Central Administration of Pharmaceutical Care

General Administration For Drug Utilization &Pharmacy Practice

National Guidance for Rational Antifungal Use 2024

National Rational Antimicrobial Use Committee

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National Guidance for Antifungal Use

Introduction

Fungi are unicellular or multi-cellular eukaryotic organisms that exist in all environments worldwide. While most fungi do not play a significant role in human disease, there are several hundred fungi that do, resulting in fungal infection or disease. Fungal infections (mycoses) range from common benign infections like 'jock itch' to serious, life-threatening infections such as cryptococcal meningitis [(1)]. Clinically, fungal infections are best categorized first according to the site and extent of the infection, then the route of acquisition, and finally, the virulence of the causative organism [(1)]. These classifications are essential when determining the most effective treatment regimen for a particular mycosis. Mycoses classify as local (superficial, cutaneous, subcutaneous) or systemic (deep, bloodborne) [(1)]. The acquisition of the fungal infection is either an exogenous (airborne/inhalation, cutaneous exposure, percutaneous inoculation) or an endogenous process (normal flora or reactivated infection) [(1)]. The virulence of the organism is classified as either a primary infection (disease arising in a healthy host) or opportunistic infection (disease arising in human hosts that have a compromised immune system or other defenses) [(1).]

Common, medically relevant fungal infections

The commonly encountered fungal infections include, but are not limited to, the following: [(1)]

Fungal infection	Causative organisms
Aspergillosis	Aspergillus fumigatus, A. flavus (common Mold)
Blastomycosis	Blastomyces dermatitidis
Candidiasis	Candida albicans, C. glabrata, C. krusei, C. parasilosis, C. tropicalis
Chromoblastomycosis (Chromomycosis)	Cladosporium carrionii, Phialophora verrucosa, Fonsecaea pedrosoi
Coccidioidomycosis	Coccidioides imitis, C. posadasii
Cryptococcosis	Cryptococcus neoformans, C. gattii
Dermatophytosis (Tinea)	Microsporum spp., Epidermophytum spp., Trichophyton spp
Fusariosis	Fusarium oxysporum, F. proliferatum, F. verticillioides
Histoplasmosis	Histoplasma capsulatum
Mucormycosis (Zygomycosis)	Mucor spp., Rhizopus spp
Paracoccidioidomycosis	Paracoccidioides brasiliensis
Pneumocystis pneumonia	Pneumocystis jirovecii (formerly called P. carinii)
Sporotrichosis	Sporothrix schenckii
Tinea (Pityriasis) Versicolor	Malassezia furfur (also called Pityrosporum orbiculare), M. globosa

Aim of this guidance

- Promote judicious and optimal use of antifungal agents.
- Provide the rationale for selecting antifungal agents, and emphasize risk assessment and management.

Part I: Guidance of Antifungal Use in Candidiasis

Overview about Candidiasis

Candidiasis is a fungal infection caused by a yeast (a type of fungus) called Candida. Some species of Candida can cause infection in people; the most common is Candida albicans. Candida normally lives on the skin and inside the body, such as the mouth, throat, gut, and vagina, without causing problems. Candida can cause infections if it grows out of control or if it enters deep into the body. For example, it can cause infections in the bloodstream or internal organs like the kidney, heart, or brain. [2],[3],[4]

Candidiasis encompasses a host of infections involving mucosal surfaces and the urinary tract, as well as more disseminated diseases (e.g., sepsis, meningitis, endocarditis, and intra-abdominal infections). [2, 3]

Invasive infection due to Candida species is largely a condition associated with medical progress and is widely recognized as a major cause of morbidity and mortality in the healthcare environment.

Invasive candidiasis (IC): encompasses severe and invasive Candida infections that include candidemia, disseminated candidiasis, endocarditis, meningitis, endophthalmitis, and other deep tissue involvement. It excludes more superficial and less severe diseases such as oropharyngeal and esophageal candidiasis. [2, 3, 4]

There are at least 15 distinct Candida species that cause human disease, but >90% of invasive disease is caused by the 5 most common pathogens, C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei. [2],[3],[4]

Candida albican is the most frequently isolated species in the case of candidemia, but infections due to non-albicans species are increasing, especially in ICU; the most common non-albicans species are C. parapsilosis and C. glabrata, followed by C. tropicalis, C. krusei, C. guilliermondii and C. lusitaniae. [2],[3],[4]

Antifungal agents for candidiasis treatment, their characteristics, and spectra of activity

Antifungal agents used for the management of Candida infections in non-neutropenic and neutropenic patients [5].

a) Polyenes (amphotericin)

- It is either the conventional form of amphotericin B [AmB] deoxycholate [AmB-d], OR lipid formulations amphotericin B [LFAmB]) e.g., liposomal AmB.
- The lipid formulation AmB agents have different pharmacological properties and rates of treatment-related adverse events and **should not** be interchanged without careful consideration.
- LFAmB (lipid amphotericin B formulation) –formulations exist with similar spectra to AmB-d but with less nephrotoxicity and higher costs.
- AmB-d (amphotericin B deoxycholate) – the most common adverse effects include nephrotoxicity, infusion-related reactions (chills, rigors, hypotension), and potassium and magnesium wasting.
- Amphotericin is antifungal category of choice for use in pregnant individuals with invasive candidiasis (IC).

b) Triazoles (fluconazole, itraconazole, voriconazole and posaconazole)

- All triazoles have good oral bioavailability and oral formulations are preferred when possible .
- All inhibit CYP450 to varying degrees, and careful evaluation for drug-drug interactions is warranted .
- Generally, triazoles should be avoided in pregnancy due to risks of fatal malformations.
- **Fluconazole** is used in patients who have mild to moderate illness (i.e. are hemodynamically stable), who have no previous exposure to azoles, and who do not belong to a group at high risk of C. glabrata infection (e.g. elderly patients, cancer patients, and diabetic patients).
- Fluconazole is the only azole with clinically significant urinary concentrations .

- Among all triazoles, fluconazole has the greatest penetration into cerebrospinal fluid (CSF) and vitreous body with concentrations of at least 50% of serum. Fluconazole urine concentrations reach 10-20 times serum concentrations.
- **Itraconazole** is generally reserved for mucosal candidiasis, and little data exist for IC .
- **Voriconazole** is effective for mucosal and IC, but is primarily used for step-down oral therapy for fluconazole-resistant, voriconazole-susceptible strains of C. krusei and C. glabrata.
- Voriconazole has good oral bioavailability, CSF (~50% of serum), and vitreous penetration .
- Voriconazole oral bioavailability is not affected by gastric pH but is decreased when consumed with food .
- Voriconazole is the only triazole to require dosage reduction for mild-to-moderate hepatic impairment .
- Voriconazole is contraindicated in pregnancy.
- **Posaconazole** does not have an indication for treatment of primary candidiasis but demonstrates in vitro activity similar to that of voriconazole.
- Posaconazole is available as oral suspension with high bioavailability especially when small doses are given frequently and administered with fatty foods and in acidic environments, and also available as IV formulation.

c) Echinocandins (caspofungin, anidulafungin, micafungin)

- Echinocandins are preferred for the treatment of proven and suspected Candida infections, especially in critically ill patients or those with previous exposure to azoles .
- Echinocandins have ***negligible*** distribution into CSF and urine.
- Have a broad spectrum of activity and are similar to each other with respect to in vitro activity against Candida sp.
- Adverse drug reactions are less frequent with micafungin and anidulafungin compared with caspofungin. (Phlebitis and elevated liver enzyme levels occur more often with caspofungin compared with micafungin and anidulafungin)

Spectra of Activity Against Candida Species of Various Antifungals [6]

Candida Sp / Antifungal	Amphotericin	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Caspofungin	Micafungin	Anidulafungin
albicans	Good Activity							
glabrata	Mild Activity	Slight Activity		Mild Activity		Good Activity		
parapsilosis	Good Activity					Mild Activity		
tropicalis	Good Activity							
krusei	Mild Activity	No Activity	Slight Activity	Mild Activity		Good Activity		
rugosa	Mild Activity			Good Activity		Mild Activity		
guilliermondii	Good Activity					Mild Activity		
lusitaniae	Good Activity							
inconspicua	Good Activity	No Activity	Mild Activity			Good Activity		
norvegensis	Good Activity	No Activity	Slight Activity			Good Activity		

N.B., consider local epidemiology and resistance profiles

The selection of any particular agent for the treatment of candidemia depends on the following factors:[5], [6]

- A history of recent azole or echinocandin exposure.
- A history of intolerance to an antifungal agent.
- The dominant Candida species and current susceptibility data in a particular clinical unit.
- Severity of illness.
- Relevant comorbidities.
- Evidence of involvement of the CNS, cardiac valves, and/or visceral organs.
- Practical considerations for individualized selection of antifungal agents include patient factors, pathogen, site of infection, and drug-related factors, such as drug–drug interaction, drug-food intervention, cost, and convenience.

N.B., Early initiation of effective antifungal therapy and source control is critical in the successful treatment of candidemia.

Risk factors for the development of invasive candidiasis:[5], [6]

- Candida colonization
- Severity of illness
- Exposure to broad-spectrum antibiotics
- Recent major surgery particularly abdominal surgery
- Necrotizing pancreatitis
- Dialysis
- Parenteral nutrition
- Corticosteroids use.
- The use of central venous catheters (CVCs)

Risk factors for non-albicans species [7]

- Glucocorticosteroid use
- Central venous catheter placement
- Prior fluconazole therapy
- Preexisting candiduria

Candida Endophthalmitis

To establish if endophthalmitis is present: [8]

- All patients with candidemia should have a dilated retinal examination.
- For non-neutropenic patients, retinal examination should be within the first week of therapy.
- For neutropenic patients, it is recommended to delay the examination until neutrophil recovery (within the first week after recovery from neutropenia).
- Decisions regarding antifungal treatment and surgical intervention should be made jointly by an ophthalmologist and an infectious diseases physician.

Diagnosis of Candidiasis

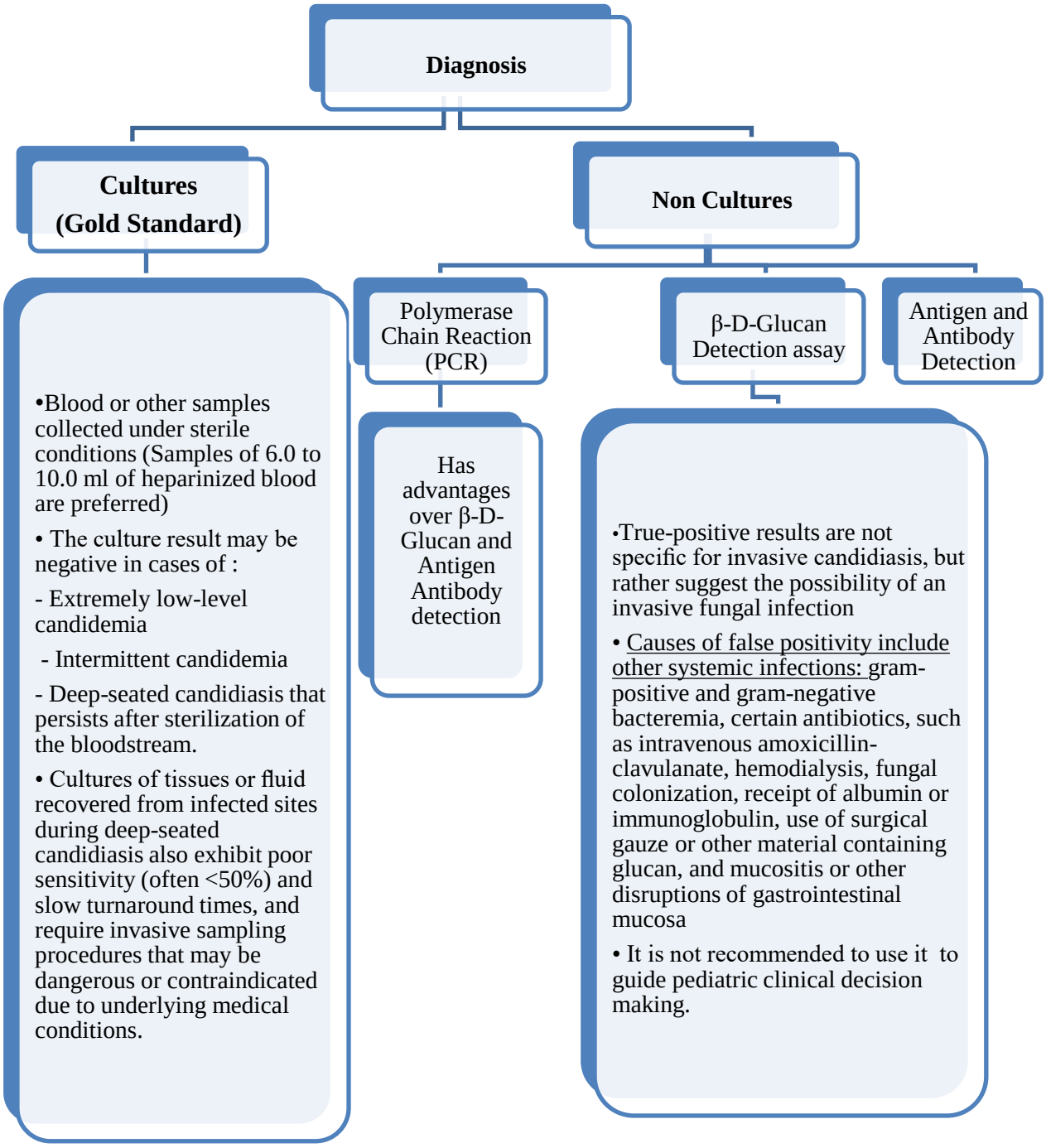

Figure 1. Diagnosis of Candidiasis [9]

Treatment of proven/suspected candidiasis according to the infection site

Infection site	Primary regimen	Alternative	Duration	Notes
Candidemia [6],[8],[9] (Nonneutropenic & Neutropenic Patients)	**Echinocandins** **Caspofungin**: Intravenous (IV) loading dose 70 mg, then 50 mg daily. **Micafungin**: 100 mg IV daily. **Anidulafungin**: loading dose 200 mg IV, then 100 mg IV daily. ➢ Echinocandins indicated for moderately severe to severe illness or with recent azole exposure.	**Fluconazole** ➢ IV or oral (PO), 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily. ➢ Can be used 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 e.g., without recent (≤3 months) azole exposure. ➢ Can be used as a transition from an Echinocandin OR AmB to Fluconazole (usually within 5–7 days) for clinically stable patients, who have isolates that are susceptible to fluconazole (e.g., C. albicans), and have negative repeat blood cultures following initiation of antifungal therapy even if having persistent neutropenia. ➢ For infection due to C. glabrata, transition to higher-dose fluconazole 800 mg (12 mg/kg) daily only for fluconazole susceptible isolates ➢ Fluconazole not recommended for treatment of C. krusei or C. glabrata without confirmation of susceptibility **Voriconazole** ➢ IV 400 mg (or 6 mg/kg) /12 hr for 2 doses (first 24 hours), then 200 mg IV or oral (3 mg/kg) twice daily is	➢ If candidemia is without obvious metastatic complications, use antifungal **for 2 weeks after documented clearance of Candida species from the bloodstream** and resolution of symptoms attributable to candidemia and neutropenia.	➢ Empiric antifungal therapy should be considered in critically ill patients with risk factors for IC 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 (start empiric antifungal as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock) ➢ 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, consideration should be given to stopping antifungal therapy ➢ Follow-up blood cultures should be performed regularly to establish the time point at which candidemia has been cleared ➢ In non-neutropenic patients, Central venous catheters (CVCs) should be removed as early as possible when the source is presumed to be the CVC and the catheter can be removed safely; this decision should be individualized for each patient. ➢ In the neutropenic patient, sources of candidiasis other

Infection site	Primary regimen	Alternative	Duration	Notes
		effective for candidemia, but offers little advantage over fluconazole as initial therapy ➢ If C.glabrata: use voriconazole 200–300 (3–4 mg/kg) twice daily in patients with voriconazole susceptible. ➢ For infections due to C. krusei in neutropenic patients: It is recommended as step-down oral therapy for selected cases of candidemia due to C. krusei or during neutropenia in clinically stable patients who have had documented bloodstream clearance and isolates that are susceptible to voriconazole. **Lipid formulation amphotericin B (AmB)** ➢ 3–5 mg/kg daily ➢ It is used if there is intolerance, limited availability, or resistance to other antifungal agents ➢ Can be used for infections due to C. krusei in neutropenic patients.		than a CVC (e.g., gastrointestinal tract) predominate. Catheter removal should be considered on an individual basis. ➢ Mortality is closely linked to both timing of therapy and/or source control, earlier intervention with appropriate antifungal therapy (within 48 hours of candidaemia being documented) and removal of a contaminated central venous catheter (CVC) or drainage of infected material is generally associated with better overall outcomes. ➢ **Management of positive candida vascular line tip** The management of patients with positive Candida line tip cultures in the absence of a positive blood culture remains uncertain. As a transient candidaemia cannot be excluded, it is recommended that antifungal treatment should be considered and a surveillance blood culture should be performed.

Infection site	Primary Regimen	Alternative	Duration	Notes
Candidiasis [6] (Empiric Treatment for Suspected Invasive Candidiasis in Nonneutropenic)	➢ Similar to proven candidemia	Amphotericin B deoxycholate for intolerance or limited availability of primary regimen. Lipid formulations of amphotericin may be used if needed due to toxicities associated with amphotericin B deoxycholate.		➢ Avoid azoles if recent exposure. ➢ Consider this for the critically ill with risk factors for IC and no other known cause of fever based on clinical assessment, serologic markers for IC, and/or culture data from non-sterile sites.
Candidiasis (Empiric Treatment for Suspected Invasive Candidiasis in neutropenic)	➢ Micafungin ➢ Voriconazole			➢ Fluconazole or Itraconazole: should not be used if recent azole exposure. ➢ Amphotericin B deoxycholate is effective but carries a higher risk of toxicity.

Infection site	Primary regimen	Alternative	Duration	Notes
Candidiasis Intra-abdominal [6],[8],[9]	The same as for the treatment of candidemia or empiric therapy for nonneutropenic patients.		➢ The duration of therapy should be determined by adequacy of source control and clinical response. ➢ In peritonitis → duration of therapy is not well established but patient should to be treated for at least 10 days after catheter removal.	➢ Empiric antifungal therapy should be considered for patients with clinical evidence of intra-abdominal infection (heterogeneous group of infections that includes peritonitis, abdominal abscess) and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis. ➢ Treatment of intra-abdominal candidiasis should include source control, with appropriate drainage and/or debridement

Infection site	Primary regimen	Alternative	Duration	Notes
Central Nervous System Candidiasis (6),(8),(9)	**For initial treatment liposomal AmB** 5 mg/kg daily. **For step-down** Therapy after the patient has responded to initial treatment ➢ Fluconazole, 400–800 mg (6–12 mg/kg) daily. OR ➢ Voriconazole oral 400 mg (6-12 mg/ kg) *2 doses then 200 mg (4 mg/kg) /12h in patients intolerant to Amp B when the candida isolate is fluconazole resistant. **For patients in whom a ventricular device cannot be removed** AmB deoxycholate could be administered through the device into the ventricle at a dosage ranging from 0.01 mg to 0.5 mg in 2 mL 5% dextrose in water.	➢ Fluconazole, 400–800 mg (6–12 mg/kg) daily in patients intolerant to amphotericin B. OR ➢ Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses then 200mg (4mg/kg)/12 hours.	➢ Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved.	➢ Infected CNS devices, including ventriculostomy drains, shunts, stimulators, prosthetic reconstructive devices, and biopolymer wafers that deliver chemotherapy should be removed if possible. ➢ Echinocandins are not recommended due to their poor CSF penetration.

Infection site	Primary regimen	Alternative	Duration	Notes
Candida Chorioretinitis with /Without Vitritis (6),(8),(9	**Candida Chorioretinitis Without Vitritis Without macular involvement** **a)For fluconazole susceptible isolates. Fluconazole** loading dose, 800 mg (12 mg/kg), then 400–800 mg (6–12 mg/kg) daily **OR** **b)For Voriconazole susceptible isolates. Voriconazole** loading dose 400 mg (6 mg/kg) intravenous twice daily for 2 doses then 300 mg (4 mg/kg) intravenous or oral twice daily for voriconazole-susceptible isolates **c)For fluconazole-/voriconazole-resistant isolates** liposomal AmB, 3–5 mg/kg intravenous daily **Candida Chorioretinitis Without Vitritis With macular involvement** **OR** **Candida Chorioretinitis With Vitritis**		➢ The duration of treatment should be at least **4–6 weeks**, with the final duration depending on resolution of the lesions as determined by repeated ophthalmological examinations	➢ Chorioretinitis is the inflammation of the choroid and the retina while endophthalmitis is the inflammation of the vitreous body. ➢ Treatment is the same for both types but an intravitreal injection is sometimes indicated in endophthalmitis in addition to systemic therapy ➢ For Candida Chorioretinitis with Vitritis: Vitrectomy should be considered to decrease the burden of organisms and to allow the removal of fungal abscesses that are inaccessible to systemic antifungal agents

	antifungal agents as noted above PLUS intravitreal injection of either **Conventional AmB** 5–10 µg/0.1 mL sterile water **OR** **Voriconazole** 100 µg/ 0.1 mL sterile water or normal saline, to ensure a prompt high level of antifungal activity			

Infection site	Primary regimen	Alternative	Duration	Notes
Candidiasis, cutaneous [6],[8],[9]	**Miconazole** 2% solution, lotion, cream or powder applied twice daily. **Clotrimazole 1%** solution, lotion, or cream applied twice daily. **Nystatin 100,000 units/gm** lotion, cream, or powder applied twice daily.	Fluconazole 100 mg PO only once a time in refractory cases.		➢ Candidiasis cutaneous is the superficial Candida infection of the epidermis, including Folliculitis. ➢ Risk factors include infants (diaper rash), obesity, diabetes, and immunosuppression. ➢ Candidiasis cutaneous Presents as erythematous plaques and erosion which may have satellite papulopustular lesions in warm, moist skin folds.

Infection site	Primary regimen	Alternative	Duration	Notes
Esophageal Candidiasis[6],[8],[9]	**Oral fluconazole** 200–400 mg (3–6 mg/kg) daily, for 14– 21 days **For patients who cannot tolerate oral therapy fluconazole IV**, 400 mg (6 mg/kg) daily, **Echinocandin** (micafungin, 150 mg daily, caspofungin, 70-mg loading dose, then 50 mg daily, or anidulafungin, 200 mg daily) ➢ Consider de-escalation to oral therapy with fluconazole 200–400 mg (3–6 mg/kg) daily once the patient is able to tolerate oral intake. **For fluconazole-refractory disease** **Itraconazole solution** 200 mg daily for 14–21 days OR **Voriconazole** 200 mg (3 mg/kg) twice daily either intravenous or oral for 14–21 days **Recurrent esophagitis** Chronic suppressive therapy with fluconazole, 100–200 mg 3 times weekly.	**Conventional AmB** 0.3–0.7 mg/kg daily ➢ (it is a less preferred alternative for those who cannot tolerate oral therapy. ➢ Consider de-escalation to oral therapy with fluconazole 200–400 mg (3–6 mg/kg) daily once the patient is able to tolerate oral intake) **Alternatives for fluconazole-refractory disease** **Echinocandin** (micafungin: 150 mg daily; caspofungin: 70 mg loading dose, then 50 mg daily; or anidulafungin: 200 mg daily) for 14–21 days OR **Conventional AmB** 0.3–0.7 mg/kg daily, for 21 days **Posaconazole suspension** 400 mg twice daily		➢ A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. ➢ For HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent infections.

Infection site	Primary regimen	Alternative	Duration	Notes
Chronic Disseminated Candidiasis [6],[8],[9] **(Hepatosplenic)**	**Lipid formulation AmB** 3–5 mg/kg daily **Echinocandin** (micafungin: 100 mg daily; caspofungin: 70-mg loading dose, then 50 mg daily; or anidulafungin: 200- mg loading dose, then 100 mg daily), for several weeks followed by oral fluconazole, 400 mg (6 mg/kg) daily, for patients who are unlikely to have a fluconazole resistant isolate.		➢ Therapy should continue until lesions resolve on repeat imaging, which usually lasts for several months. ➢ Premature discontinuation of antifungal therapy can lead to relapse ➢ If chemotherapy or hematopoietic cell transplantation is required, it should not be delayed, and antifungal therapy should be continued throughout the period of high risk to prevent relapse.	➢ Chronic disseminated candidiasis (hepatosplenic candidiasis) can ensue as a complication of candidemia in neutropenic patients especially when patients with gastrointestinal tract mucositis do not receive antifungal prophylaxis. ➢ Chronic disseminated candidiasis is an uncommon syndrome seen almost entirely in patients who have hematologic malignancies and who have just recovered from neutropenia ➢ For patients who have debilitating persistent fevers, short term (1–2 weeks) treatment with nonsteroidal anti-inflammatory drugs or corticosteroids (0.5–1 mg/kg daily of oral prednisone) can be considered for several weeks, given as a tapering dose

Infection site	Primary regimen	Alternative	Duration	Notes
Intravascular Infections, Including Endocarditis and Infections of Implantable Cardiac Devices[6],[8],[9]	**Native endocarditis, pacemaker and implantable cardiac defibrillator** **Lipid formulation AmB** 3–5 mg/kg daily **High-dose Echinocandin** Caspofungin 150 mg daily, Micafungin 150 mg daily, or Anidulafungin 200 mg daily ➢ **Step-down therapy** 1. **Fluconazole**, 400–800 mg (6–12 mg/ kg) daily, is recommended for patients who have susceptible Candida isolates, have demonstrated clinical stability, and have cleared Candida from the bloodstream 2. **Oral voriconazole**, 200–300 mg (3–4 mg/kg) twice daily, can be used as step-down therapy for isolates that are susceptible to it but not susceptible to fluconazole **Prosthetic valve Endocarditis** ➢ The same antifungal regimens suggested for native valve endocarditis are recommended ➢ Chronic suppressive antifungal therapy with fluconazole,400–		**In native and prosthetic valve endocarditis**→ Valve replacement is recommended particularly in prosthetic valve endocarditis ➢ Treatment should continue for at **least 6 weeks** after surgery and for a longer duration in patients with perivalvular abscesses and other complications ➢ For patients who cannot undergo valve replacement, long term suppression with fluconazole, 400–800 mg (6–12 mg/ kg) daily, if the	➢ Endocarditis should be suspected when blood cultures are persistently positive, when a patient with candidemia has persistent fever despite appropriate treatment, or when a new heart murmur, heart failure, or embolic phenomena occur in the setting of candidemia ➢ Most cases occur following cardiac valvular surgery, but other risk factors include injection drug use, cancer chemotherapy, prolonged presence of CVCs, and prior bacterial endocarditis. The signs, symptoms, and complications are generally similar to those of bacterial endocarditis

Infection site	Primary regimen	Alternative	Duration	Notes
	800 mg (6–12 mg/kg) daily, is recommended if no valve replacement to prevent recurrence. **For ventricular assist devices that cannot be removed** The antifungal regimen is the same as that recommended for native valve endocarditis Chronic suppressive therapy with fluconazole if the isolate is susceptible, for as long as the device remains in place .		isolate is susceptible, is recommended **For pacemaker and implantable cardiac defibrillator infections** ➢ The entire device should be removed ➢ For infections limited to generator pockets, 4 weeks of antifungal therapy after removal of the device is recommended ➢ For infections involving the wires, at least 6 weeks of anti-fungal therapy after wire removal is recommended	

Infection site	Primary regimen	Alternative	Duration	Notes
Oropharyngeal Candidiasis[6],[8],[9]	**For mild disease** Miconazole applied to the mucosal surface over the canine fossa once daily for 7–14 days **For moderate to severe disease** Oral fluconazole 100–200 mg daily, for 7–14 days. **For fluconazole-refractory disease** Itraconazole solution, 200 mg once daily Posaconazole suspension, 400 mg twice daily for 3 days then 400 mg daily, for up to 28 days **Recurrent infection** Fluconazole, 100 mg 3 times weekly	**For mild disease,** nystatin suspension (100 000 U/mL) 4–6 mL 4 times daily for 7–14 days **Alternatives for fluconazole-refractory disease** **Voriconazole** 200 mg twice daily **Intravenous echinocandin** (caspofungin: 70-mg loading dose, then 50 mg daily; micafungin: 100 mg daily; or anidulafungin: 200-mg loading dose, then 100 mg daily) **Conventional AmB** 0.3 mg/kg daily		➢ For HIV-infected patients, antiretroviral therapy is strongly recommended to reduce the incidence of recurrent infections. ➢ For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy

Infection site	Primary regimen	Alternative	Duration	Notes
Osteoarticular Infections (osteomyelitis) [6],[8],[9]	**Fluconazole** 400 mg (6 mg/kg), daily OR **Echinocandin** Caspofungin 50–70 mg daily OR **Micafungin** 100 mg daily OR Anidulafungin 100 mg daily for at least 2 weeks followed by fluconazole 400 mg (6 mg/kg) daily for 6–12 months	**Lipid formulation AmB** 3–5 mg/kg daily, for at least 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months It is a less attractive alternative	➢ Fluconazole: 6-12 months ➢ Echinocandin or Lipid formulation AmB: at least 2 weeks	➢ Surgical debridement is recommended in selected cases of Osteoarticular infections ➢ Surgery is indicated in patients who have neurological deficits, spinal instability, large abscesses, or persistent or worsening symptoms during therapy

Infection site	Primary regimen	Alternative	Duration	Notes
Septic Arthritis (6),(8),(9)	**Fluconazole** 400 mg (6 mg/kg) daily OR **Echinocandin** Caspofungin 70 mg loading dose then 50 mg daily OR Micafungin 100 mg daily OR Anidulafungin 200 loading dose then 100 mg daily for 2 weeks followed by fluconazole, 400 mg (6 mg/kg) daily, for at least 4 weeks ➢ **If the prosthetic device cannot be removed,** chronic suppression with fluconazole 400 mg (6 mg/kg) daily, if the isolate is susceptible	**Lipid formulation AmB** 3–5 mg/kg daily for 2 weeks followed by fluconazole 400 mg (6 mg/kg) daily, for at least 4 weeks It is a less attractive alternative	➢ Fluconazole: 6 weeks. ➢ Echinocandin or Lipid formulation AmB: for 2 weeks followed by fluconazole for at least 4 weeks	➢ Surgical drainage is indicated in all cases of septic arthritis ➢ For septic arthritis involving a prosthetic device, device removal is recommended

Infection site	Primary regimen	Alternative	Duration	Notes
Suppurative Thrombophlebitis, Pericarditis, myocarditis [6],[8],[9]	**Lipid formulation AmB** 3–5 mg/kg daily OR **Fluconazole** 400–800 mg (6–12 mg/kg) daily OR **Echinocandin** (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) **Step-down therapy** to fluconazole, 400–800 mg (6–12 mg/ kg) daily, should be considered for patients who have initially responded to AmB or an echinocandin, are clinically stable, and have a fluconazole-susceptible isolate		➢ The recommended duration of therapy for at least 2 weeks after candidemia (if present) has cleared. ➢ Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. ➢ Several months of therapy is usually needed for pericarditis or myocarditis. Pericardial window or pericardiectomy recommended.	➢ Catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. ➢ Surgical excision of the vein plays an important role in the treatment of peripheral-vein Candida thrombophlebitis. ➢ Systemic anticoagulation or thrombolytic therapy has been used as adjunctive therapy, but there are insufficient data to recommend their use. ➢ Thrombolytic therapy, in conjunction with antifungal therapy, have been used successfully in the management of an infected thrombus attached to a CVC in a patient with persistent candidemia

Infection site	Primary regimen	Alternative	Duration	Notes
Urinary Tract Infections Due to Candida Species [6],[8],[9]	**Asymptomatic Candiduria in patients undergoing urologic procedures** should be treated with oral **fluconazole** 400 mg (6 mg/kg) daily before and after the procedure OR **Conventional AmB** 0.3–0.6 mg for several days before and after the procedure **Symptomatic Candida Cystitis & pyelonephritis** ➢ For fluconazole-susceptible organisms, **oral fluconazole** 200 mg (3 mg/kg) daily for 2 weeks is recommended in cystitis but 200–400 mg (3–6 mg/kg) in pyelonephritis ➢ **For fluconazole-resistant C. glabrata, C. krusei** **Conventional AmB IV**0.3–0.6 mg/kg daily for 1–7 days OR **Conventional AmB bladder irrigation** 50 mg/L sterile water daily for 5 days **Candida Urinary Tract Infection Associated with Fungus Balls**			➢ Asymptomatic Candiduria treatment with antifungal agents is **NOT** recommended unless the patient belongs to a group at high risk for dissemination including: • Neutropenic patients • Very low-birth-weight infants (<1500 g) • Patients who will undergo urologic manipulation ➢ The patients at most risk for candiduria are those who are elderly, female, diabetic, have indwelling urinary devices, are taking antibiotics, and have had prior surgical procedures. ➢ Elimination of predisposing factors, such as indwelling bladder catheters, is recommended whenever feasible. ➢ Rule out urinary tract obstruction in patients with recurrence or systemic signs of infections. ➢ Antifungals that achieve poor urinary levels include: Liposomal amphotericin B, Echinocandins, Itraconazole, Voriconazole & Posaconazole but may be considered for treatment in selected cases. ➢ Pregnant patients identified to have asymptomatic candiduria may have vaginal colonization and not urinary colonization (urine is contaminated). Given the risks associated

	Surgical intervention in adults (**Use same agents** as for cystitis &pyelonephritis) **Irrigation** through nephrostomy tubes, if present, with AmB deoxycholate, 25–50 mg in 200–500 mL sterile water			with systemic antifungal treatment of candida in urine in pregnancy and absence of clear data showing benefit, routine treatment of asymptomatic candiduria may not be needed.

Infection site	Primary regimen			Notes
Vulvovaginal Candidiasis	**Uncomplicated Candida vulvovaginitis** ➢ Topical antifungal agents (e.g., butoconazole, clotrimazole, miconazole, terconazole & ticonazole) ➢ A single 150-mg oral dose of fluconazole **For severe acute Candida vulvovaginitis** Fluconazole, 150 mg, given every 72 hours for a total of 2 or 3 doses or intravaginal topical agents for 5–7 days **C. glabrata** Nystatin intravaginal suppositories, 100 000 units daily for 14 days			➢ Recurring vulvovaginal candidiasis is defined as ≥4 episodes of symptomatic infection within one year. ➢ Most Candida species, with the exception of C. krusei and C. glabrata, respond to oral fluconazole. ➢ Single dose therapy (fluconazole 150 mg oral) during the first- trimester of pregnancy may be associated with miscarriage.

	For recurring vulvovaginal candidiasis Topical agent or oral fluconazole for 10-14 days, followed by fluconazole, 150 mg weekly for 6 months.			

Antifungal Prophylaxis for Candidiasis in the Intensive Care Unit (Medical/Surgical)

Several risk factors arranged into scoring systems are used to predict IC. [5],[10]

A well-designed risk score that identifies subgroups of patients (similar to those being treated at the clinician's ICU) with increased risk over the general population can help in the decision to use antifungal prophylactic therapy.[5],[10]

Clinical Prediction Scores for Invasive Candidiasis

Score (year)	Patient Population	Model Risk Factors	Cutoff Value (value at which antifungal is initiated)
Candida Score (2006) [10],[12]	Admitted to medical/ surgical ICUs for ≥ 7 days in non-neutropenic critically ill patients with candida colonization.	➢ Severe sepsis (2 points) ➢ Major surgery (1 point) ➢ Total parenteral nutrition (1 point) ➢ Multi-focal candida colonization (1 point)	➢ Score ≥ 3
Ostrosky Rule (2007, 2011) [11],[12]	Medical/ Surgical ICUs for ≥ 4 days	**Major criteria:** ➢ Systemic antibiotic use ➢ Central venous catheter **Minor criteria** ➢ Surgery ➢ Immunosuppressants ➢ Corticosteroids ➢ Pancreatitis ➢ Dialysis ➢ Total parenteral nutrition	➢ Two major factors OR ➢ One major + at least two minor factors
Nebraska Medical Center Rule (2011) [12]	Medical/ Surgical ICUs for ≥ 4 days	➢ Broad spectrum antibiotics (1.5 points) ➢ Central venous catheter (0.9 points) ➢ Total parenteral nutrition (0.9 points) ➢ Steroid use in the 7 days before ICU admission up to day 3 (0.4 points), ➢ Abdominal surgery (0.9 points) ➢ Pre-ICU length of stay x 0.039	➢ Score ≥ 2.45
Candidemia Rule (2015) [12]	All hospitalized Patients with culture Positive severe sepsis or septic shock	➢ Antibiotics within 30 days (2 points) ➢ Central venous catheter (2 points) ➢ Admitted from nursing home (2 points) ➢ Total parenteral nutrition (2 points) ➢ Transferred from outside hospital (1 point) ➢ Receiving mechanical ventilation (1 point) ➢ Lung as presumed source of sepsis (**subtract** 6 points)	➢ Score ≥ 3

Antifungal regimens used for prophylaxis [10]

Primary regimen	Alternative	Vulnerable People	Notes
Fluconazole, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily	• Echinocandin (caspofungin: 70 mg loading dose, then 50 mg daily; anidulafungin: 200 mg loading dose and then 100 mg daily; or micafungin: 100 mg daily)	Patients who achieved the Cutoff Value of any of the risk scores chosen based on the patient population especially those in adult ICUs with a high rate (>5%) of invasive candidiasis	➢ Daily bathing of ICU patients with chlorhexidine, decreases the incidence of bloodstream infections including candidemia,

General approach to preemptive/empiric antifungal therapy

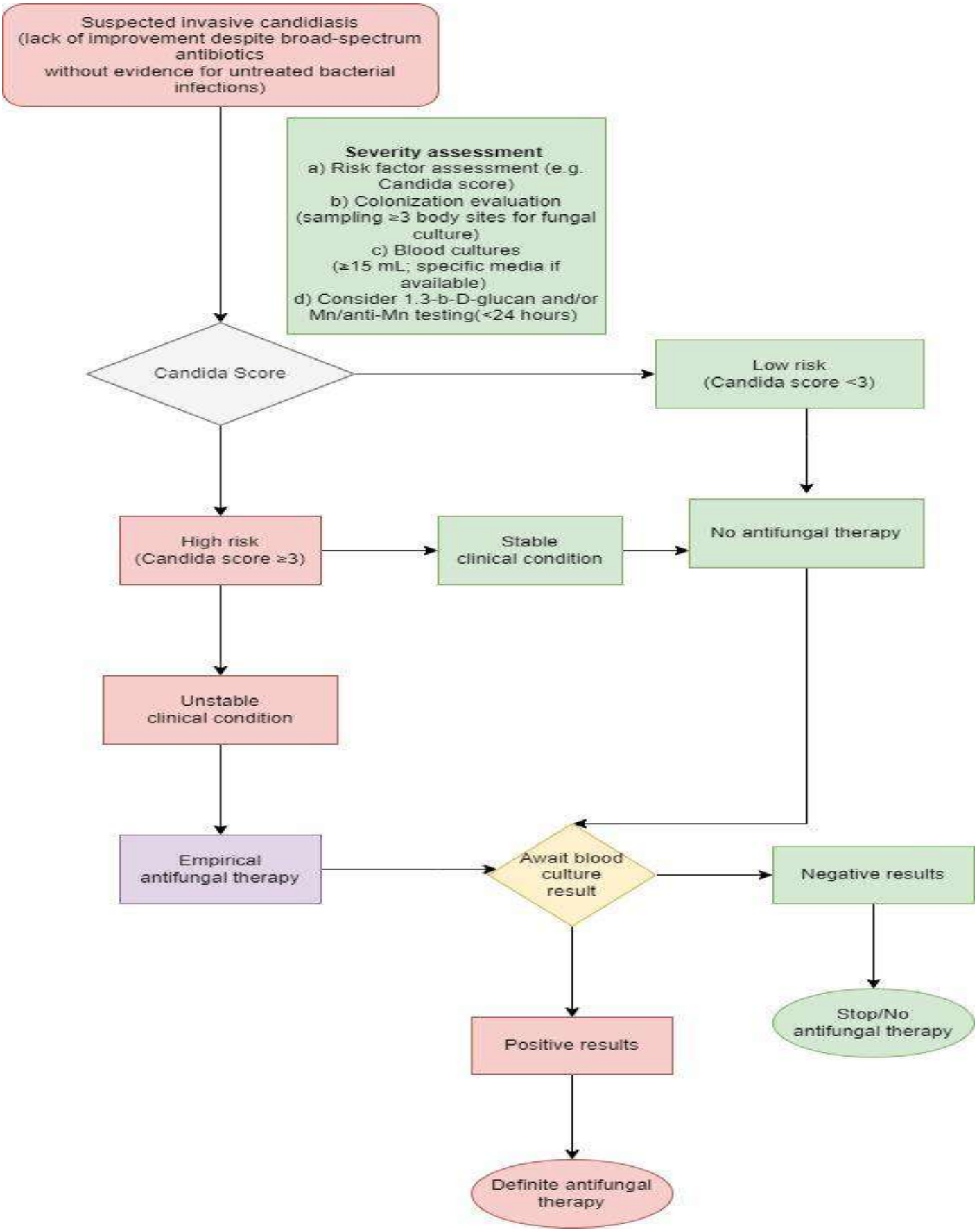

Figure 2. General approach to preemptive/empiric antifungal therapy [12]

Antifungal use in Neonatal Intensive Care Unit (NICU)

Prophylaxis for Candidiasis in Neonatal Intensive Care Unit (NICU) [13], [14]

Primary regimen	Alternative	Vulnerable People	Notes
➢ Fluconazole IV/Oral (3–6 mg/kg) twice weekly for 6 weeks	➢ Nonabsorbable antifungal agents are used to decrease the burden of Candida in the gut and therefore the probability of translocation into the bloodstream. ➢ Nonabsorbable antifungal agents e.g., Oral nystatin, 100 000 units 3 times daily for 6 weeks or during high-risk period, which is considered an alternative to fluconazole in neonates with birth weights <1500 gm in situations in which availability or resistance preclude the use of fluconazole. ➢ Oral bovine lactoferrin (100 mg/day) alone or in combination with Lactobacillus may be effective in neonates <1500 g, and used until either the end of the sixth week of life or until discharge from the NICU	➢ All neonates <1000 g in NICUs with a relatively high frequency of IC > 10% with additional risk factors for IC such as central venous catheterization, receipt of third-generation cephalosporins or carbapenems . N. B, For NICUs with a lower incidence of IC (i.e. <2%), the decision to use the same fluconazole prophylaxis regimen should be made on a case by- case basis.	➢ Candida albicans is the most frequent Candida species causing invasive candidiasis in neonates. ➢ Candida parapsilosis, Candida tropicalis and other Candida species are seen less commonly. ➢ Unlike adults, Candida glabrata and Candida krusei are infrequent causes of IC in the NICU. N.B., Treatment of maternal vaginal candidiasis prior to delivery may prevent subsequent neonatal colonization. The risk factors for development of invasive candidiasis in NICU: • Prematurity. • Central vascular catheterization. • Abdominal surgery. • Necrotising enterocolitis (NEC). • Exposure to broad-spectrum antibacterial agents (e.g. third-generation cephalosporins and carbapenems). • Parenteral nutrition. • Antacids administration. • Endotracheal intubation. • Infants with a smaller gestational age (e.g. neonates with gestational age of less than 27 weeks smaller infants (low birth weight <1000 g) • In nurseries with high rates (>10%) of invasive candidiasis.

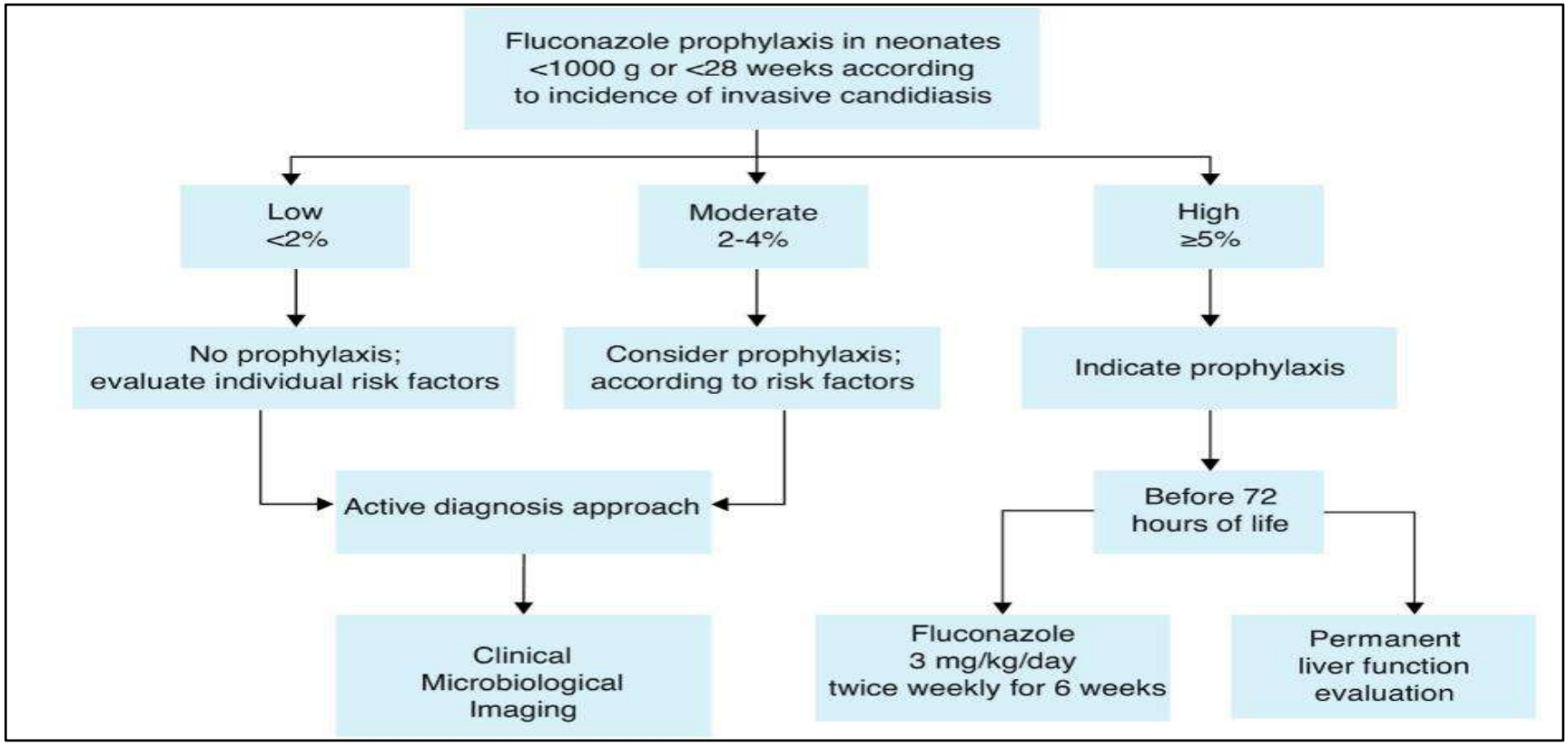

Figure 3. Prophylaxis with fluconazole in neonates if gestational age < 28 weeks and birth weight < 1000g
Adopted from: Santolaya, María E., et al. "Recomendaciones para el manejo de la candidemia en neonatos en América Latina." Revista iberoamericana de micologia 30.3 (2013): 158-170

Treatment of proven/ suspected candidiasis according to the infection site in Neonates [6], [9]

Infection site	Primary regimen	Alternative	Duration	Notes
Neonatal Candidiasis, Including Central Nervous System Infection	**AmB deoxycholate (Conventional Amphotericin B) (AmB)** for neonates with disseminated candidiasis 1 mg/kg daily	**Neonatal Candidiasis except for Central Nervous System Infection** **Fluconazole** ➢ 12 mg/kg/day, IV or oral, is an alternative in patients who have not been on fluconazole prophylaxis. ➢ **More recent data suggest that a loading dose of fluconazole of 25 mg/kg achieves the therapeutic target more rapidly than traditional dosing.`** **Lipid formulation AmB** 3–5 mg/kg, daily, but should be used with caution, particularly in the presence of urinary tract involvement **(A recent comparative effectiveness study found that neonates treated with AmB lipid formulations had higher mortality than infants treated with AmB deoxycholate or fluconazole)** **Echinocandins** ➢ should be used with caution and generally limited to **salvage therapy** or to situations in which resistance or toxicity preclude the use of AmB deoxycholate or fluconazole ➢ Higher doses of micafungin (10-15 mg/kg/day) may be needed to achieve adequate concentrations in brain tissue	➢ The 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 signs attributable to candidemia	**Neonatal Candidiasis except Central Nervous System Infection** ➢ The primary risk factor for neonatal candidiasis is prematurity with those neonates who have an extremely low birth weight ➢ A lumbar puncture and a dilated retinal examination are recommended in neonates with cultures positive for Candida species from blood and/or urine. ➢ Computed tomographic or ultrasound imaging of the genitourinary tract, liver, and spleen should be performed if blood cultures are persistently positive for Candida species. ➢ CVC removal is strongly recommended. ➢ Micafungin or caspofungin may have similar efficacy compared to amphotericin B deoxycholate. ➢ Micafungin now FDA approved for infants less than 4 months. **Central nervous system infection** ➢ All AmB preparations, including the lipid

Infection site	Primary regimen	Alternative	Duration	Notes
		when meningoencephalitis cannot be reliably excluded **Central nervous system infection** AmB deoxycholate 1 mg/kg intravenous daily liposomal AmB 5 mg/kg daily ➢ **Fluconazole For step-down** treatment after the patient has responded to initial treatment, fluconazole, 12 mg/kg daily, is recommended for isolates that are susceptible to fluconazole		formulations, penetrate the CNS and have fungicidal activity in the CNS ➢ Echinocandins are still not well studied for neonatal CNS and urinary infections. ➢ Therapy should continue until all signs, symptoms, and cerebrospinal fluid (CSF) and radiological abnormalities, if present, have resolved. ➢ Infected central nervous system (CNS) devices, including ventriculostomy drains and shunts, should be removed if possible.

Antifungal use in Pediatric Intensive Care Unit (PICU)

Risk factors for candidemia in pediatric intensive care unit (PICU) [13]

- The presence of a CVC.
- A diagnosis of malignancy.
- Receipt of vancomycin.
- Oncology patients at high risk of invasive candidiasis (eg, Acute myeloid leukemia (AML), recurrent Acute lymphocytic leukemia (ALL), myelodysplastic syndrome [MDS], Haematopoietic stem cell transplantation (HSCT recipients) should receive antifungal prophylaxis. [15]
- Patients in ICUs at institutions with high rates of IC (>5%) or high-risk patients (e.g., abdominal surgery) should receive antifungal prophylaxis.

Primary prophylaxis of invasive candidiasis in children [14]

Condition	Primary Therapy
Allogeneic hematopoietic stem cell transplantation (HSCT)	Fluconazole 8–12 mg/kg daily IV. or orally; from day 0 until day +75 post-transplant Fluconazole should only be used if the institutional incidence of invasive mold infections is low OR Micafungin 1 mg/kg daily IV; studied from the start of the preparative regimen until day +30 OR Voriconazole 8 mg/kg every 12 hours (day 1: 9 mg/kg every 12 hours) for I.V., and 9 mg/kg every 12 hours for oral administration (max.: 350 mg every 12 hours) from day 0 until at least day +100 OR Posaconazole suspension 200 mg every 8 hours orally for patients with >/= grade II Graft-versus-host disease (GVHD) and >/=13 years of age
AML and recurrent leukemia	Fluconazole 8–12 mg/kg I.V. or orally after last dose of chemotherapy until neutrophil recovery OR Micafungin 1 mg/kg daily I.V.; after the last dose of chemotherapy until neutrophil recovery OR Liposomal amphotericin B 1 mg/kg daily I.V OR Voriconazole (with the same doses as allogenic HSCT) until neutrophil recovery
Autologous HSCT	Fluconazole OR Micafungin OR Liposomal amphotericin B

Candidiasis treatment in the Paediatrics [13], [14], [15]

Echinocandins preferred first line in patients over 3– 4 months of age for IC treatment

- Micafungin <40 kg: 2–4 mg/kg/day
- Anidulafungin received FDA approval in patients 1 month and older
- Anidulafungin 3 mg/kg as a single loading dose followed by 1.5 mg/kg/day
- Caspofungin Loading dose 70 mg/m2/day, followed by 50 mg/m2/day. Option to increase to 70 mg/m2/day if clinically indicated, maximum absolute dose of 70 mg/day.
- Amphotericin B deoxycholate 0.6–1 mg/kg/day.
- Liposomal amphotericin B 3 mg/kg/day.
- Fluconazole 8–12 mg/kg/day.
- Voriconazole (IV dose: day 1: 9 mg/kg every12h, then 8 mg/kg every 12 hours I.V.); (Oral dose: 9 mg/kg every 12 hours (max.: 350 mg every 12 hours) for the ages of 2–14 years.

Antifungal Combinations in Difficult-to-Treat Candida Infections

The advantages of combining antifungal drugs include: [16], [17]

- A possible wider spectrum of drug activity
- Faster antifungal effect
- Synergy effect
- Lower dosing diminishes side effects and toxicity while maintaining efficacy,
- Delay in the emergence of resistant mutants and broad coverage, especially in mixed or resistant infections.

N.B., Wrong combinations can lead to antagonism and worsening of side effects with negative clinical outcomes on a patient that is already immunosuppressed and in critical condition.

Main antifungal combinations used for difficult-to-treat Candida infections. [16], [17]

Condition	Combining Regimen	Notes
Mural endocarditis	Caspofungin 70–50 mg/day PLUS Voriconazole 6mg/kg/12 hours	Mural endocarditis is the inflammation and disruption of the non-valvular endocardial surface of the cardiac chambers
Valve endocarditis	Fluconazole IV 400 mg/day PLUS Caspofungin 70–50 mg/day	
Candida meningitis	AMBd IV 0.5–1 mg/kg/day (or intrathecal 0.025–0.4 mg) + Fluconazole 3–8 mg/kg/day	
Endophthalmitis	Voriconazole PLUS Caspofungin	In advanced disease, surgery with intraocular amphotericin B deoxycholate and systemic fluconazole has been applied successfully
Lumbar spine infection	Caspofungin PLUS Posaconazole	
Oropharyngeal candidiasis	Fluconazole PLUS Terbinafine	**This combination** was shown to clear oropharyngeal candidiasis in a refractory patient with AIDS, first treated with fluconazole
➢ Terbinafine-fluconazole and terbinafine-itraconazole combinations have synergistic effects against Candida albican.		
➢ C. glabrata infection with low susceptibility to fluconazole might also benefit from terbinafine added to fluconazole, voriconazole or itraconazole. ➢ Fluconazole combined with AmB in treatment of candidemia (other than C. krusei) in non-neutropenic subjects studied showed higher rate and more rapid fungemia clearance ➢ Echinocandin (eg., micafungin) with azole (e.g., posaconazole) has been another well-known antifungal combination in the treatment of invasive candida infection.		

Part II: National Guidance of Antifungal Use in Mucormycosis

Overview about Mucormycosis

- Mucormycosis (previously called zygomycosis) is a rare but serious angio-invasive infection caused by a group of fungi called mucormycetes. [19]
- These fungi grow rapidly and release large numbers of spores that can become airborne. [19]
- Spores of these fungi (commonly found in soil, fallen leaves, compost, animal dung and air) [19]
- **Routes of infection include** inhalation, ingestion, and traumatic inoculation [19].
- Can't be transmitted from person to person, so there is no need for people to be isolated unless they have another reason. [19]
- Although most cases are sporadic, healthcare-associated outbreaks have been linked to adhesive bandages, wooden tongue depressors, hospital linens, negative pressure rooms, water leaks, poor air filtration, non-sterile medical devices, and building construction. [19]
- **High-risk groups** include people with diabetes (especially diabetic ketoacidosis), solid organ transplantation, hematopoietic cell transplantation, neutropenia, long-term systemic corticosteroid use, recent coronavirus disease-2019, treatment with deferoxamine and iron overload (hemochromatosis), people living with HIV, and those using immunomodulating drugs, including the anti-fungal voriconazole in some high-risk groups. [19]
- Deferasirox and deferiprone (iron chelators) can be used instead of deferoxamine as they do not increase the risk of mucormycosis. [19]
- Mucormycosis can invade different body systems. Sites of infection include the lung, central nervous system, paranasal sinuses, gastrointestinal system, and skin. Its clinical manifestations are varied but characteristically demonstrate rapid progression. [19]
- Mucormycosis is an aggressive, life-threatening infection requiring prompt diagnosis and early treatment. Treatment usually consists of antifungal medications and surgery. [19]
- Prevention of COVID-associated mucormycosis needs to focus on addressing the underlying risk factors: [19]
    - Better glycemic control in those with diabetes
    - Appropriate use of systemic corticosteroids
    - Prevention of unnecessary use of antibiotics, antifungals, and other immunomodulators.
    - Infection prevention and control measures at the facility level are essential to prevent the environmental spread of this pathogen.
- Complications: [19]

  Complications of mucormycosis are subdivided into those that result from the disease itself and those that are caused by the antifungal treatment.

    - Complications associated with the disease are cavernous sinus thrombosis, disseminated infection, periorbital destruction, palatine ulcers, osteomyelitis, and death.
    - Complications due to treatment are nephrotoxicity, hypokalemia, and prolonged hospitalization (specifically with the use of deoxycholate amphotericin B).

Types of Mucormycosis

- Clinical presentation is classified according to organ involvement.

Type	General characteristics	Common Symptoms
Rhinocerebral (sinus and brain)	➢ An infection in the sinuses that can spread to the brain. This is most common in people with uncontrolled diabetes and in people who have had a kidney transplant.	➢ One-sided facial swelling ➢ Headache ➢ Nasal or sinus congestion ➢ Black lesions on nasal bridge or upper inside of mouth that quickly become more severe ➢ Fever ➢ Lethargy, seizures, slurred speech, partial paralysis.
Pulmonary	➢ The most common type of mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant.	➢ Fever ➢ Cough ➢ Chest pain ➢ Shortness of breath ➢ Hemoptysis
Gastrointestinal	➢ More common among young children than adults. ➢ Premature and low-birth-weight infants less than 1 month of age are at risk if they have had antibiotics, surgery, or medications that lower the body's ability to fight germs and sickness.	➢ Abdominal pain ➢ Nausea and vomiting ➢ Gastrointestinal bleeding
Cutaneous (skin)	➢ Occurs after the fungi enter the body through a break in the skin. ➢ This type of infection might occur after a burn, scrape, cut, surgery, or other types of skin trauma. ➢ This is the most common form of mucormycosis among people who do not have weakened immune systems.	➢ Skin lesion that resembles blisters or ulcers. ➢ The infected area may turn black. ➢ Other symptoms include pain, warmth, excessive redness, or swelling around a wound.
Disseminated mucormycosis	➢ occurs when the infection spreads through the bloodstream to affect another part of the body. ➢ The infection most commonly affects the brain, but also can affect other organs such as the spleen, heart, and skin.	➢ Tends to occur in people who are already sick from other medical conditions, which makes it difficult to identify which symptoms are related to mucormycosis. ➢ Patients with disseminated infection in the brain may develop mental status changes or coma.

Diagnosis

- Diagnostic methods include biopsy and fungal staining (KOH mount), which remains the mainstay of laboratory diagnosis. [19]
- Imaging tests such as a CT scan of the lungs, sinuses, or other parts of the body, depending on the location of the suspected infection, may also be used to support the diagnosis. [19]

Treatment of Mucormycosis

- Suspected and confirmed mucormycosis are emergencies and require rapid action. [22]
- The standard management of mucormycosis requires early diagnosis, a reversal of risk factors and underlying illness, surgical debridement, and prompt administration of intravenous antifungals - usually amphotericin B. This entails the prompt management of hyperglycemia, acidosis, and cessation of immunosuppressive agents when possible. [22], [23]

Treatment of Mucormycosis in adults

Primary regimen [22]	Duration [22]	Notes [20]
➢ Liposomal amphotericin B 5-10 mg/kg (10mg/kg If CNS involvement or if solid organ transplants) ➢ Conventional Amphotericin B (deoxy cholate) in the dose 1-1.5mg/kg may be used If liposomal form is not available (renal functions and serum electrolytes monitoring) ➢ If a pre-existing renal compromise: Posaconazole IV 300mg/12 hrs on day 1 then 300mg once daily from day 2 **Stepping Down** **If stable disease once a favorable clinical response has been achieved, which usually takes at least 4-6 weeks.** ➢ **Continue 1st line treatment** **OR shift to:** ➢ **Isavuconazole po 200mg/8hrs for first 2 days then 200mg/day from day 3** **Salvage therapy** (Therapy for patients who do not respond to or cannot tolerate amphotericin B.) ➢ Posaconazole OR ➢ Isavuconazole should be given as a loading dose of 200 mg (equivalent to 372 mg of the prodrug isavuconazonium sulfate) IV or orally every 8 hours	Therapy should continue until: ➢ There is clinical resolution of the signs and symptoms of infection ➢ Resolution of radiographic signs of active disease ➢ Reversal of underlying immunosuppression has been achieved when feasible **N.B.,**: Therapy often extends for months, and some patients remain on therapy for life if immunosuppression cannot be corrected.	Other medicines, including fluconazole, voriconazole, and echinocandins, do not work against fungi that cause mucormycosis.

for the first six doses followed by 200 mg IV or orally every 24 hours thereafter.		

Treatment of Mucormycosis in neonates and pediatrics

Primary regimen
➢ Liposomal amphotericin B 5-10 mg/kg/day [23]
Salvage therapy
➢ Liposomal Amphotericin B + Posaconazole oral suspension [23]
OR
➢ Liposomal Amphotericin B + Caspofungin IV 70mg/m2 day 1, 50mg/m2 from day 2 [23]

Antifungal Combinations in Mucormycosis Infections Treatment

- AmB combined with Posaconazole or Caspofungin is used in combination with intent to cure for the refractory disease or in case of intolerance to prior antifungal therapy for treatment of mucormycosis. [24]
- Combination of AmB with Caspofungin or Posaconazole is recommended for refractory disease caused by mucormycosis. [24]

Part III: Guidance of Antifungal Use in Aspergillosis

Overview about Aspergillosis

- Aspergillus fungi, usually found outdoors, in dead leaves, plants, soil or compost and may be found in moist environments indoors. They are the common mold that cause aspergillosis. [25], [26]
- Aspergillus spores are breathed in every day without cause a sick (They aren't contagious), but they can cause allergic reactions, chronic lung conditions and invasive disease and may spread to brain, kidneys, lungs or other organs. [25], [26]
- Aspergillosis is considered as opportunistic infections, which can be life-threatening and cause invasive disease in people with weakened immune systems. [25], [26]

Types of Aspergilloses

- There are different types of aspergilloses (ranging from mild & very serious). [26], [27]

- **Allergic bronchopulmonary aspergillosis (ABPA):** [27]
  Occurs when Aspergillus causes inflammation in the lungs and allergy symptoms such as coughing and wheezing but doesn't cause an infection.
- **Allergic Aspergillus sinusitis**
  Occurs when Aspergillus causes inflammation in the sinuses and symptoms of a sinus infection (drainage, stuffiness, headache) but doesn't cause an infection. [27]
- **Azole-Resistant Aspergillus fumigatus**
  Occurs when one species of Aspergillus, A. fumigatus, becomes resistant to certain medicines used to treat it. Patients with resistant infections might not get better with treatment. [27]
- **Aspergilloma**
  Occurs when a ball of Aspergillus grows in the lungs or sinuses, but usually does not spread to other parts of the body. Aspergilloma is also called a "fungus ball". [27]
- **Chronic pulmonary aspergillosis**
  Occurs when Aspergillus infection causes cavities in the lungs and can be a long-term (3 months or more) condition. One or more fungal balls (aspergillomas) may also be present in the lungs. [27]
- **Invasive aspergillosis (IA)**
  Occurs when Aspergillus causes a serious infection, and usually affects people who have weakened immune systems, such as people who have had an organ transplant or a stem cell transplant. IA most commonly affects the lungs, but it can also spread to other parts of the body. [26], [27]
- **Cutaneous (skin) aspergillosis**
  Occurs when Aspergillus enters the body through a break in the skin (for example, after surgery or a burn wound) and causes infection, usually in people who have weakened immune systems. Cutaneous aspergillosis can also occur if invasive aspergillosis spreads to the skin from somewhere else in the body, such as the lungs. [27]

Precautions for Aspergillosis Prevention

- Hospitalized allogeneic Haematopoietic Stem Cell Transplant (HSCT) recipients should be placed in a protected environment to reduce mold exposure. [27]
- In hospitals in which a protected environment is not available→ they should be admitted to a private room, no connection to construction sites, and not allowing plants or cut flowers to be brought into the patient's room. [27]
- Precautions to reduce mold exposure among outpatients at high risk for IA, including avoidance of gardening, spreading compost, or close exposure to construction or renovation. [27]
- Leukemia and transplant centers should perform regular surveillance of cases of invasive mold infection. [27]
- The effectiveness of masks (surgical or N95) to protect against mold infections is unknown. [27]

Patients at risk for IA

The following patients are at high risk for IA: [27],[28]

- Patient with prolonged neutropenia (the intensity and duration of neutropenia predict the risk of IA).
- Allogeneic HSCT recipients

N.B. In allogeneic HSCT recipients, 3 periods of risk for invasive mold disease occur:

1. Neutropenia following the conditioning regimen
2. Exogenous immunosuppression for treatment of acute Graft-versus-host disease (GVHD)
3. Exogenous immunosuppression for treatment of chronic GVHD (after day 100 of transplant)

- Solid organ transplant (SOT) recipients.
- Patients receiving corticosteroids, those with advanced AIDS, and those with Chronic granulomatous disease (CGD).
- In patients with hematologic malignancies, myelodysplastic syndrome (MDS), and other diseases associated with marrow failure (e.g., aplastic anemia).
- Patients with refractory or relapsed acute leukemia treated with reinduction regimens are at particularly high risk for IA and other mold infections.

Symptoms of Aspergillosis

The symptoms vary depending on the type of aspergillosis and location in the body as follows: [25], [27], [28]

- **Lung infections or allergic reactions**; Cough, sometimes coughing up blood, fever, shortness of breath (dyspnea), noisy breathing (wheezing), and chest pain.
- **Chronic pulmonary aspergillosis**; Fatigue and weight loss.
- **Eye fungal keratitis**; Red eyes, Eye pain, Blurred vision.
- **Skin cutaneous aspergillosis**: Red, hardened patches, may progress to ulcers that turn black.
- **Brain cerebral aspergillosis**; Mood changes, confusion, seizures, and weakness.
- **Gastrointestinal aspergillosis**; Fever, abdominal pain, diarrhea, or constipation.
- **Rhino cerebral aspergillosis** (sinuses, nasal passages, mouth, and brain); fever, swelling on one side of face, headache, stuffy nose, nasal pain, bloody mucus in nose, drooping eyelids, black pus draining from mouth and nose.

Diagnosis

Galactomannan and (1,3)-β-D-Glucan

- Galactomannan (GM) detection in fluids (especially Broncho alveolar Lavage (BAL)) is more sensitive than culture for diagnosis of IA. [31]
- Serum and BAL galactomannan (GM) is recommended as an accurate marker for the diagnosis of IA when used in certain patient subpopulations (hematologic malignancy, HSCT). [27]
- Serum and BALGM is recommended as an accurate marker for the diagnosis of IA when used in certain patient subpopulations as follows: [27], [33]
  - Hematologic malignancy, HSCT. [27], [29]
  - Lung and non-lung transplant recipients (in combination with other diagnostic modalities (e.g., chest CT scan, culture). [28], [32]
- Serum assays are not specific for Aspergillus. [27]
- GM is not recommended for screening in SOT recipients or patients with chronic granulomatous disease. [27]
- Serial screening is not recommended in patients on mould-active prophylaxis. [31], [32]

Radiographic Diagnosis of Invasive Pulmonary Aspergillosis (IPA)

- CT is used in patients at risk for IA with fever of unknown origin or clinical symptoms of lower respiratory tract infection who remain febrile despite broad-spectrum antibacterial treatment. [31], [32]

- Routine use of contrast during a chest CT scan for a suspicion of IPA is not recommended, Contrast is recommended when a nodule or a mass is close to a large vessel. [27]
- A follow-up chest CT scan to assess the response of IPA to treatment after a minimum of 2 weeks of treatment; but earlier assessment is indicated if the patient clinically deteriorates. When a nodule is close to a large vessel, more frequent monitoring may be required. [27]

Bronchoscopy in the Diagnosis of IPA

- Bronchoscopy with BAL is recommended in patients with a suspicion of IPA. [27]
- BAL is not preferred in severe hypoxemia, bleeding, and platelet transfusion-refractory thrombocytopenia. [27]
- Percutaneous or endobronchial lung biopsy should be considered in the presence of peripheral nodular lesions as the yield of BAL is low in this condition. [27]

Antifungal Susceptibility Testing (AFST)

Both microscopy and culture should be attempted on appropriate specimens from patients at risk for IA with a priority for culture in most cases where insufficient material is available. [32], [33]
Used to identify fungal elements in fresh clinical specimens (e.g. BAL)

- AFST of Aspergillus isolates using a reference method is reserved for: [27]
  - Patients suspected to have an azole-resistant isolate.
  - Patients unresponsive to antifungal agents.
  - Epidemiological purposes.

Nucleic Acid Testing

- The use of blood or serum Aspergillus PCR testing is recommended in patients with severe immunocompromise, such as those with hematological malignancy or recipients of hematological stem cell or solid organ transplants who are suspected of having IPA. [33], [35]
- When PCR assays are used, results should be considered in conjunction with other diagnostic tests and the clinical context. [27]
- Aspergillus PCR requires two positive readings to qualify as a 'positive' result either from: consecutive blood samples; or duplicate samples if BAL fluid is used; or a single positive from blood and a single positive from BAL fluid. [27]

Appropriate fungal diagnostics performed for suspected invasive mould infection

- If lung infiltrates present: BAL with galactomannan, microscopy, culture, and Aspergillus PCR within 72 h. [35]
- If a mold is isolated from culture: identification to species level and susceptibility testing performed. [35]
- Repeat imaging after 2 weeks as clinically indicated. [35]

Complications

- All types of aspergillosis can cause lung damage, including Scarring (fibrosis), widening of airways (bronchiectasis), and collapsed areas of lung (atelectasis). [25]
- Invasive and chronic aspergillosis can cause additional complications, including: moving to and damaging other organs, tissue destruction, respiratory failure, and sepsis. [25]

Treatment of Aspergillosis

- Noninvasive aspergillosis could be cured by surgery or antifungals. [27]
- In some cases, there is a recurrence probability. However, invasive aspergillosis could be very hard to cure. [27]

Indications for empirical antifungal therapy in aspergillosis: [27], [31]

High-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy.
Empiric antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia <10 days) unless other findings indicate a suspected invasive fungal infection (IFI)
N.B., the use of serum or BAL fungal biomarkers such as GM or (1→3)-β-D-glucan to guide antifungal therapy in asymptomatic or febrile high-risk patients can reduce unnecessary antifungal therapy.

Antifungal agents that are used for the treatment of IA

a) Triazoles (Itraconazole, Voriconazole, Posaconazole)
   - Triazoles are preferred agents for the treatment and prevention of IA in most patients. [27]

b) Echinocandin
   - Effective in salvage therapy (either alone or in combination) against IA, but it is not recommended to be used as monotherapy for the primary treatment of IA. [27]

c) Amphotericin B (AmB) deoxycholate and its lipid derivatives [27]
   - Appropriate options for initial and salvage therapy of Aspergillus infections when voriconazole cannot be administered (contraindicated or not tolerated).
   - AmB deoxycholate should be reserved for use in resource-limited settings in which no alternative agents are available.

The general strategies for salvage therapy (for refractory or progressive Aspergillosis) typically includes: [27]

1) Changing the class of antifungal.
2) Tapering or reversal of underlying immunosuppression when feasible.
3) Surgical resection of necrotic lesions in selected cases.

In the context of salvage therapy, an additional antifungal agent may be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used.

- Antifungal Agents used as salvage: [27]
  1) Amphotericin B (AmB) deoxycholate and its lipid derivatives.
  2) Echinocandins (either alone or in combination).
  3) The use of a triazole as salvage therapy should consider prior antifungal therapy, host factors, pharmacokinetic considerations, and possible antifungal resistance.

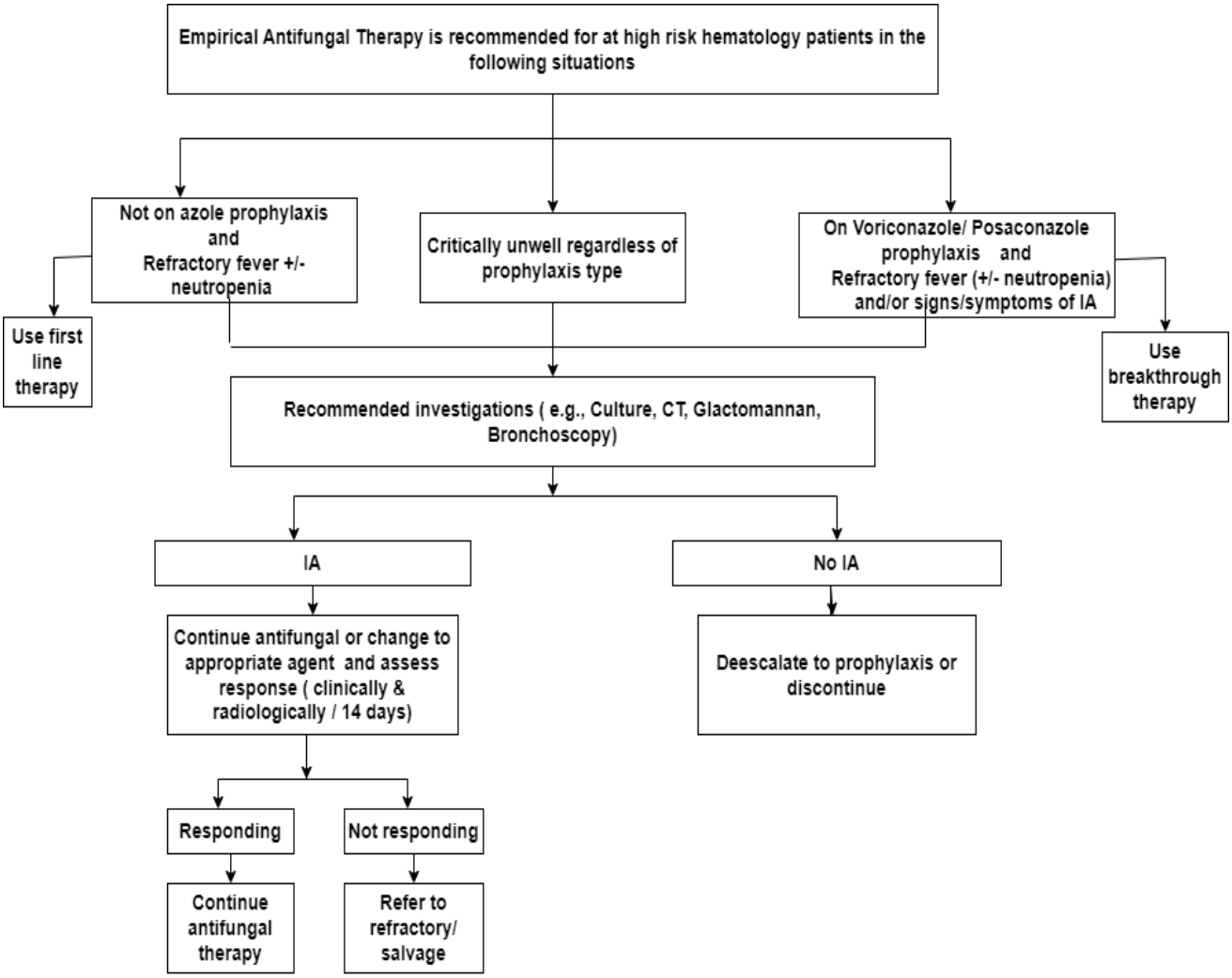

Figure 4. Approach to the diagnosis and management of suspected and confirmed invasive aspergillosis
Adopted from: Morrissey et al., 2014 (36)

Treatment of Aspergillosis according to the infection site

Infection site	Primary Agents	Alternative	Notes	Duration
IPA [27],[28], [29],[30],[31],[33], [36]	Voriconazole IV 6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg every 12 hr. Oral 200–300 mg every 12 hr. ➢ Oral switch could be conducted on day **10-14** if CT improved & neutropenia resolved [4] ➢ If CT worsened at day **10-14** → go for Liposomal AmB 3mg/kg IV once daily [28]	Liposomal AmB (3–5 mg/kg/day IV) OR Caspofungin (70 mg/day IV day 1, then 50 mg/day IV) OR Micafungin (100–150 mg/day IV) OR Posaconazole (Oral suspension: 200 mg 3 times daily; IV: 300 mg /12 hours on day 1, then 300 mg daily)	➢ Early initiation of therapy is warranted while a diagnostic evaluation is conducted. ➢ Amphotericin B deoxycholate is considered to have no role in the treatment of IA when more effective and less toxic agents are available. Its limited efficacy and its poor safety profile led to a recommendation against its use. ➢ Secondary prophylaxis should be initiated for patients with successfully treated IPA who require subsequent immunosuppression, to prevent recurrence. ➢ Combination antifungal therapy with voriconazole and an echinocandin may be considered in select patients with documented IPA (in the setting of severe disease, especially in patients with hematologic malignancy and those with profound and persistent neutropenia) ➢ Surgical resection of Aspergillus-infected tissue may be useful in: • Localized disease that is eacausing recalcitrant hemoptysis from a single focus. • Lesions eroding into bone. This decision should be mindful of the probability of structural spillage of organisms into the pleural space.	6–12 weeks dependent on degree, duration of immunosuppression, disease site and clinical improvement.

Infection site	Primary Agents	Alternative	Notes	Duration
Invasive sinus aspergillosis. (27), (31), (36)	➢ Surgery and either systemic voriconazole or a lipid formulation of AmB (the same dose as IPA) ➢ Surgical removal alone can be used to treat Aspergillus **fungal ball** of the paranasal sinus.	Same as IPA		Same as IPA

Infection site	Primary Agents	Alternative	Notes	Duration
CNS Aspergillosis (27),(31),(36)	**Voriconazole** (The same as IPA)	Lipid formulations of AmB (dose as IPA) are reserved for those intolerant or refractory to Voriconazole.	➢ Surgical intervention e.g., resection of infected tissue or abscesses (eliminates areas containing viable fungi) may be beneficial in selected cases. ➢ Intrathecal or intralesional antifungal therapy is not recommended as AmB delivered intrathecally can`t penetrate beyond the pia mater. ➢ Combination of antifungal, no data suggesting better outcomes.	As IPA

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergillus Endocarditis, Pericarditis, and Myocarditis (27)	➢ Similar to IPA ➢ Surgical intervention combined with antifungal therapy in attempts to prevent embolic complications and valvular decompensation. ➢ Voriconazole or a lipid formulation of AmB is recommended as initial therapy.	Similar to IPA	➢ Aspergillus pericarditis usually requires Pericardiectomy.	➢ Following surgical replacement of an infected valve, lifelong antifungal therapy should be considered.

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergillus Osteomyelitis and Septic Arthritis (27), (36)	• Similar to IPA. • There is little reported experience in the use of Posaconazole or Echinocandins in the treatment of Aspergillus osteomyelitis.		• Surgical intervention is recommended combined with voriconazole.	➢ Therapy should be continued for a minimum of **8 weeks**, with longer courses (>6 months) frequently necessary.

Infection site	Primary Agents	Alternative	Notes	Duration
Cutaneous Aspergillosis (27)	➢ Similar to IPA. ➢ Voriconazole in addition to evaluation for a primary focus of infection.		➢ In cases of aspergillosis in burns or massive soft tissue wounds, **surgical debridement** is recommended, in addition to antifungal therapy.	

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergillus peritonitis (27)	➢ Peritoneal dialysis catheter removal accompanied by systemic antifungal therapy with voriconazole.	➢ Posaconazole and echinocandins have been successfully used in fungal peritonitis from causes other than peritoneal dialysis and may have utility as salvage therapy in Aspergillus peritonitis.	➢ In cases where the catheter cannot be promptly removed some practitioners use intraperitoneal AmB in conjunction with voriconazole, but it should be recognized that intraperitoneal AmB administration may cause a chemical peritonitis and is not recommended.	6–8 weeks

Infection site	Primary Agents	Alternative	Notes	Duration
Gastrointestinal, and Hepatic Aspergillosis (27)	➢ Voriconazole or a lipid formulation of AmB. ➢ Similar to IPA.		**Gastrointestinal** surgical consultation in attempts to prevent complications of hemorrhage, perforation, obstruction, or infarction. **For extrahepatic or perihepatic biliary obstruction**, or localized lesions that are refractory to medical therapy, surgical intervention should be considered.	

Infection site	Primary Agents	Alternative	Notes	Duration
Renal Aspergillosis (27)	➢ Parenchymal disease is best treated with voriconazole. ➢ Obstruction of one or both ureters should be managed with decompression if possible and local instillation of AmB deoxycholate.		a combined approach of medical and urologic management for renal aspergillosis.	

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergillus infections of the eye (endophthalmitis and keratitis) (27),(36)	**Endophthalmitis** Voriconazole IV/PO **plus** intravitreal AmB 5–10 µg OR Voriconazole 100 µg with partial vitrectomy **Keratitis** Topical Natamycin 5% ophthalmic suspension	Similar to IPA		

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergillus Ear Infections (27)	➢ Prolonged course of systemic voriconazole combined with surgery.		➢ Noninvasive Aspergillus otitis externa also called otomycosis, is treated by thorough mechanical cleansing of the external auditory canal followed by topical antifungals or boric acid	

Infection site	Primary Agents	Alternative	Notes	Duration
Allergic syndromes of Aspergillosis a) Allergic bronchopulmonary aspergillosis (ABPA) [27], [30]	• Corticosteroids (doses and durations vary widely, with doses adjusted on level of airflow obstruction, eosinophilia, and levels of IgE). • Oral Itraconazole (200 mg twice daily) has been used as a steroid-sparing agent.	Oral voriconazole (200 mg PO every 12 h)	Allergic syndromes of aspergillosis: ➢ Symptomatic asthmatic patients with bronchiectasis or mucoid impaction, despite oral or inhaled corticosteroid therapy, with oral itraconazole ➢ Cystic Fibrosis patients with frequent exacerbations and/or falling forced expiratory volume 1 (FEV1). Diagnosis of allergic syndrome of aspergillosis: Elevated Aspergillus IgE and total IgE are recommended to establish the diagnosis and are useful for screening.	16 weeks [5]

Infection site	Primary Agents	Alternative	Notes	Duration
Allergic syndromes of Aspergillosis b) Allergic Fungal Rhinosinusitis [27], [31]	➢ oral antifungal therapy using mold-active triazoles (usually itraconazole) for refractory infection and/or rapidly relapsing disease, although this approach is only partially effective		➢ Polypectomy and sinus washout as the optimal means of symptom control and inducing remission; however, relapse is frequent. ➢ Fungal culture of nasal secretions is usually unhelpful as it reflects airborne fungi	

Infection site	Primary Agents	Alternative	Notes	Duration
Chronic Pulmonary Aspergillosis CPA. Chronic cavitary pulmonary	➢ Oral itraconazole ➢ Oral voriconazole	➢ Posaconazole 400 mg twice daily (liquid) ➢ IV therapy should be used in patients with progressive	➢ CPA is a severe fungal infection usually seen in immunocompetent or mildly	➢ Optimal duration of oral therapy in CPA is preferred to be long-

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergillosis (CCPA). Chronic fibrosing pulmonary aspergillosis (CFPA). Subacute invasive pulmonary aspergillosis (SAIA) [27],[31],[34]		disease, who fail, are intolerant of or have triazole resistance: Micafungin 150 mg/day. OR Caspofungin 50–70 mg/day. OR Amphotericin B deoxycholate 0.7–1.0 mg/kg/day. OR Liposomal AmB 3 mg/kg/day.	immunosuppressed patients with underlying respiratory disorders. The diagnosis of CCPA requires: (i) 3 months of chronic pulmonary symptoms or chronic illness or progressive radiologic radiographic abnormalities, with cavitation, pleural thickening, pericavitary infiltrates, and sometimes a fungal ball. (ii) Aspergillus IgG antibody elevated or other microbiological data (iii) No or minimal immunocompromise, usually with one or more underlying pulmonary disorders. ➢ Surgical resection is an option for some patients with localized disease, unresponsive to medical therapy, including those with pan-azole-resistant Aspergillus fumigatus infection or persistent hemoptysis despite bronchial artery embolization. ➢ The outcomes from surgery are less favorable than those with single aspergilloma, and a careful risk assessment prior to surgical intervention is required.	term therapy for 6 months. (4-9 mo.) (adjust with therapeutic drug monitoring). ➢ Patients with CCPA and either pulmonary or general symptoms or progressive loss of lung function or radiographic progression should be treated with a minimum of 6 months of antifungal therapy. ➢ Patients with CCPA without pulmonary symptoms should be observed (without antifungal) every 3-6 months.

Infection site	Primary Agents	Alternative	Notes	Duration
Aspergilloma [27],[29],[30]	➢ Asymptomatic: needs observation only ➢ Symptomatic and fit for surgery: Surgery. ➢ Symptomatic and unable for surgery -Itraconazole oral solution PO 200mg twice daily.	Voriconazole If 40kg: 400mg PO twice daily, then 200mg PO twice daily If azole intolerant: - Caspofungin 70mg IV day one followed by 50mg IV once daily. If weight >80kg continue 70mg IV once daily	➢ Patients with symptoms, especially significant hemoptysis, with a single aspergilloma, should have it resected, assuming that there is no contraindication. ➢ Peri-/postoperative antifungal therapy is not routinely required, but if the risk of surgical spillage of the aspergilloma is moderate (related to location and morphology of the cavity), antifungal therapy with voriconazole (or another mold-active azole) or an echinocandin is suggested to prevent Aspergillus empyema.	➢ Asymptomatic patients with a single aspergilloma and no progression of the cavity size over 6–24 months should continue to be observed for 6-12 months. ➢ Antifungal duration: 6-9 mo.

Management of breakthrough infection

- Breakthrough IA: IA which occurs during exposure to an antifungal drug (given as either antifungal prophylaxis or treatment). [36]
- Refractory IA: Progression of disease, with worsening or new clinical symptoms, signs, or radiological features attributed to IA as a result of failure to respond to anti-Aspergillus antifungal treatment. [36]
- Breakthrough aspergillosis typically occurs in the setting of antifungal prophylaxis. [36], [27]
- Documentation of serum azole levels should be verified if TDM is available for patients receiving mold-active triazoles. [27]
- Antifungal therapy should be empirically changed to an alternative class of antifungal with Aspergillus activity. [36]
- Other considerations include reduction of underlying immunosuppression if feasible, and susceptibility testing of any Aspergillus isolates recovered from the patients. [27]
- If the patient develops breakthrough aspergillosis in the setting of non-mold-active prophylaxis (e.g., fluconazole), we recommend the same approach for the treatment of IA in the absence of prophylaxis. [27]
- In a patient who develops breakthrough aspergillosis in the setting of mold-active prophylaxis (posaconazole, voriconazole, itraconazole, echinocandins), a “salvage” treatment plan individualized to patient circumstances and comorbidities is required. [27]
- For patients with apparent breakthrough aspergillosis on prior voriconazole, **a lipid formulation of AmB (3–5 mg/kg/day)** is recommended, especially in centers where mucormycosis is seen.
- In patients with breakthrough aspergillosis while on **posaconazole** prophylaxis, some data support the use of an alternative triazole as salvage therapy, such as **voriconazole.** [27]
- A typical approach would be to administer broad-spectrum antifungal therapy until the diagnosis is established and a response to treatment can be documented. [27]
- The benefits of combination antifungal therapy for breakthrough aspergillosis are unknown. If a decision is made to use combination therapy, we favor the initial use of a combination of antifungal agents from different classes than the antifungal the patient was initially receiving when the breakthrough aspergillosis was diagnosed. [27]

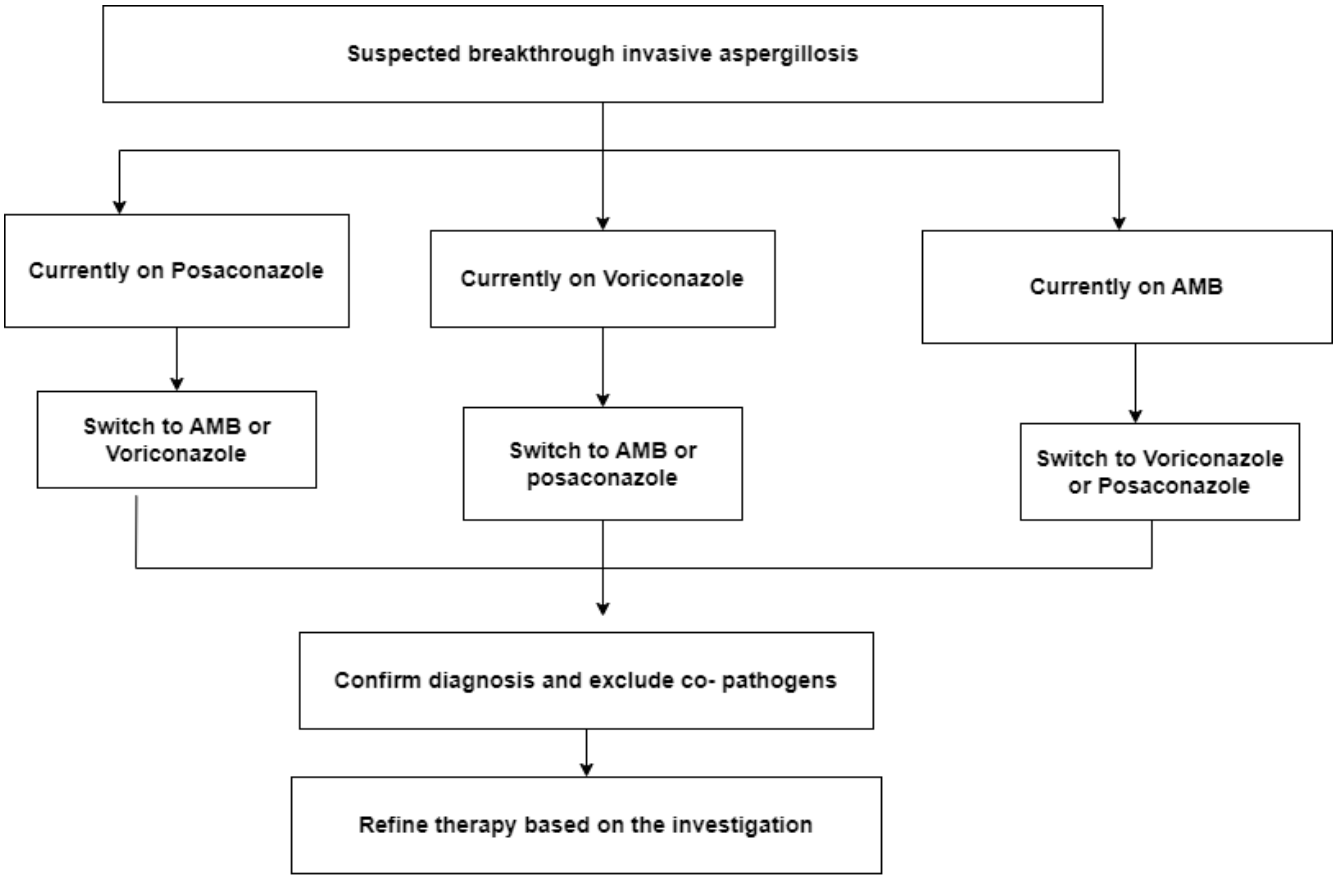

Figure 5. Suggested approaches for suspected breakthrough invasive aspergillosis treatment change [36]

When Is It Safe to Proceed with Chemotherapy or Transplantation in a Patient with Invasive Aspergillosis?

- IA is not an absolute contraindication to additional chemotherapy or HSCT.
- Decisions about when to proceed with additional chemotherapy or HSCT following the diagnosis of aspergillosis should involve both infectious disease specialists and hematologists/oncologists. These decisions must consider the risk of progressive aspergillosis during periods of subsequent antineoplastic treatment versus the risk of death from the underlying malignancy if this treatment is delayed. [27]

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