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Special Article

Recommendations for the management of candidemia in adults in Latin America

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ABSTRACT

Candidemia is one of the most frequent opportunistic mycoses worldwide. Limited epidemiological studies in Latin America indicate that incidence rates are higher in this region than in the Northern Hemisphere. Diagnosis is often made late in the infection, affecting the initiation of antifungal therapy. A more scientific approach, based on specific parameters, for diagnosis and management of candidemia in Latin America is warranted.

'Recommendations for the diagnosis and management of candidemia' are a series of manuscripts that have been developed by members of the Latin America Invasive Mycosis Network. They aim to provide a set of best-evidence recommendations for the diagnosis and management of candidemia.

This publication, 'Recommendations for the management of candidemia in adults in Latin America', was written to provide guidance to healthcare professionals on the management of adults who have, or who are at risk of, candidemia.

Computerized searches of existing literature were performed by PubMed. The data were extensively reviewed and analyzed by members of the group. The group also met on two occasions to pose questions, discuss conflicting views, and deliberate on a series of management recommendations.

'Recommendations for the management of candidemia in adults in Latin America' includes prophylaxis, empirical therapy, therapy for proven candidemia, patient work-up following diagnosis of candidemia, duration of candidemia treatment, and central venous catheter management in patients with candidemia.

This manuscript is the second of this series that deals with diagnosis and treatment of invasive candidiasis. Other publications in this series include: 'Recommendations for the diagnosis of candidemia in Latin America', 'Recommendations for the management of candidemia in children in Latin America', and 'Recommendations for the management of candidemia in neonates in Latin America'.

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Recomendaciones para el manejo de la candidemia en adultos en América Latina

Palabras clave:
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R E S U M E N

La candidemia es una de las micosis oportunistas más frecuentes en todo el mundo. El escaso número de estudios epidemiológicos llevados a cabo en América Latina indica que las tasas de incidencia en esta región son mayores que las descritas en el hemisferio norte. A menudo el diagnóstico de la infección se establece tardíamente, lo que afecta al inicio del tratamiento antimicótico. Por esta razón, para el diagnóstico y el manejo de la candidemia está justificada una estrategia más científica, basada en parámetros específicos.

Recomendaciones para el diagnóstico y manejo de la candidemia constituye una serie de artículos preparados por miembros del grupo Latin America Invasive Mycosis Network. Su objetivo es proporcionar las mejores evidencias disponibles para el diagnóstico y el manejo de la candidemia.

El presente artículo, *Recomendaciones para el manejo de la candidemia en adultos en América Latina*, ha sido redactado con el objetivo de orientar a los profesionales de la salud en el manejo de los pacientes adultos que padecen, o pueden padecer, candidemia.

Mediante la base de datos PubMed se emprendió una búsqueda informatizada de los estudios publicados. Los miembros del grupo revisaron y analizaron exhaustivamente los datos. El grupo también se reunió en dos ocasiones para proponer preguntas, abordar los puntos de vista conflictivos y deliberar sobre las recomendaciones terapéuticas.

Recomendaciones para el manejo de la candidemia en adultos en América Latina está orientado al tratamiento de pacientes neutropénicos y no neutropénicos, e incluye aspectos sobre la profilaxis, el tratamiento empírico, el tratamiento de la candidemia confirmada, el seguimiento del paciente después del diagnóstico de la candidemia, la duración del tratamiento y el manejo del catéter venoso central.

Esta publicación es la segunda de los artículos de esta serie dedicada al diagnóstico y tratamiento de las candidiasis invasoras. Otras publicaciones de esta serie son *Recomendaciones para el diagnóstico de la candidemia en América Latina, Recomendaciones para el manejo de la candidemia en niños en América Latina*, y *Recomendaciones para el manejo de la candidemia en neonatos en América Latina.*

Este artículo está publicado en español en este mismo número. Puede encontrarlo en http://dx.doi.org/10.1016/j.riam.2013.06.001

Candidemia in Latin America

Candidemia is one of the most frequent opportunistic mycoses worldwide.[74] The epidemiology of candidemia in Latin America has not been studied as extensively as in the Northern Hemisphere.[14,62] In the Brazilian Network Candidemia Study, a prospective laboratory-based surveillance study in 11 tertiary care hospitals, the overall incidence of candidemia was 2.49 cases per 1000 admissions.[14] More recently, a prospective laboratory-based survey was carried out in 22 hospitals throughout eight countries in Latin America and showed an incidence of 0.98 per 1000 hospital admissions, with a broad variation across countries (e.g. 0.32 in Chile and 1.75 in Argentina).[57] This is in contrast with the lower incidence rates of candidemia reported in the USA (0.28–0.96 cases per 1000 hospital admissions)[7,35,80,109] and Europe (0.20–0.38 per 1000 admissions).[93]

Candida species in Latin America

The most common species causing candidemia in Latin America are *Candida albicans* (40–50%), followed by *Candida tropicalis* and *Candida parapsilosis* (20–25%). Similarly, in the Latin America Invasive Mycosis Network survey, the most frequent species were *C. albicans* (42%), *C. tropicalis* (21%), *C. parapsilosis* (19%), and *Candida glabrata* (7%).[57] These species distributions are consistent with those found in other Brazilian studies[4,5,18] and in other studies conducted in Latin America.[20,87,88,91]

Remarkably, in Latin America, the frequency of candidemia due to *C. glabrata* is relatively low (4–7%).[15,57,73] However, a retrospective study from Brazil reported an increase from 3.5% in the 1995–2003 period to 10.6% in the 2005–2007 period. In this study, centers with higher consumption of fluconazole exhibited the highest incidences of candidemia due to *C. glabrata*.[71]

The increased incidence of candidemia due to *C. glabrata* has important clinical implications, as this species is characteristically less susceptible to fluconazole. In Latin America, *C. glabrata* isolates are less frequently resistant to fluconazole (10.6–13.2%) than in North America (18.0%).[74] In addition to those seen in *C. glabrata*, elevated rates of fluconazole resistance were found among isolates of *Candida guilliermondii* and *Candida rugosa* in a global surveillance study conducted between 1997 and 2003.[16,21,76] Regarding *C. glabrata*, although minimum inhibitory concentrations of voriconazole are lower than those of fluconazole, there is a potential for cross-resistance.[66] Conversely, *Candida krusei* is intrinsically resistant to fluconazole[27,75] but susceptible to voriconazole.[77] The incidence of candidemia due to *C. krusei* is low in Latin America (1.7%).[75]

Impact of early diagnosis in the outcome of candidemia

The outcome of patients with candidemia is directly related to the timing of initiation of appropriate therapy.[30] Therefore, strategies to diagnose candidemia early have been developed.

Candidemia affects patients of all ages, but the highest rates occur in infants younger than 1 year of age and in adults over the age of 65.[33,36] Major risk factors for invasive candidiasis (IC) include: broad-spectrum antibiotic use, central venous catheterization (CVC), intensive care unit (ICU) admission, major surgery, parenteral nutrition, renal replacement therapy, neutropenia, use of implantable prosthetic devices, and use of immunosuppressive

Table 1
Clinical scores for identifying patients at risk of candidemia.

	Colonization index	Candida score	Ostrosky-Zeichner score
Authors	Pittet et al.[79]	Leon et al.[42]	Ostrosky-Zeichner et al.[65]
Type of study	Six-month prospective cohort study in patients admitted to surgical and neonatal ICUs	Analysis of data collected from EPCAN database (ongoing prospective cohort, observational, multicenter surveillance study)	Retrospective review and statistical modeling of data
Inclusion criteria	Patients with significant *Candida* colonization (presence of *Candida* in three or more samples taken from the same or different body sites on at least two consecutive screening days	Non-neutropenic patients >18 years admitted to an ICU for at least 7 days between May 1998 and January 1999	Patients who stayed at least 4 days in hospital
Patients (n)	29	1699	2890
Prediction rule	(1) Single blood culture that grew *Candida* spp. and either histologically documented invasive candidiasis or ophthalmic examination consistent with candidal endophthalmitis; OR (2) at least two blood cultures obtained at different times from a peripheral vein that grew the same *Candida* spp.; OR (3) single blood culture obtained via indwelling central line and single blood culture obtained peripherally, both of which grew identical *Candida* spp.	A Candida score >2.5 accurately predicted proven candidal infection and identified patients who would benefit from antifungal treatment	(1) Any systemic antibiotic (days 1–3); OR (2) presence of a CVC (days 1–3) AND at least two of the following: TPN (days 1–3), any dialysis (days 1–3), any major surgery (days -7–0), pancreatitis (days -7–0), any use of steroids (days -7–3), or use of other immunosuppressive agents (days -7–0)
Candidemia n (%)	8 (28)	–	88 (3)
Sensitivity (%)	–	81	34
Two sites or more	100	–	–
More than two sites	73	–	–
Three sites or more	45	–	–
Specificity (%)	–	74	90
Two sites or more	22	–	–
More than two sites	56	–	–
Three sites or more	72	–	–
PPV (%)	–	–	1
Two sites or more	44	–	–
More than two sites	50	–	–
Three sites or more	50	–	–
NPV (%)	–	–	97
Two sites or more	100	–	–
More than two sites	77	–	–
Three sites or more	68	–	–

CVC = central venous catheter; ICU = intensive care unit; NPV = negative predictive value; PPV = positive predictive value; TPN = total parenteral nutrition.

therapies (including glucocorticosteroids, chemotherapeutic, and immunosuppressive agents).[48,68,93,94,99,110]

Clinical scores for identifying patients at risk of candidemia

Efforts have been made to better identify patients at risk of candidemia using clinical scores and predictive rules. Some of these have been validated but none are universally accepted, as each presents its own limitations (Table 1). One scoring system is based on *Candida* colonization as an independent risk factor for candidemia and can help predict subsequent infection in critically ill patients.[79] This score is determined by the calculation of a colonization index (CI; defined as the ratio of number of distinct body sites colonized with identical strains: total number of distinct body sites tested) or a corrected CI (CCI; defined as the ratio of heavily colonized: all colonized sites, multiplied by the CI). A CI $\geq$ 0.5 to predict the occurrence of candidemia or IC had a specificity of 69%, a positive predictive value of 66%, and a negative predictive value of 100%. These values were 100% each when a CCI $\geq$ 0.4 was used.[79] Although highly predictive for IC, CCI has issues related to practicality, logistics, and cost that present a challenge to its universal application.[64]

The Candida score (CS) was designed as a scoring system to select ICU patients for antifungal therapy.[43] The CS model assigns a score of 1 each for surgery, multifocal colonization, and total parenteral nutrition (TPN), and a score of 2 for severe sepsis. The incidence of candidemia or IC among non-neutropenic, critically ill, colonized patients was 13.8% with a CS $\geq$ 3 and 2.3% with a CS < 3.[64] Patients with a CS > 3 had an 11.5% risk of *Candida* and IC. Furthermore, this risk increased to 30.3% in patients with a CS > 3 who also had abdominal surgery. A CS $\geq$ 3 was found to be a significantly better predictor of IC than a CI $\geq$ 0.5. More recently, a study compared different scoring systems, and incorporated the level of serum 1,3-β-D-glucan (BDG), a component of the fungal cell wall. The best predictor of candidemia was BDG level (sensitivity 93%, specificity 86%), followed by CS and CI.[82] Further investigation is needed to validate the benefit of early antifungal therapy based on CS and BDG, and future studies are being planned.[64,105]

Prophylaxis

Antifungal prophylaxis is used to prevent fungal infection in patients who have no clinical evidence of infection but are at risk of developing an infection.

Non-neutropenic patients

Several groups have conducted meta-analyses of the randomized controlled trials (RCTs) investigating antifungal prophylaxis in non-neutropenic ICU patients.[19,34,81,90,97] Individual and aggregated results demonstrated that the use of prophylaxis reduced the risk of IC (50–80%). However, the effect on mortality has not been well defined, with only three meta-analyses demonstrating a trend toward reduction in mortality: one in adult trauma and surgical intensive care patients[19]; one in immunocompetent high-risk surgical patients[34]; and one in non-neutropenic critically ill and surgical patients.[81] The great heterogeneity of patients in the different studies likely influences these results.

When comparing the enrollment criteria of individual candidemia prophylaxis studies, it is evident that careful patient selection is necessary to maximize the benefit of prophylaxis in non-neutropenic patients.[22,29,72,85] Trials in patients at high risk of infection have provided evidence of a potential for prophylaxis in reducing the incidence rate of proven IC, when given to appropriately selected patients (i.e. critically ill patients who do not have neutropenia).[72,85] Therefore, a highly selective approach to identify high-risk non-neutropenic patients for prophylaxis therapy is recommended.

There is no universal recommendation for antifungal prophylaxis in non-neutropenic patients. However, risk-stratification strategies and related scoring systems to determine potential candidates for prophylaxis are available and have been used with varying degrees of success. Prophylaxis should be considered in settings with high incidence (>2%) of IC. Fluconazole at 400 mg (6 mg/kg) daily dose is the drug of choice. No recommendation exists regarding a standard duration of prophylaxis but, conceptually, prophylaxis should continue for the duration of exposure to risk factors.

Neutropenic patients

Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) undergoing intensive chemotherapy for induction remission and hematopoietic stem cell transplant (HSCT) recipients have high incidences of invasive fungal infection.[8,89] The risk of fungal infection in these patients is related to the intensity of the cytotoxic regimen, which results in severe oral and gastrointestinal mucositis, and to the duration of neutropenia.[11,32] In a study that investigated the relationships between cytotoxic regimen, intestinal mucosal damage, and fungal colonization in the pathogenesis of invasive fungal disease, patients with AML taking a high-dose chemotherapeutic regimen had a greater incidence of invasive fungal disease.[11] Furthermore, cytotoxic therapy-related damage to the functional integrity of the intestinal epithelium is predictive of invasive infections.[12] As such, neutropenic patients with severe mucositis should be strongly considered for antifungal prophylaxis.

The Working Group recommends prophylaxis for high-risk neutropenic patients (i.e. patients receiving intensive chemotherapy with strong potential to induce severe neutropenia and mucositis). For HSCT recipients, fluconazole (200–400 mg [3–6 mg/kg] daily), voriconazole (200 mg [3 mg/kg] twice daily), itraconazole oral solution (2.5 mg/kg three times per day), and micafungin (50 mg daily) have been tested, with equal efficacy to prevent IC.[31,47,92,96,105,108] Fluconazole is the drug of choice, unless anti-mold coverage is needed.

For patients with leukemia, fluconazole (400 mg [6 mg/kg] daily) or posaconazole (200 mg, three times per day) is recommended.[17,55,107] Again, fluconazole is the drug of choice for anti-*Candida* prophylaxis unless additional coverage against molds is needed.

Recommendations summary for *Candida* prophylaxis in non-neutropenic adults:

1. Non-neutropenic patients must be carefully selected for prophylaxis. Although no universal recommendations can be made regarding patient selection, scoring systems and predictive rules may help clinicians make treatment decisions on a case-by-case basis.
2. If prophylaxis is given, fluconazole at 400 mg (6 mg/kg) daily is recommended. There is no recommendation for duration of prophylaxis; however, patients should continue prophylaxis for the duration of their exposure to risk factors.

Recommendations summary for *Candida* prophylaxis in neutropenic adults:

1. Prophylaxis should be strongly considered in neutropenic patients with a potential to develop severe mucositis.
2. Patients with AML should receive prophylaxis during induction therapy.
3. For HSCT recipients, fluconazole (400 mg [6 mg/kg] daily) is the drug of choice. If anti-mold coverage is needed, voriconazole (200 mg [3 mg/kg] twice daily) is recommended.
4. For patients with leukemia, fluconazole (400 mg [6 mg/kg] daily) is the drug of choice, and if anti-mold coverage is needed then posaconazole (200 mg three times per day) is recommended.

Empirical therapy

Non-neutropenic patients

The Working Group recommends that empirical treatment should not be used in non-neutropenic patients who have not been exposed to risk factors for a long period of time, have no colonization, and are BDG negative. Empirical treatment may be considered in non-neutropenic patients with suspected candidiasis. The prediction rules summarized in Table 1 are important tools for the selection of appropriate patients for empirical therapy. The drug of choice for empirical therapy should be the same as for documented candidemia (see *Therapy for proven hematogenous candidiasis*).

Neutropenic patients

Empirical antifungal therapy is considered standard of care in neutropenic patients with persistent fever despite appropriate antibiotic therapy, and it is usually intended to cover both *Candida* species and molds. Its application exclusively for IC is occasional, and only considered in a patient who did not receive prophylaxis, has persistent fever and severe mucositis, and is not at risk of invasive mold infection. In such instances, empirical antifungal therapy with fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) is recommended.

Recently, attempts to change from empirical to a pre-emptive (or diagnostic-driven) approach have been made.[45] This is because, in the classical empirical approach, the trigger for starting antifungal therapy (persistent fever) is too sensitive, resulting in a substantial number of patients receiving antifungal agents unnecessarily. However, despite the appealing arguments for the diagnostic-driven approach, no formal recommendations can be made at this point.

Recommendations summary for the empirical treatment of candidemia in non-neutropenic adults:

1. Empirical treatment may be considered in non-neutropenic patients with risk factors for candidemia.
2. Prediction rules may be used at bedside to help clinicians to select candidates for empirical therapy.
3. No formal recommendations can be made regarding the use of serum biomarkers (such as BDG).
4. Empirical treatment agent and dosing recommendations are the same as for treatment of infection.
5. No recommendations can be made regarding duration of empirical therapy.

Recommendations summary for the empirical treatment for candidemia in neutropenic adults:

1. Empirical antifungal therapy is considered standard of care for persistently febrile neutropenic patients.
2. Although a diagnostic-driven approach seems reasonable, no formal recommendations can be made owing to a lack of studies supporting this strategy.
3. An AmB lipid formulation, an echinocandin, or voriconazole are options for initial empirical treatment for febrile neutropenic patients.
   a. L-AmB: 3 mg/kg daily.
   b. ABLC: 5 mg/kg/daily.
   c. Caspofungin: loading dose 70 mg, then 50 mg daily.
   d. Micafungin: 100 mg daily.
   e. Voriconazole: loading dose 6 mg/kg twice a day, then 3 mg/kg twice a day.
4. Empirical antifungal therapy with fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) is recommended if a patient did not receive anti-*Candida* prophylaxis, has persistent fever and severe mucositis, and is not at risk of invasive mold infection.

The decision on whether to treat empirically should be based on a patient's risk for both *Candida* infection and mold infection (mainly aspergillosis), and is therefore beyond the scope of this recommendations document. Nevertheless, acceptable options include treatment with an echinocandin (caspofungin [loading dose of 70 mg, then 50 mg daily][102] or micafungin [100 mg daily][70]), a lipid formulation of amphotericin B (liposomal amphotericin B [L-AmB; 3 mg/kg daily][100] or AmB lipid complex [ABLC; 5 mg/kg daily][106]) and voriconazole (6 mg/kg twice a day loading dose, then 3 mg/kg twice a day).[101]

Anidulafungin has not been investigated as an empirical therapy for neutropenic patients. However, there is no evidence to suggest that anidulafungin would perform differently from other echinocandins in this setting. As such, the Working Group would expect anidulafungin to have a similar effect as caspofungin and micafungin for empirical treatment in neutropenic patients.

Therapy for proven hematogenous candidiasis

Non-neutropenic patients

Echinocandins – First-choice recommendation

The Working Group recommends an echinocandin for initial treatment of candidemia in non-neutropenic adults. Echinocandins are noncompetitive inhibitors of the synthesis of BDG, a constituent of the *Candida* cell wall. Their administration schedule is convenient (once daily), and their activity is fungicidal against all *Candida* species.[10] Echinocandins include anidulafungin, caspofungin, and micafungin, all three of which are indicated for the treatment of candidemia.[6,50,78] There is currently no evidence to support the use of one echinocandin over another in non-neutropenic patients.

Several factors help favor the use of echinocandins (fungicidal agents) over azoles (fungistatic agents) for initial treatment of candidemia. First, the rising prevalence of *C. glabrata* and its relationship with fluconazole use, as well as the decreased susceptibility of *C. krusei* to azoles, suggest that echinocandins should be preferred over azoles for initial treatment.[27,71,75] Second, in randomized controlled trials (RCTs), higher rates of persistent candidemia have been observed with fluconazole (15–17%) than with other agents (8–9%).[56] The greatest difference in rate of persistent candidemia was seen in a trial that compared fluconazole with anidulafungin (16% versus 6%, $p = 0.01$).[83] Third, meta-analyses of RCTs have also shown echinocandins to be preferred over azoles. A meta-analysis that compared antifungal treatments for IC found that anidulafungin was associated with significantly higher clinical (relative risk [RR], 0.61; 95% confidence interval: 0.42, 0.89) and microbiological (RR, 0.50; 95% confidence interval: 0.29, 0.86) success rates compared with fluconazole.[28] In the same meta-analysis, echinocandins compared favorably with all comparators in adverse events requiring discontinuation.[28] In a patient-level meta-analysis of seven RCTs, use of an echinocandin rather than another antifungal agent was associated with decreased mortality.[3] Fourth, in a recent decision analysis model, anidulafungin appeared to be a cost-effective option versus fluconazole in the treatment of IC.[53] Last, fluconazole is the most frequent antifungal agent used as primary therapy for candidemia in Latin America, but the overall mortality is very high.[57]

Table 2
Recommended doses of fluconazole under normal and impaired renal function.

Renal function	Fluconazole dose
Normal	Loading dose of 800 mg (12 mg/kg), then 400 mg (6 mg/kg) daily
Creatinine clearance (ml/min)	
>50	Loading dose of 50–400 mg, then 100% of recommended normal dose
≤50 (no dialysis)	Loading dose of 50–400 mg, then 50% of recommended normal dose
Regular dialysis	Loading dose of 50–400 mg, then 100% of recommended normal dose *after each dialysis*

Azoles

After the treatment with an echinocandin, and if the patient is doing well and has an isolate susceptible to fluconazole, step-down therapy to fluconazole is possible; however, careful consideration regarding dosage based on renal function is recommended (Table 2). The optimal duration of echinocandin treatment prior to step-down therapy is not known. In one study, 159 patients with candidemia or IC switched from anidulafungin treatment (average treatment length: 8.6 days) to either fluconazole or voriconazole therapy (average total antifungal therapy: 14.1 days) and demonstrated an effective global treatment response of 80.1% (95% confidence interval: 84.0, 96.2) for patients switched to fluconazole and 93.6% (95% confidence interval: 86.6, 100.0) for patients switched to voriconazole.[98] In a similar but smaller study conducted in Latin America, short-course anidulafungin treatment (minimum 5 days of treatment) followed by oral voriconazole therapy also appeared to be an effective treatment for candidemia or IC.[61]

In the treatment of fungal eye infections, triazoles (fluconazole or voriconazole) are recommended over echinocandins.[46] For brain

and eye fungal infections, voriconazole is recommended over an echinocandin.

Amphotericin B formulations

The Working Group recommends avoiding the use of AmB deoxycholate (AmB-d) in ICU patients because of its unacceptable toxicity (especially renal). Lipid formulations of AmB include ABLC, AmB colloidal dispersion (ABCD), and L-AmB. These three lipid formulations of AmB have different pharmacological properties and rates of adverse effects, and they are only interchangeable with careful consideration. The Working Group recommends L-AmB over ABLC in the treatment of candidemia in non-neutropenic adults. The dose for L-AmB (3 mg/kg daily) was standardized in a randomized study comparing L-AmB with micafungin,[39] whereas for ABLC there is no standard dose and no randomized study has been performed.

Neutropenic patients

No more than 10% of the study populations in the RCTs of treatment of candidemia were neutropenic patients. Therefore, the strengths of evidence in neutropenic patients are lower than in non-neutropenic patients.

Considering the risks of renal toxicity associated with the use of AmB-d, the Working Group strongly discourages the use of this agent to treat candidemia. As in non-neutropenic patients, an echinocandin should be considered the drug of choice for primary treatment of candidemia in neutropenic patients. Although the RCT of anidulafungin in the treatment of candidemia did not include neutropenic patients, there is no pre-clinical evidence to suggest that anidulafungin would not be effective in neutropenic patients with candidemia. Alternatives to an echinocandin include a lipid formulation of AmB, voriconazole, and fluconazole. However, the use of these azoles may be limited by the fact that most neutropenic patients have previously been exposed to fluconazole, given as prophylaxis, and because candidemia due to *C. glabrata* is more frequent in this group of patients. Step-down therapy to an oral agent, such as fluconazole or voriconazole, may be advanced when information on species identification and antifungal susceptibility is available, provided that the patient is improving.

Recommendations summary for the treatment of candidemia in non-neutropenic adults:

1. Echinocandins are recommended as first-choice treatment for candidemia in non-neutropenic adults.
2. Step-down therapy to fluconazole is possible when a patient is doing well and has a fluconazole-susceptible infection.
3. In the treatment of fungal brain and eye infections, triazoles are recommended over echinocandins.
4. The use of AmB-d in ICU patients is not recommended.
   a. L-AmB is recommended over ABLC.

Recommendations summary for the treatment of candidemia in neutropenic adults:

1. Echinocandins are recommended as primary therapy.
2. Treatment can be stepped down to fluconazole if the patient is improving and species identification and susceptibility tests have indicated that the *Candida* isolate is susceptible to fluconazole.

Patient work-up on diagnosis of hematogenous candidiasis

Following a confirmed diagnosis of hematogenous candidiasis, in addition to commencing therapy (see *Therapy for proven hematogenous candidiasis*), a series of investigations need to be performed. However, current guidelines for the treatment of candidemia provide limited information on recommended post-diagnosis patient work-up.[67]

Patients – Non-neutropenic and neutropenic

For patient work-up after candidemia diagnosis, the Working Group recommends repeating blood cultures at baseline (day 1 of therapy), day 3, and day 5, or until clearance of blood cultures.

Blood culture

Studies of testing parameters for blood cultures have found that the number of pathogens recovered from a sample relates to the volume of blood cultured.[13] In adults, 20–30 ml of blood per blood culture set is generally recommended.[86] Blood samples should be divided between culture bottles.[86] Single blood culture sets should not be used to evaluate any patient with suspected candidemia, as the optimum detection of microorganisms is achieved with $\geq$3 sets of blood cultures.[40] Out of these sets, a single positive test result should be interpreted as candidemia and not as contamination (if other test results are negative). No more than two blood culture sets should be drawn in any given 24-h period,[95] and blood cultures should be collected from different puncture sites.[104]

Recommendations summary for blood culture:

1. Repeat sets of blood cultures should be taken until clearance of the infection is detected.
   a. The optimum detection of microorganisms is achieved with $\geq$3 sets of blood cultures.
2. In adults, 20–30 ml of blood should be collected per blood culture set.

Additional tests

Additional tests to blood culture are recommended under specific circumstances, which are outlined in Table 3.

A dilated ophthalmological evaluation is recommended, to exclude *Candida* endophthalmitis. One study found a significantly higher incidence of ocular candidiasis among hospitalized candidemia patients.[37] A delay in the diagnosis of *Candida* ocular infection can lead to loss of vision.[69]

Native valve endocarditis is rare as a complication of candidemia in non-neutropenic patients (1%). Therefore, an echocardiogram is not recommended as routine work-up for all candidemia patients[26] at baseline, but it should be considered in patients who have persistent candidemia for more than 72 h. In addition, as patients with prosthetic heart valves who develop candidemia are at notable risk of either having or developing *Candida* prosthetic valve endocarditis, an echocardiogram is recommended for this patient group at baseline.[52] Other risk factors or predisposing conditions for fungal endocarditis in non-neutropenic patients include previous surgery, vascular lines, antibiotic use, and underlying heart disease.[9,23,24]

Table 3
Additional tests for patient work-up in adults.

Treatment timeline	Adults Circumstance (recommendation)
Baseline (day 1)	Dilated ophthalmological evaluation when *Candida* endophthalmitis is suspected Check for skin lesions when disseminated candidiasis is suspected Abdominal imaging when peritonitis is suspected Check for signs of CVC exit-site skin infection
Day 3	Consider catheter removal if blood cultures remain positive or the patient is clinically unstable
Day 5	If invasive candidiasis persists, the following is recommended when applicable: Echocardiogram (preferably a transesophageal echocardiogram) Use vascular ultrasound to screen for CVC-related thrombophlebitis Further abdominal imaging, if required Repeat dilated ophthalmological evaluation Remove/change all central lines

CVC = central venous catheter.

Neutropenic patients

In neutropenic patients, if fever persists after 7 days, eye examination, repeated blood cultures, and imaging studies are recommended. In patients who have had previous episodes of candidemia or have recovered from neutropenia and persistent fever, an X-ray computed tomography (CT) scan or ultrasound is recommended to rule out chronic disseminated candidiasis (CDC).

Recommendations summary for patient work-up after candidemia diagnosis:

Adults – Non-neutropenic and neutropenic:

1. The Working Group recommends repeating blood cultures at baseline (day 1 of treatment), day 3 and day 5.
2. Additional tests are recommended under specific circumstances.
   a. Day 1: dilated ophthalmological evaluation, visual check for skin lesions and CVC exit-site infection, and abdominal imaging.
   b. Day 3: consider catheter removal if blood culture remains positive or patient is clinically unstable. If candidemia persists to day 5, remove/change all central lines.
   c. Day 5: (if candidemia persists) repeat dilated ophthalmological evaluation and abdominal imaging. Echocardiogram and vascular ultrasound are recommended.

Neutropenic adults:

1. If a patient is still febrile after 7 days, eye exam, repeat blood cultures, and imaging studies are recommended.
2. A CT scan or ultrasound is recommended to rule out CDC in patients who have had previous episodes of candidemia or have recovered from neutropenia but have persistent fever.

Duration of candidemia treatment

Non-neutropenic patients

The appropriate duration of therapy for candidemia has not been studied. Based on the RCTs of treatment of candidemia, the recommended duration of antifungal treatment for non-neutropenic adults is 14 days after the first negative blood culture indicating clearance of *Candida* species from the bloodstream, and resolution of signs and symptoms of infection. Longer therapy may be required for patients with metastatic foci of infection or endocarditis.[59] Long-term antifungal therapy has been given to patients who are not deemed appropriate surgical candidates for valve replacement as an intended cure for candidemia infection.[54]

Neutropenic patients

Treatment for candidemia in neutropenic adults should continue for 14 days after the first negative blood culture, provided that clinical resolution of infection has occurred. Longer treatment is typically recommended for patients who develop CDC.[49] For CDC, treatment duration is not established but should be longer than 14 days and may be continued for weeks or months, until calcification occurs or lesions resolve.[67] The use of corticosteroids has been shown to accelerate recovery from CDC.[41]

Recommendations summary for the duration of candidemia treatment in non-neutropenic adults:

1. Fourteen days after the first negative blood culture and resolution of signs and symptoms of infection is recommended.
2. Longer therapy may be required for patients with metastatic foci of infection or endocarditis.

Recommendations summary for duration of candidemia treatment in neutropenic adults:

1. Fourteen days after the first negative blood culture, provided that clinical resolution of infection has occurred.
2. Longer therapy may be required for patients with CDC.

Catheter management – Removing or retaining central venous catheterizations

In patients with candidemia, catheter removal has been found to correlate with more rapid clearance of *Candida* from the bloodstream and/or better prognosis.[2,25,84] However, there is conflicting evidence in the literature regarding the removal of CVCs in this setting, and this is reflected in the most recent Infectious Diseases Society of America (IDSA) guidelines. In the 2009 IDSA guidelines for the management of candidemia, early CVC removal is recommended for all non-neutropenic patients with candidemia.[67] The corresponding IDSA guideline on the management of intravascular catheter-related infection has a more conservative recommendation, limiting removal of CVCs to patients with CVC-related candidemia only.[51]

It is unlikely that there will be any large prospective RCTs with outcome of CVC retention versus removal as the primary endpoint in the future.[58] Recommendations that call for early CVC removal in non-neutropenic patients are based on studies that have only a small sample size of patients, are retrospective, do not define 'early' CVC removal and include patients who died before diagnosis of candidemia and therefore could not have undergone optimal antifungal therapy.[1,2,44,60,63,103] A subgroup analysis of two Phase III, multicenter, double-blind RCTs examined the effects of early CVC removal (within 24 or 48 h of treatment initiation) in a large cohort of patients (842 adults).[58] Multivariate analysis failed to show any benefit of early CVC removal on the time to mycological eradication, rates of persistent or recurrent candidemia, or success and mortality at 28 and 42 days. All patients in these trials were treated with an echinocandin or L-AmB, drugs that have good penetration in biofilms.[38]

Central venous catheterization management recommendation – Non-neutropenic patients

Based on published evidence, the Working Group considers that prompt removal of all CVCs is not needed in non-neutropenic adults with candidemia who are receiving an echinocandin or L-AmB therapy, provided that a CVC is needed. However, assessment after 3–5 days of treatment (including repeated blood cultures) is warranted, and clinicians should consider removing CVCs if patients are not responding to treatment. Early CVC removal is indicated if there are clear signs of infection at the CVC exit site and/or tunnel. No evidence-based recommendations can be made regarding CVC management in patients receiving treatments other than echinocandins or L-AmB therapy.

Similar recommendations of CVC management can be applied to neutropenic patients with candidemia. However, these recommendations did not reach consensus in all members of the group, with a few experts suggesting that prompt removal of all CVCs should be recommended for candidemic patients who present with septic shock (a minority of candidemic patients though).

Recommendations summary for catheter management in non-neutropenic and neutropenic adults:

1. CVCs may be retained in non-neutropenic adult patients who are receiving an echinocandin or L-AmB therapy, provided a CVC is needed.
2. If a patient does not respond to treatment (3–5 days of treatment), removal of CVCs must be considered.
3. If there is evidence of infection at the catheter exit site and/or tunnel, early (baseline) removal of the CVC is recommended.

Conflict of interests

A.L. Colombo has received research grants from Pfizer, MSD, United Medical and Luminex, medical education grants from Pfizer, MSD, United Medical and Astellas. Moreover, he has also been a consultant for MSD, Pfizer and Gilead. *J.A. Cortes* has received research grants and support to attend educational meetings from Pfizer and MSD. *M. Nucci* has received research grants from Pfizer and MSD, and has acted as a consultant and speaker for Pfizer, MSD, Astellas and Gilead. *F. de Queiroz Telles* has participated in Continuing Education activities in laboratories for Astellas, MSD, Pfizer and United Medical, and in research activities in laboratories for Astellas, MSD and Pfizer. *I.N. Tiraboschi* has been a speaker for Pfizer and Gilead. *J. Zurita* has been advisory board member and consultant for Pfizer, and has received research grants from Wyeth and MSD for participating in the SMART study.

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