although it is not an attractive strategy in ICU patients)[110, 111]. In such situations, the antifungal drugs recommended are LF-AmB (active in both planktonic and sessile biofilm forms) and echinocandins (active against sessile form only), while azoles are less reliable. Of note, these recommendations are based mostly upon poor quality data and expert opinion as no RCTs have been conducted on this topic.

Consensus statements

- The panel recommends that AmB-d should not be used as a first-line treatment in critically ill patients with documented or suspected IC due to its significant nephrotoxicity (strong recommendation, moderate quality of evidence).
- The panel recommends that the use of LF-AmB (liposomal amphotericin B) should be preferred over other lipid formulations when previous treatment with echinocandins and azoles has already failed (strong recommendation, moderate quality of evidence).

Question 8 In non-neutropenic critically ill patients, does de-escalation of antifungal therapy yield similar outcomes (in terms of clinical success and mortality) as ongoing treatment with first-line antifungal agents?

De-escalation of treatment from echinocandins to intravenous azoles appears feasible once the patient has been stabilized, and when it is known that the isolate is azole-susceptible. Garnacho-Montero et al. [101] demonstrated that de-escalation of empirical echinocandins to fluconazole is safe and effective in fluconazole-susceptible infections. While most trials allowed step-down to azoles after at least 10 days of echinocandin therapy, a recent non-comparative trial examined step-down to an oral azole as early as 5 days after initiation of intravenous treatment [112]. More recently, Bailly et al., assessed the impact of de-escalation within the first 5 days of therapy in the ICU. Early withdrawal of antifungal treatment in cases of unnecessary empirical therapy and de-escalation to fluconazole in cases of documented IC were not associated with impaired survival or an increased rate of fungal infections at day 28 [113]. Although these studies were not designed to compare early step-down to ongoing treatment with echinocandins, the efficacy and survival rates in patients undergoing early step-down were similar in both studies.

Indirect evidence of the safety of de-escalation is also provided by antifungal stewardship experiments. A study by Guarascio et al. [114] evaluated a care bundle designed to decrease the use of echinocandins. Clinicians had to document daily the appropriateness of the initial diagnosis or indication, the planned duration of therapy, and the potential for de-escalation or discontinuation of the therapy in order to obtain authorization for renewing antifungal treatment. This approach significantly decreased the use of caspofungin in the bundle group as compared to a matched control group (median 4.00 vs 2.00 days, $p=0.001$), without adversely affecting patient outcome. Although the low sensitivity of blood cultures complicates the decision on whether antifungal treatment can safely be stopped, blood cultures should nevertheless be obtained before treatment decisions are made as they do provide some information that may improve treatment accuracy and allow early discontinuation of therapy. Biomarker data (BDG, Mn–Ag, Mn–Ab, CAGTA) can function as an additional de-escalation decision-support tool [115].

Biomarker combinations have proven effective in directing de-escalation strategies. In an RCT conducted in a mixed ICU, Rouze et al., prospectively compared a strategy of discontinuation of antifungal therapy after day 4 based on the results of Mn-Ag/Mn-Ab, BDG and traditional mycology results. Early discontinuation in the case of negative test results halved antifungal consumption and had no adverse effects on mortality, organ failure or the rate of recurrent fungal infections [116]. Antifungal susceptibility testing is not routinely performed in all institutions but can identify patients with resistant *Candida* species who are receiving an inappropriate agent and patients who would be candidates for de-escalation.

Consensus statement

- The panel recommends de-escalating from an echinocandin to fluconazole when the patient is clinically stable and the isolate is susceptible to fluconazole (Strong recommendation, moderate quality of evidence.)
- Echinocandins should not be de-escalated if central venous catheter or any other foreign material has not been removed. This recommendation is particularly pertinent to cases with an intravascular catheter that cannot be removed or if an intravascular device (e.g. pacemaker) must be left in place. (strong recommendation, moderate quality of evidence).
- The panel recommends that antifungal treatment should be stopped in patients with suspected (but not proven) IC with negative blood cultures and/or other negative culture specimens taken from suspected infectious foci before starting antifungal therapy (best practice statement).

Question 9 What is the recommended duration of antifungal treatment in patients with candidemia and IC?

The duration of treatment depends on the extent of organ involvement. Source control, which encompasses all measures to control invasive infection and restore optimal function of the affected area, has been shown to be an important determinant of outcome in patients with candidiasis. Although catheter removal in patients with candidemia remains a controversial issue, data reported in expert recommendations and previous studies suggest that central venous catheter and device withdrawal should be attempted, any identified collection should be drained, and adequate surgical source control should be performed [117].

For uncomplicated candidemia, treatment should continue for 14 days after the first negative blood culture. However, this relatively brief treatment duration applies only to patients in whom the presence of disseminated disease, abscesses, or end-organ disease has been excluded. According to the ESCMID guidelines on the diagnosis and management of invasive infection due to *Candida* species, adult patients with native valve *Candida* species endocarditis should undergo surgical treatment within 1 week combined with antifungal treatment consisting of LF-AmB or caspofungin for 6–8 weeks, with or without additional flucytosine, followed by

fluconazole [13]. Therefore, all patients with candidemia must undergo an evaluation to detect organ involvement. Work-up should include transthoracic (TTE) or transoesophageal echocardiography (TEE), fundoscopy and a thorough search for thrombus sites. TEE is preferred for critically ill patients as the quality of visualization with TTE can be suboptimal [118].

In a recent study, *Candida* species infective endocarditis was reported in 4.2% of patients with candidemia [119]. Ocular candidiasis may be found in 16% of patients with candidemia. Ocular candidiasis is manifested mainly as chorioretinitis. Endophthalmitis is rare (1.6%) [120].

With the exception of endocarditis, the duration of treatment in deep-seated IC infections does not necessarily have to be longer than 2 weeks; intra-abdominal candidiasis, for example does not require prolonged therapy. The duration of treatment depends on the site of infection and on the quality of the source control.

Consensus statement

- The panel recommends that candidemia should be treated for at least 14 days after the first negative blood culture (strong recommendation, low quality of evidence).
- The panel suggests that IC without positive blood cultures should be treated for 10–14 days (weak recommendation, low quality of evidence).
- The panel recommends that adequate source control (catheter removal, appropriate drainage, surgical control) should be performed early, if clinically feasible, in every critically ill patient with IC (strong recommendation, moderate quality of evidence).
- The panel recommends that in critically ill patients with IC and inadequate source control, the treatment duration for deep-seated infection due to Candida species (including endocarditis) should be individualized and based on a multidisciplinary approach (best practice statement).
- In cases where an intravascular catheter or any other foreign material cannot be removed, echinocandins should not be de-escalated to an azole because of their enhanced activity against biofilm (best practice statement).

Consensus was not achieved with regard to recommendation of the need for daily blood culture sampling until negativity in critically ill patients. The panel acknowledges that further research should be conducted in order to define how often blood cultures should be taken in critically ill patients who have had a positive culture.

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Compliance with ethical standards

Conflicts of interest

COIs declared by the authors: IML: Lectures: Thermofisher, Polyphor, J&J, Virogates, MSD. Advisory board: Fresenius Kabi, MaaT Pharma, Bayer, Gilead, Clinigen, Biotest, Accelerate. JGM has received speaker honoraria from Astellas and MSD. MB has participated in the past five years in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRx, and Vifor. SSK has received honoraria for participating in advisory boards or as a speaker for Merck, Pfizer, Hikma, Pasteur Aventis, Gilead. JDW has consulted for Accelerate, AtoxBio, Bayer Healthcare, Cubist, MSD, Pfizer (honoraria were paid to his institution). PM: Personal fees and non-financial support from Astellas, Astrazeneca, Basilea, Bayer, Cubist, Menarini, MSD, Parexel, Pfizer, Tetraphase, and The Medicines Company unrelated to the submitted work. GD: Advisory boards and/or received speaker honoraria from Astellas, Bayer, Cidara, Gilead, MSD, Nabriva, Paratek, Pfizer, Tetraphase, Cipla India, Glenmark India, Infectopharm Germany. MCE has received grant support from Astellas Pharma, bioMerieux, Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering Plough, CIDARA, Amplyx, F2G, Scynexis, Soria Melguizo SA, and Ferrer International. He is a founding Partner of the start-up Micología Molecular SL.

Ethical approval

An approval by an ethics committee was not applicable.

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