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Invasive Fungal Infections (IFIs) – *Candida* spp & Others : The Role of Azole

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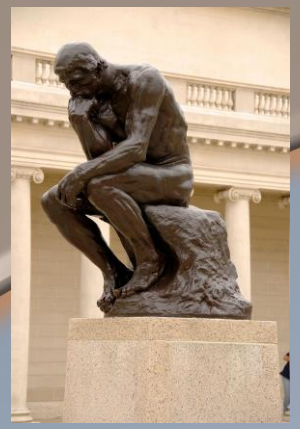
Issue : When to Start the Systemic Antifungal Treatment?



Invasive Fungal Infections (IFIs)

Considering

Host Factor

Risk Factor

Approach

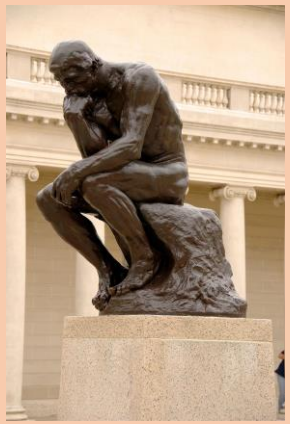
Definitive
Empiric
Pre-Emptive
(Prophylaxis?)

Treatment Option

Amphoterisin
5FC
Azole
Echinocandin

Approach

Definitive
Empiric
Pre-Emptive
(Prophylaxis?)



Host / Risk factor + Clinical features + Culture Findings → DEFINITIVE

Host / Risk factor + Clinical features +/- Serology Antigen/ colonization /others → EMPIRIC

Host / Risk factor + Serology Antigen/ colonization /others → PRE-EMPTIVE

Host - Fungal Clearance

Lymphocytes (CD4+)

***Cryptococcus* spp**

***Histoplasma* spp**

Neutrophils

***Candida* spp**

***Aspergillus* spp**

GUIDELINES FOR
DIAGNOSING, PREVENTING AND MANAGING CRYPTOCOCCAL DISEASE AMONG ADULTS, ADOLESCENTS AND CHILDREN LIVING WITH HIV

World Health Organization

Since 2018, WHO guidelines have recommended that all adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 be screened for cryptococcal antigen before ART initiation or reinitiation; cryptococcal antigen screening may also be considered for adults and adolescents living with HIV who have a CD4 cell count <200 cells/mm^3. These recommendations were supported by evidence favouring the clinical benefit and cost–effectiveness of cryptococcal antigen screening *(20,22,24–30)*. All individuals screening positive for cryptococcal antigen should be given pre-emptive antifungal therapy (fluconazole 800–1200 mg/day for adults and 12 mg/kg per day for adolescents for two weeks), followed by consolidation and maintenance fluconazole therapy, as for treatment. The 2019 guidelines from the Southern African HIV Clinicians Society recommend 1200 mg for first 2 weeks given safety and concerns over breakthrough infection *(21)*.

PAHO
Pan American Health Organization
World Health Organization Americas
World Health Organization

GUIDELINES FOR
DIAGNOSING AND MANAGING DISSEMINATED HISTOPLASMOSIS AMONG PEOPLE LIVING WITH HIV

Prognostic factor	Weight
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension (systolic blood pressure >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumour or no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Outpatient status	3
Age <60 years	2

MASCC Risk Index score ≥21 indicates that the patient is at a low risk of complications and mortality, classified as low-risk febrile neutropenia.

Histoplasmosis has a high endemicity in certain areas of the Americas *(7)*. Although most frequently diagnosed in the Americas, it is also diagnosed in certain countries of Asia (China, India, Indonesia, Japan, Malaysia, Singapore, Thailand, and Viet Nam) and Africa (Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gambia, Guinea Bissau, Liberia, Senegal, South Africa, and Uganda) *(8)*. Among people living with HIV, the most frequent clinical presentation of this disease is disseminated histoplasmosis. Symptoms of disseminated histoplasmosis are nonspecific and may be indistinguishable from those of other infectious diseases, especially TB, thus complicating diagnosis and treatment *(9)*. Most histoplasmosis reports come from the Region of the Americas, and each year there are up to 15,600 new cases and 4,500 deaths among people living with HIV *(4)*.

Risk Factors

IFIs - *Candida* spp

Evaluation of *Candida* Scoring Systems to Predict Early Candidemia: A Prospective and Observational Study at a Tertiary Care Hospital, Uttarakhand

Priyanka Gupta, Pratima Gupta, Biswaroop Chatterjee[1], Garima Mittal[1], Shashank Prateek[2], Aroop Mohanty[3]
Department of Microbiology, AIIMS, Rishikesh, [1]Department of Microbiology, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun, [2]PI Disease, Consultant Lab Medicine, Q Health Diagnostics, [3]AIIMS, Rishikesh, Uttarakhand, India

Indian Journal of Critical Care Medicine | Volume 21 | Issue 12 | December 2017

Leon et al
- Clinical sepsis
- Surgery
- TPN
- Multifocal colonization

Wenzel et al
- Intravenous catheters
- Hemodialysis
- Antibiotic usage
- Colonization with Candida

Matteo Basseti

All Patients :
- Prior abdominal surgery
- Intravascular catheters
- Parenteral Nutrition
- Use of Broad Spectrum Antibiotic
- Immunosuppresion including corticosteroid therapy
- Acute Renal Failure
- Diabetes Melitus
- Transplantation
- Haemodialysis
- Pancreatitis

ICU patients :
- Prolong stay in ICU
- Candida Colonization particularly if multifocal
- High APACHE II Score
- Low birth weight for Neonatal ICU

Scudeller et al
- Broad spectrum antibiotic treatment ongoing for at least 5 days
- Central venous catheter (CVC) or peripherally inserted central catheter (PICC)
- Parenteral nutrition
- Chemotherapy for solid and hematological tumors (including steroids)
- Hospitalization > 10 days in previous 3 months (including nursing homes/long-term care facilities)
- Prior candidemia Candida colonization in >1 site
- Transferred from ICU Dialysis

Gupta P

Prolonged antibiotic usage ($P < 0.00001$)
Prolonged ICU stay ($P = 0.00024$)
Multifocal colonization ($P = 0.00025$),

Risk Factors IFIs - *Candida* spp

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RASCANDIS 1.0 Form: Therapeutic Approach of Systemic Anti-Candidiasis for Non-Transplant Patients

Ronald Irwanto Natadidjaja[1,2], Aziza Ariyani[1], Hadianti Adlani[1], Anti Dharmayanti[1,3], Joyce Bratanata[1,4]

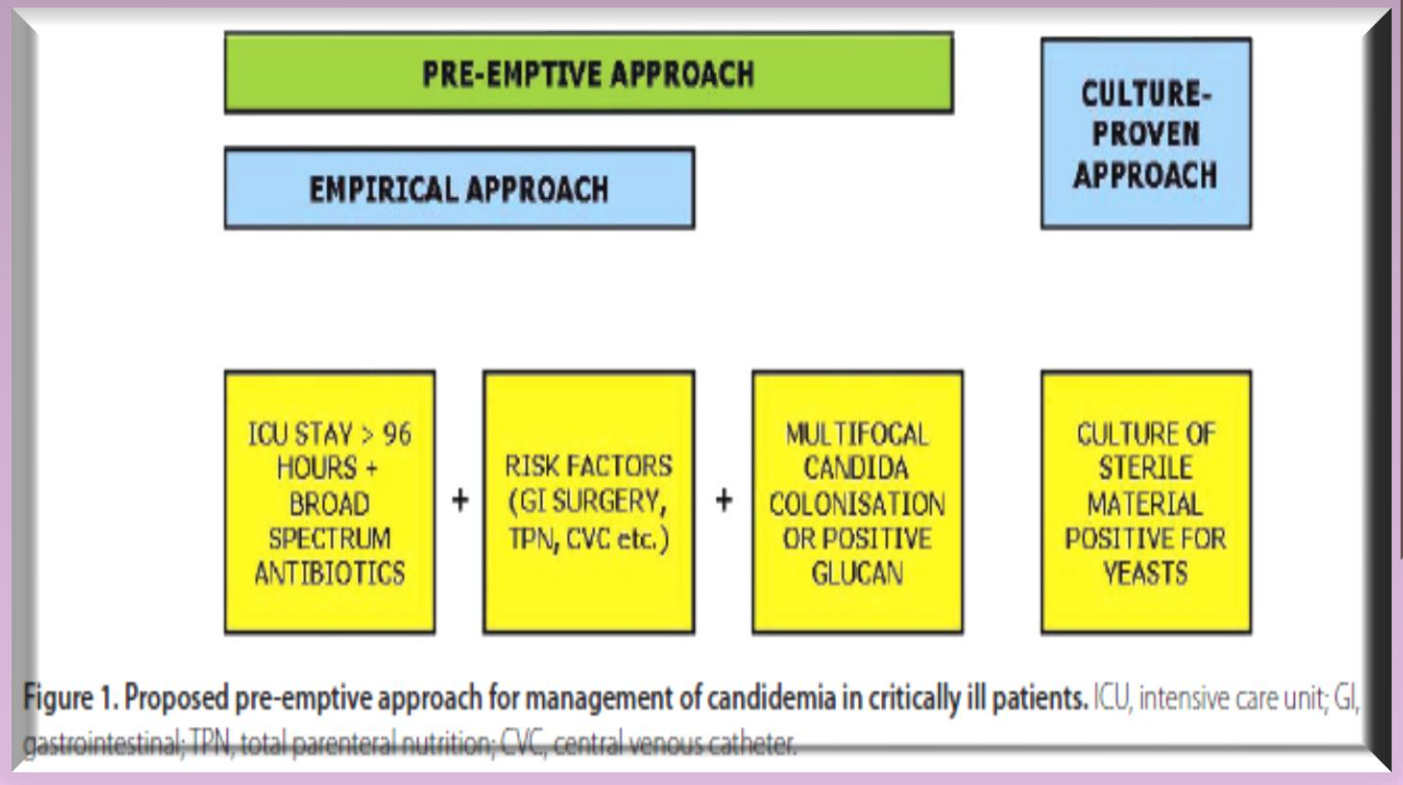

Figure 1. Proposed pre-emptive approach for management of candidemia in critically ill patients. ICU, intensive care unit; GI, gastrointestinal; TPN, total parenteral nutrition; CVC, central venous catheter.

Bassetti *et al. Critical Care 2010*

- **Sepsis**
- **Long ICU stay**
- **Using Total Parenteral Nutrition (TPN)**
- **Candida sp multifocal colonization findings**
- **Using deep vein catheters, including Central Venous Catheter (CVC)**
- **Hemodialysis**
- **History of long-term use of wide-spectrum antibiotics**
- **History of abdominal surgery**
- **Transplantation**
- **Long ICU stay**
- **Babies with low birth weight in ICU**

Gupta P, Gupta P, Chatterjee B, Mittal G, Prateek S, Mohanty A. Evaluation of Candida scoring systems to predict early candidemia: A prospective and observational study at a tertiary care hospital, Uttarakhand. Indian J Crit Care Med. 2017;21(12):830–5. doi: 10.4103/ijccm.IJCCM_159_17

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REVIEW ARTICLE

RASCANDIS 1.0 Form: Therapeutic Approach of Systemic Anti-Candidiasis for Non-Transplant Patients

Formulir RASCANDIS 1.0: Pendekatan Terapi Anti-Kandida Sistemik untuk Pasien Non-Transplantasi

Ronald Irwanto Natadidjaja[1,2], Aziza Ariyani[1], Hadianti Adlani[1], Anti Dharmayanti[1,3], Joyce Bratanata[1,4]

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No.	Specification	Flow	Explanation	Approach
1	**Clinical progressive :** With positive culture finding from sterile	Yes	STOP Circle : *Blood *Liver biopsy *Spleen biopsy *Etc,...	Definitive Systemic Anti Candida
		No		
2	**Clinical progressive :** (With≥48-hours use of deep vascular catheter AND/OR TPN) without improvement with antibiotic use	Yes	STOP	Empiric Systemic Anti Candida
		No		
3	**Clinical progressive :** Post Extensive intraabdominal surgery without improvement with antibiotic use	Yes	STOP	Empiric Systemic Anti Candida
		No		
4	**Clinical progressive :** High risk neutropenia AND / OR with MASCC Index<21	Yes	STOP	Empiric Systemic Anti Candida
		No		
5	(Found ≥1 candida colonization AND/OR positive of other candida biomarker) with neutropenic condition	Yes	STOP Circle : *Oropharynx *Faeces *Skin *Etc,... *Urine	Pre-emptive Systemic Anti Candida
		No		
6	(Found ≥1 candida colonization AND/OR positive of other candida biomarker) with >48 hours of deep vascular catheterization AND/OR TPN	Yes	STOP Circle : *Oropharynx *Faeces *Skin *Etc,... *Urine	Pre-emptive Systemic Anti Candida
		No		
7	(Found ≥1 candida colonization AND/OR positive of other candida biomarker) following extensive intraabdominal surgery	Yes	STOP Circle : *Oropharynx *Faeces *Skin *Etc,... *Urine	Pre-emptive Systemic Anti Candida
		No	Systemic Anti Candidiasis is not necessary	

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RASCANDIS 1.0 Form: Therapeutic Approach of Systemic Anti-Candidiasis for Non-Transplant Patients

Formulir RASCANDIS 1.0: Pendekatan Terapi Anti-Kandida Sistemik untuk Pasien Non-Transplantasi

Ronald Irwanto Natadidjaja[1,2✉], Aziza Ariyani[1], Hadianti Adlani[1], Anti Dharmayanti[1,3], Joyce Bratanata[1,4]

GUIDELINES FOR

DIAGNOSING, PREVENTING AND MANAGING CRYPTOCOCCAL DISEASE AMONG ADULTS, ADOLESCENTS AND CHILDREN LIVING WITH HIV

World Health Organization

Prevention and screening (2018 recommendations)

Screening[a] for cryptococcal antigen followed by pre-emptive antifungal therapy *(21)*[3] among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm³.

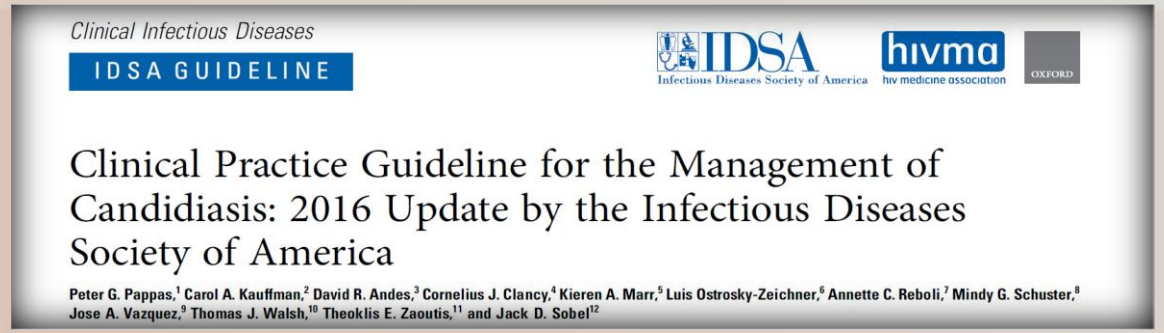
Strong recommendation; moderate-certainty evidence

This may be considered at a higher CD4 cell count threshold of <200 cells/mm³.

Conditional recommendation; moderate-certainty evidence

Cryptococcal antigen screening followed by pre-emptive therapy is preferred over providing fluconazole primary prophylaxis after considering cost, the potential for developing antifungal resistance and concerns about fetal safety among women of childbearing age without access to adequate contraception. Fluconazole primary prophylaxis should be made available in settings in which cryptococcal antigen screening is not available or there may be prolonged delays in receiving the result since cryptococcal disease and mortality peak in the first four weeks among people presenting with a CD4 cell count <100 cells/mm³ *(31)*.

Part of Guidelines



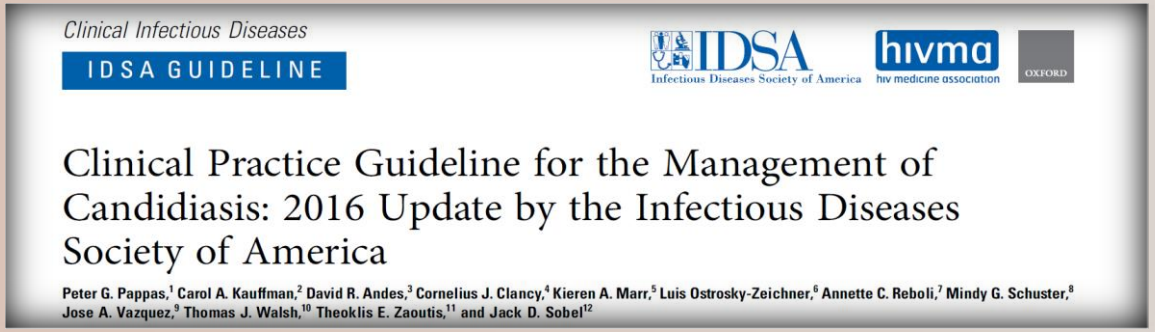
What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

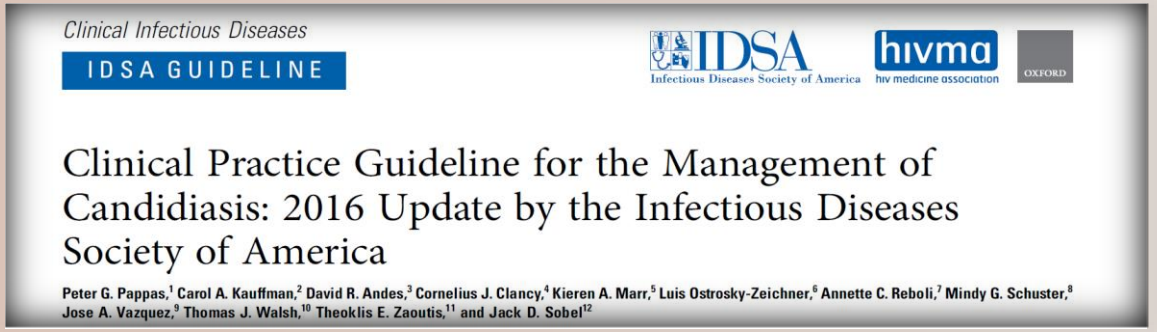
1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy (strong recommendation; high-quality evidence).
2. **Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients,** including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant Candida species (strong recommendation; high-quality evidence).
3. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant Candida isolates. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and among those who have infection with C. glabrata or C. parapsilosis (strong recommendation; low-quality evidence).
4. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, C. albicans), and have negative repeat blood cultures following initiation of antifungal therapy (strong recommendation; moderate-quality evidence).
5. For infection due to C. glabrata, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily or voriconazole 200–300 (3–4 mg/kg) twice daily should only be considered among patients with fluconazole-susceptible or voriconazole-susceptible isolates (strong recommendation; low-quality evidence).
6. Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents (strong recommendation; high-quality evidence).
7. Transition from AmB to fluconazole is recommended after 5–7 days among patients who have isolates that are susceptible to fluconazole, who are clinically stable, and in whom repeat cultures on antifungal therapy are negative (strong recommendation; high-quality evidence).

What Is the Treatment for Candidemia in Nonneutropenic Patients?

8. Among patients with suspected azole- and echinocandin resistant Candida infections, lipid formulation AmB (3–5 mg/kg daily) is recommended (strong recommendation; low-quality evidence).
9. Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily is effective for candidemia, but offers little advantage over fluconazole as initial therapy (strong recommendation; moderate-quality evidence). Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to C. krusei (strong recommendation; low-quality evidence).
10. All nonneutropenic patients with candidemia should have a dilated ophthalmological examination, preferably performed by an ophthalmologist, within the first week after diagnosis (strong recommendation; low-quality evidence).
11. Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared (strong recommendation; lowquality evidence).
12. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of Candida species from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; moderate-quality evidence).



Part of Guidelines



What Is the Role of Empiric Treatment for Suspected Invasive Candidiasis in Nonneutropenic Patients in the Intensive Care Unit?

Recommendations

28. Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites (strong recommendation; moderate-quality evidence). Empiric antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock (strong recommendation; moderate-quality evidence).
29. Preferred empiric therapy for suspected candidiasis in nonneutropenic patients in the intensive care unit (ICU) is an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) (strong recommendation; moderate-quality evidence).
30. **Fluconazole, 800-mg (12 mg/kg**) loading dose, then 400 mg (6 mg/kg) daily, is an acceptable alternative for patients who have had no recent azole exposure and are not colonized with azole-resistant Candida species (strong recommendation; moderate-quality evidence).
31. Lipid formulation AmB, 3–5 mg/kg daily, is an alternative if there is intolerance to other antifungal agents (strong recommendation; low-quality evidence).
32. Recommended duration of empiric therapy for suspected invasive candidiasis in those patients who improve is 2 weeks, the same as for treatment of documented candidemia (weak recommendation; low-quality evidence).
33. For patients who have no clinical response to empiric antifungal therapy at 4–5 days and who do not have subsequent evidence of invasive candidiasis after the start of empiric therapy or have a negative non-culture-based diagnostic assay with a high negative predictive value, consideration should be given to stopping antifungal therapy (strong recommendation; low-quality evidence).
VI.

Part of Guidelines

Global guideline recommendations of anidulafungin in neutropenic patients

Infectious Diseases Society of America (IDSA) 2016 Clinical Practice Guideline for the Management of Candidiasis[1]

- Strongly recommends an echinocandin (e.g. anidulafungin) with moderate quality evidence in treatment for candidemia in neutropenic patients

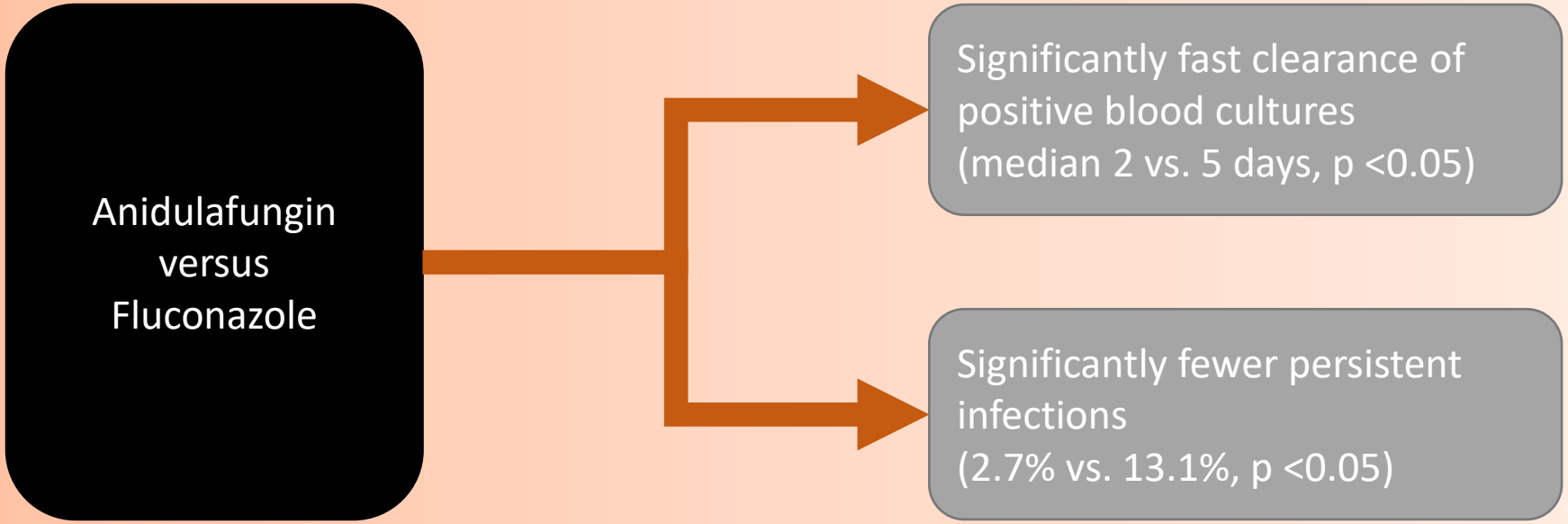
Sixth European Conference on Infections in Leukaemia (ECIL-6)[2]

- Strongly recommends an echinocandin (e.g. anidulafungin) as first line therapy of candidemia irrespective of the underlying predisposing factors

References: 1. Pappas PG, et al. *Clin Infect Dis*. 2016;62(4):e1–e50. **2.** Tissot F, et al. *Haematologia*. 2017;102(3):433–444.

Anidulafungin is the only echinocandin proven superior to fluconazole[1]

Post-hoc analysis of patients with *C albicans* infection[2]



Adapted from Reboli et al, 2011..

References: 1. Glockner A, et al. *Mycoses*. 2009;52(6):476–486. **2.** Reboli AC, et al. *BMC Infect Dis*. 2011;11:261.

INVASIVE SYNDROMES OF ASPERGILLUS

What Are the Recommended Treatment Regimens and Adjunctive Treatment Measures for the Various Clinical Presentation of Invasive Aspergillosis? How Should IPA (Invasive Pulmonary Aspergillosis) Be Treated?

Recommendations.

25. We recommend primary treatment with **voriconazole (strong recommendation; high-quality evidence).**

26. Early initiation of antifungal therapy in patients with strongly suspected IPA is warranted while a diagnostic evaluation is conducted (strong recommendation; high-quality evidence).

27. **Alternative therapies include liposomal AmB (strong recommendation; moderate-quality evidence), isavuconazole (strong recommendation; moderate-quality evidence), or other lipid formulations of AmB (weak recommendation; low-quality evidence).**

28. **Combination antifungal therapy with voriconazole and an echinocandin may be considered in select patients with documented IPA (weak recommendation; moderate-quality evidence).**

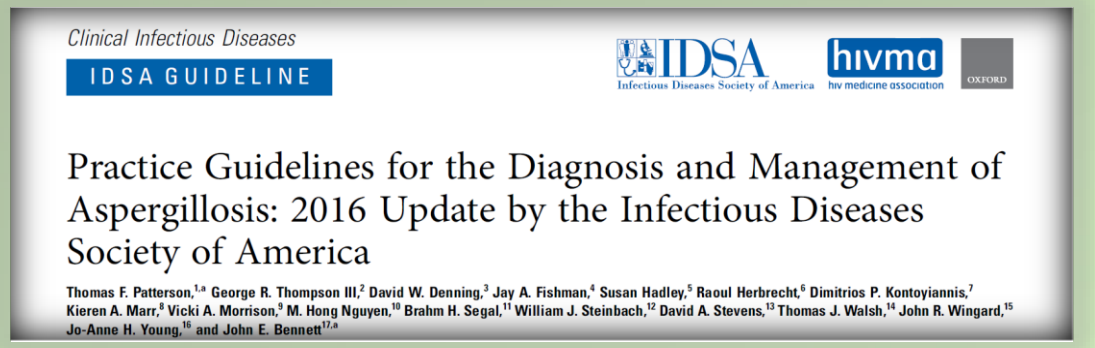
29. Primary therapy with an echinocandin is not recommended (strong recommendation; moderate-quality evidence). Echinocandins (micafungin or caspofungin) can be used in settings in which azole and polyene antifungals are contraindicated (weak recommendation; moderate-quality evidence).

30. We recommend that treatment of IPA be continued for a minimum of 6–12 weeks, largely dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement (strong recommendation; lowquality evidence).

31. For patients with successfully treated IPA who require subsequent immunosuppression, secondary prophylaxis should be initiated to prevent recurrence (strong recommendation; moderate-quality evidence).

Echinocandins are effective in salvage therapy (either alone or in combination) against IA, but we do not recommend their routine use as monotherapy for the primary treatment of IA (strong recommendation; moderatequality evidence).

Part of Guidelines



Antifungal Agents with Activity against *Aspergillus* Species

Class	Agents	Advantages and Limitations
Polyene	Amphotericin B deoxycholate (AmB)	Efficacy limited; substantial toxicity associated with increased mortality and increased hospital costs; potential decreased toxicity with continuous infusions
	Lipid formulations of amphotericin B: L-AmB, ABLC, ABCD	Less toxicity than AmB; systemic toxicities: ABCD≫ABLC > L-AmB; higher doses anecdotally more effective; cost significant barrier to extensive use
Triazole	Voriconazole	Recommended primary therapy for most patients due to survival advantage vs AmB; drug interactions; visual, liver, skin toxicities
	Isavuconazole	As effective as voriconazole and better tolerated
	Posaconzole	Evaluated as salvage therapy of aspergillosis and prophylaxis; oral suspension only; well-tolerated in clinical trials
	Itraconazole	Indicated for second-line therapy and sequential oral therapy; suspension improves bioavailability; limited efficacy data for intravenous form; renal/liver toxicity from chemotherapy interactions; liver, gastrointestinal toxicity
Echinocandin	Caspofungin, micafungin, anidulafungin	Salvage and combination therapy; regulatory approval only for caspofungin; well-tolerated; potential cyclosporine interaction for caspofungin

Data extracted from: Patterson TF. Treatment of invasive aspergillosis: Polyenes, echinocandins, or azoles?. Medical Mycology. 2006 Sep 1;44(Supplement_1):S357-62.

Voriconazole

Approved indications

- Treatment of invasive aspergillosis.
- Treatment of candidemia in non-neutropenic patients
- Treatment of serious invasive Candida infections (including C. krusei)
- Treatment of esophageal candidiasis
- Treatment of serious fungal infections caused by Scedosporium apiospermum (asexual form of Pseudallescheria boydii) and Fusarium spp. including Fusarium solani, in patients intolerant of, or refractory to, other therapy.

Voriconazole is available in both IV and oral formulations and listed in e-catalog BPJS [1,2]

The first-line gold-standard treatment for IA [1-5]

IDSA

- **Recommend as primary treatment with voriconazole (strong recommendation; high-quality evidence) [4]**

ECIL-6

- **Recommended for first line treatment of invasive aspergillosis. [5]**

IA, invasive aspergillosis.
IDSA: Infectious Diseases Society of America
ECIL: European Conference on Infections in Leukemia

References:
1. VFEND IV Summary of Product Characteristics, Jan 2017
2. VFEND tablet Summary of Product Characteristics, Jan 2017
3. Maschmeyer, G., et al. (2007). Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. *Drugs*; 67(11), pp. 1567-1601.
4. Patterson, T.F., et al. (2016): Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*.;63(4):e1-e60.
5. Tissot F, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2016 Dec 23. pii: haematol.2016.152900. doi: 10.3324/haematol.2016.152900.
6. Herbrecht, R., et al., (2002). Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*; 347(6), pp. 408-415.

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

Part of Guidelines

HIV-Infected Individuals

Primary therapy: induction and consolidation

Amphotericin B (AmB) deoxycholate (AmBd; 0.7–1.0 mg/kg per day intravenously [IV]) plus flucytosine (100 mg/ kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by **fluconazole (400 mg [6 mg/kg] per day orally)** for a minimum of 8 weeks (A-I). Lipid formulations of AmB (LFAmB), including liposomal AmB (3–4 mg/kg per day IV) and AmB lipid complex (ABLC; 5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction (B-II).

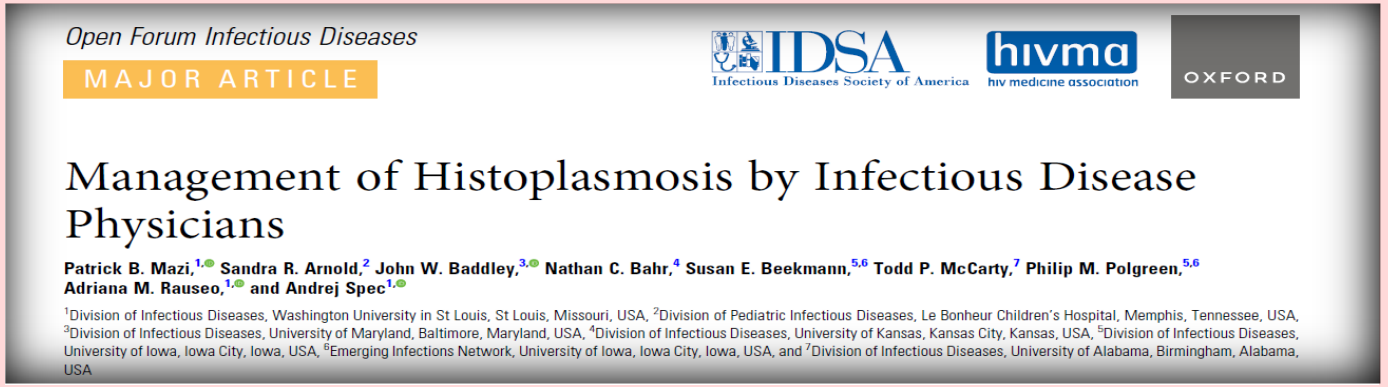
Primary therapy: **alternative regimens** for induction and consolidation

AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by fluconazole (800 mg per day orally) for a minimum of 8 weeks (B-I).

Fluconazole (800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 6 weeks (B-II).

Fluconazole (800–2000 mg per day orally) for 10–12 weeks; a dosage of 1200 mg per day is encouraged if fluconazole alone is used (B-II).

Itraconazole (200 mg twice per day orally) for 10–12 weeks (C-II), although use of this agent is discouraged.



Open Forum Infectious Diseases

MAJOR ARTICLE

Management of Histoplasmosis by Infectious Disease Physicians

Patrick B. Mazi,[1] Sandra R. Arnold,[2] John W. Baddley,[3] Nathan C. Bahr,[4] Susan E. Beekmann,[5,6] Todd P. McCarty,[7] Philip M. Polgreen,[5,6] Adriana M. Rauseo,[1] and Andrej Spec[1]

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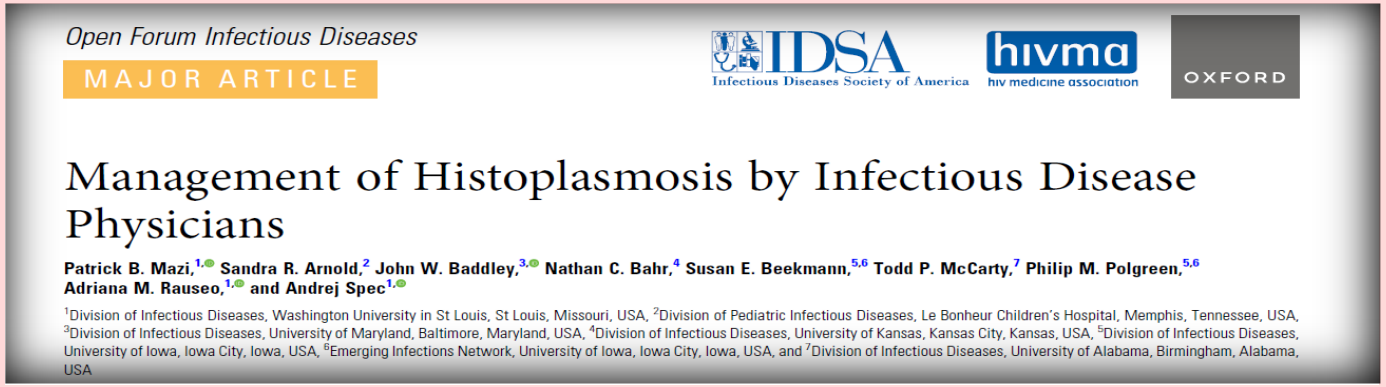
The Infectious Diseases Society of America (IDSA) last updated clinical guidelines for the management of histoplasmosis in 2007, using literature from 1 January 1999 through 31 June 2006 [8]. Since the release of the guidelines, new treatment options have been developed. **Posaconazole was approved by the United States (US) Food and Drug Administration shortly before the release of the 2007 guidelines and isavuconazole was approved in 2015. Both maintain in vitro activity against Histoplasma even in the setting of fluconazole resistance [9, 10],** though there are limited clinical data to support their use in treating histoplasmosis [11–13]. Since the arrival of these new medications, there have been no changes to clinical practice recommendations [14], and very little new data have been published to guide therapy [15, 16]. Additionally, the population at risk to develop clinically significant histoplasmosis has increased substantially with millions of patients on an everexpanding variety of immunosuppressive medications and/or with immunosuppressive medical conditions [17–19].

Management of Acute Pulmonary and Progressive Disseminated Histoplasmosis

For a patient with mild-to-moderate acute pulmonary histoplasmosis, 75% (189/253) of respondents treat with itraconazole as is recommended in both the IDSA and the European Confederation of Medical Mycology guidelines [8, 14]. Six percent (16/253) chose treatment with another azole and 4% (9/ 253) chose amphotericin B. Forty-seven (19%) respondents recommended no treatment for the patient in this case. For a patient presenting with mild-to-moderate disseminated histoplasmosis in the outpatient setting, 75% (189/253) of respondents chose to treat with itraconazole in concordance with the guidelines. Fewer respondents recommended no treatment in this situation (14% [35/253]) and more recommended amphotericin B induction therapy (9% [22/253]). The remainder of respondents chose another azole.



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Part of Guidelines

Preferences in Azole

Therapy Most respondents chose itraconazole as their azole of choice in each clinical scenario. Preferred formulations of itraconazole were evenly split between oral solution (46% [117/253]) and capsules (43% [110/253]). A minority of physicians (7% [18/ 253]) preferred the newest formulation, SUBA-itraconazole. There were 6 physicians (2%) who did not treat histoplasmosis with itraconazole.

Itraconazole was recommended for step-down therapy for severe disseminated histoplasmosis without central nervous system (CNS) involvement by 92% (232/253) of respondents. Where severe disseminated histoplasmosis was complicated by CNS involvement, a smaller majority (145/253 [57%]) recommended itraconazole. For CNS involvement, 19% (48/253) recommended voriconazole, 5% (12/253) posaconazole, 4% (9/253) isavuconazole, and 8% (20/253) fluconazole. Continued therapy with amphotericin B was recommended by 7% (17/253) of respondents.

The 10 most remarkable rules for developing antifungal stewardship program in ICU

1. **Restrict or avoid antifungal prophylaxis**
2. Differentiate infection from colonisation
3. Use non-culture-based diagnostics for early detection of IC
4. Limit the use of empirical therapy based on risk-factors
5. Promote early pre-emptive antifungal treatment based on risk factors and biomarkers
6. Get treatment right the first time with adequate drugs (echinocandins)
7. Have adequate source control within 48 hours (catheter removal, appropriate drainage, surgical control)
8. Use an adequate dose: low dose is associated with resistance
9. De-escalate whenever possible (if possible, within day 5)
10. Stop early useless therapy and check duration of therapy

Slide of Prof Basseti March 6th, 2021

IC, invasive candidiasis.

Bassetti M et al. Intensive Care Med 2017: DOI: 10.1007/s00134-017-4922-x.

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