A Fungus Among Us! When to Suspect & Treat Fungal Infections in the Intensive Care Unit

A HealthTrust Webinar

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Objectives

1. Identify the types of invasive fungal infections prevalent in the intensive care unit
2. Recognize risk factors for invasive fungal infections in the intensive care unit
3. Recall the difference between pre-emptive, prophylactic, empiric and definitive treatment for fungal infections in the intensive care unit

Overview

- Background
- Types of Fungal Infections
- Risk Factors
- Rapid Diagnostic Tests
- Treatment Strategies
- Summary

Background

Key features of fungal infections:

- Low incidence rate
- Difficult diagnosis
- Difficult treatment
- Ability to involve multiple organs
- High morbidity & mortality

Critically ill patients:

- Complex medical and surgical problems
- Disruption of natural barriers
- Invasive procedures
- Prolonged antibiotic treatment
- High morbidity & mortality

Source: Suleyman G, Alangaden GJ. Nosocomial Fungal Infections: Epidemiology, Infection Control, and Prevention. Infect Dis Clin North Am. 2021 Dec;35(4):1027-1053. doi: 10.1016/j.idc.2021.08.002. PMID: 34752219. Accessed Jan 7, 2023; Image obtained from Shelton J. The Future is Fungal. The Imperial Medicine Blog. April 2021. Available at: https://blogs.imperial.ac.uk

Types of Fungal Infections

DIMORPHIC FUNGI	YEASTS	MOLDS
Histoplasma spp.	*Candida* spp.	*Aspergillus* spp.
Blastomyces spp.	Cryptococcus spp.	*Zygomycetes* spp.
Coccidioides spp.		

Source: Centers for Disease Control and Prevention. Types of Fungal Diseases. CDC. June 16, 2023. Accessed Jan 7, 2023; Available at: Types of Fungal Diseases | Fungal Diseases | CDC

Types of Fungal Infections

Endemic Pathogens

Histoplasma spp.

Blastomyces spp.

Coccidioides spp.

Opportunistic Pathogens

Candida spp.

Aspergillus spp.

Cryptococcus spp.

Zygomycetes spp.

Source: Centers for Disease Control and Prevention. Types of Fungal Diseases. CDC. June 16, 2023. Accessed Jan 7, 2023; Available at: Types of Fungal Diseases | Fungal Diseases | CDC

Endemic Pathogens

Histoplasma capsulatum (Histoplasmosis)
Soil-dwelling dimorphic fungus

Entry: respiratory tract

Presentation: mild to chronic pulmonary disease; can progress to severe or disseminated histoplasmosis infections

Blastomyces dermatitidis (Blastomycosis)
Soil-dwelling dimorphic fungus

Entry: respiratory tract
Extrapulmonary: skin, bones, genitourinary tract

Presentation: community-acquired pneumonia not responding to usual antibiotics

Source: Bajwa S, Kulshrestha A. Fungal infections in intensive care unit: challenges in diagnosis and management. Ann Med Health Sci Res. 2013 Apr. Accessed November 15, 2023.; Akram SM, Koirala J. Histoplasmosis. StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448185/

Endemic Pathogens

Coccidioides immitis (Coccidioidomycosis)
Soil-dwelling dimorphic fungus

Entry: respiratory tract
Extrapulmonary: skin, bones, central nervous system (CNS)

Presentation: community-acquired pneumonia, osteomyelitis, meningitis

Source: Bajwa S, Kulshrestha A. Fungal infections in intensive care unit: challenges in diagnosis and management. Ann Med Health Sci Res. 2013 Apr;3(2):238-44. doi: 10.4103/2141-9248.113669. PMID: 23919197; PMCID: PMC3728870. Accessed November 15, 2023.

Opportunistic Pathogens

***Candida* spp.** (Candidiasis)
Found on the skin and inside the body (mouth, throat, gut, and vagina)

- *C. albicans*
- Non-albicans Candida (NAC): *C. krusei*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*

Entry: Endogenous opportunistic pathogen

Presentation: Bloodstream, genitourinary tract, skin, meningitis, and intra-abdominal Infections

Cryptococcus neoformans (Cryptococcosis)
Commonly found in soil contaminated by bird droppings and in decaying wood

Entry: Respiratory tract

Presentation: Flu-like symptoms, pulmonary manifestations

Source: Bajwa S, Kulshrestha A. Fungal infections in intensive care unit: challenges in diagnosis and management. Ann Med Health Sci Res. 2013 Apr;3(2):238-44. doi: 10.4103/2141-9248.113669. PMID: 23919197; PMCID: PMC3728870. Accessed November 15, 2023.

Opportunistic Pathogens

***Aspergillus* spp.** (Aspergillosis)
Found in soil, household dust, decomposing organic matter, and plants

- *A. fumigatus*, *A. flavus*, *A. terreus*

Entry: Respiratory tract

Presentation: Pulmonary infection

***Zygomycetes* spp**. (Zygomycosis)
Found in soil dead organic matter/necrotic tissues and hospital environment

- *Rhizopus* spp., *Absidia* spp., *Mucor* spp.

Entry: Respiratory tract, percutaneous exposure

Presentation: similar to *Aspergillus*; pulmonary infection, CNS, gastrointestinal

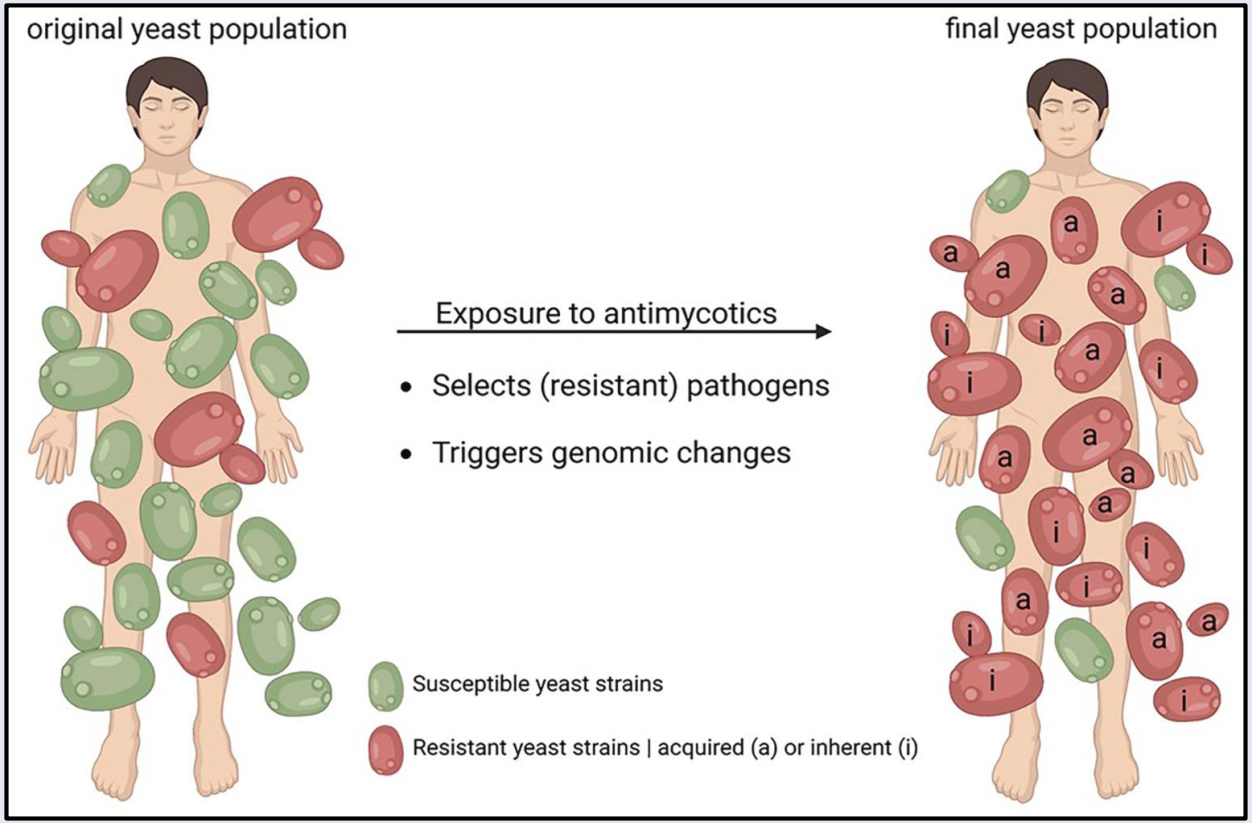
Source: Bajwa S, Kulshrestha A. Fungal infections in intensive care unit: challenges in diagnosis and management. Ann Med Health Sci Res. 2013 Apr;3(2):238-44. doi: 10.4103/2141-9248.113669. PMID: 23919197; PMCID: PMC3728870. Accessed November 15, 2023.

Epidemiology

Most prevalent invasive fungal infections (IFI) in the ICU

- ***Candida* spp.**
  - Superficial mycosis (mucosal infections)
  - Invasive infections
    - Less frequent
    - Higher mortality (35-80%)
    - Globally 1.5 million deaths per year
- ***Aspergillus* spp.**
  - Invasive aspergillosis (IA)
    - Mortality of up to 50% when treated; up to 99% when untreated
    - Affects approximately 300,000 patients per year
    - Early diagnosis can improve survival up to 50%

Source: Cornelia Lass-Flörl, Stephan Steixner, The changing epidemiology of fungal infections, Molecular Aspects of Medicine, Volume 94, 2023, 101215, ISSN 0098-2997, https://doi.org/10.1016/j.mam.2023.101215.



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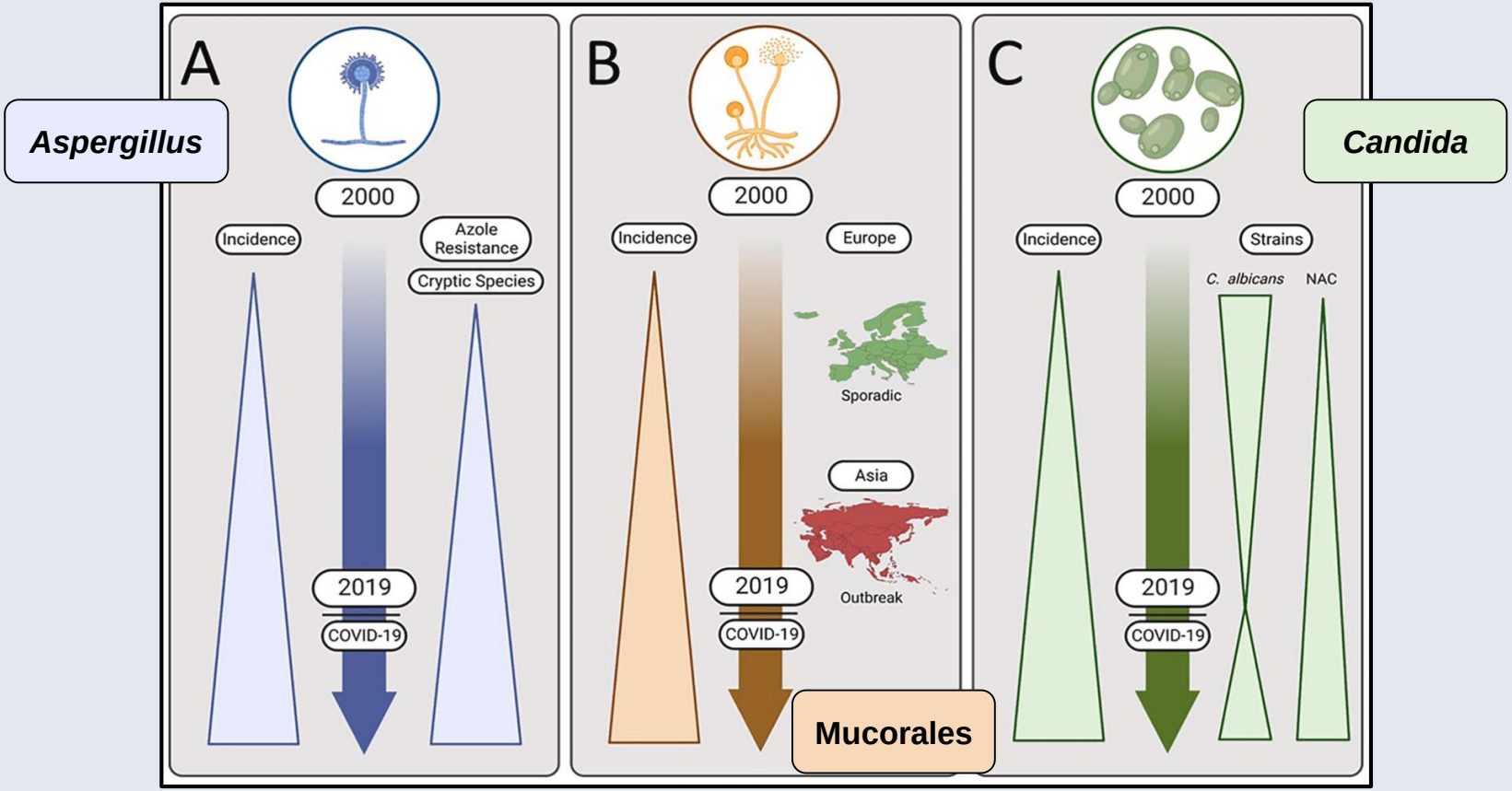


Source: Cornelia Lass-Flörl, Stephan Steixner, The changing epidemiology of fungal infections, Molecular Aspects of Medicine, Volume 94, 2023, 101215, ISSN 0098-2997, https://doi.org/10.1016/j.mam.2023.101215.

Epidemiology

Increased incidence of IFI over the last two decades

USA candidemia incidence

- 2000-2005: Increased from 3.65 to 5.56 per 100,000 people
- 2013-2017: 9 per 100,000 people

USA IA incidence

- 1992-1993: 1.24 per 100,000 people
- 2000-2013: Increased from 3.27 to 4.57 per 100,000 people

➔ Azole resistant infections

➔ Non-albicans *Candida* (NAC) infections

Source: Cornelia Lass-Flörl, Stephan Steixner, The changing epidemiology of fungal infections, Molecular Aspects of Medicine, Volume 94, 2023; Tsay S. et al. 363. National Burden of Candidemia, United States, 2017, Open Forum Infectious Diseases, Volume 5, Issue suppl_1, November 2018

Knowledge Check 1

Which of the following species of mold is considered to be a leading cause of fungal infections in the ICU?

A. *Aspergillus* spp.
B. *Candida* spp.
C. *Histoplasma* spp.
D. *Zygomycetes* spp.
E. *Blastomyces* spp.

Knowledge Check 1: Correct Response

Which of the following species of mold is considered to be a leading cause of fungal infections in the ICU?

A. ***Aspergillus* spp.**
B. *Candida* spp.
C. *Histoplasma* spp.
D. *Zygomycetes* spp.
E. *Blastomyces* spp.

Risk Factors

Severity of illness	
Prolonged ventilation / ICU stay	
APACHE II >20	Major surgery

Comorbidities	
Diabetes mellitus	Liver / Renal failure
Structural lung disease	

Infection Risk
Broad-spectrum antimicrobials
Central venous / Urinary catheter
Total parenteral nutrition
Hemodialysis

Immunosuppression	
Malignancy	Chemotherapy
Corticosteroids	Neutropenia
Graft-versus-host disease	AIDS
Solid organ transplant	Burns

Source: ACCP CCSAP 2016 Book 1. Accessed November 14, 2023. Available at https://www.accp.com/docs/bookstore/ccsap/c16b1_sample.pdf

Rapid Diagnostic Tests

- Antigen testing
- Serological testing
- Nucleic acid-based assays

β-D-glucan	*Candida* spp. and *Aspergillus* spp.
Mannan antigen/ Anti-mannan antibody	*Candida* spp. only
Galactomannan	*Aspergillus* spp. and some other molds
Nucleic-acid PCR	*Candida* spp. and *Aspergillus* spp.

Source: Hage, CA et al. Microbiological Laboratory Testing in the Diagnosis of Fungal Infections in Pulmonary and Critical Care Practice: An Official American Thoracic Society Clinical Practice Guideline. American Thoracic Society. Sept 01, 2019; Accessed December 13, 2023.

β-D-glucan (BDG)

Fungal cell wall constituent of *Candida spp*. and *Aspergillus spp*.

- Pan-fungal marker (except *Mucorales* spp., cryptococci)

Fungitell® assay (Cape Cod, MA, USA)

- Detects activation of the coagulation cascade by BDG
- General indicator of potential invasive fungal infection

One single positive test is only suggestive

- False positives
  - Albumin or immunoglobulin
  - Contaminated dressings or dialysis membranes
  - Gram-positive infections, gut inflammation, or certain antibiotics
- High true negative predictive value
  - Useful tool to prevent unnecessary use of antifungals

Source: Paramythiotou E et al. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014 Jan 17. Accessed November 15, 2023; Image obtained from Fungitell® Promo Video. AssociatesofCapeCod. 2021. Accessed December 20, 2023. Available at https://youtube.com.

Mannan antigen/Anti-mannan antibody

Polysaccharide component of the fungal cell wall

- Specific to *Candida* spp.

Latex agglutination test

Enzyme-linked immunosorbent assay (ELISA)

- Detects mannan antigen (Mn) and anti-mannan antibodies (Anti-Mn)
- Not FDA cleared for use in the United States
- More specific than BDG
- Not as sensitive
- Delayed detection in the course of disease

Source: Paramythiotou E et al. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014 Jan 17. Accessed November 15, 2023; Image obtained from Explainer: what is Candida auris and who is at risk? Accessed December 20, 2023. Available at: https://theconversation.com

Galactomannan (GM)

Fungal cell wall component of *Aspergillus* spp.

- *Aspergillus* spp. and some other molds

Galactomannan

- Released in body fluids during *Aspergillus* growth
- Detected in serum and bronchoalveolar lavage (BAL) fluid before clinical manifestation of IA
  - BAL testing may represent colonization over infection
- Serial measurements
- False positives
  - Concomitant use of beta-lactam antibiotics; antifungal therapy
  - Dietary source of galactomannan (cereal, pasta)
  - Plasma-Lyte (sodium gluconate)

Source: Paramythiotou E et al. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014 Jan 17. Accessed November 15, 2023; Image obtained from Mould Aspergillus Versicolor. 2018. Accessed December 20, 2023. Available at: https://fineartamerica.com/

Nucleic acid-based detection

Nucleic acid-based assays using polymerase chain reaction (PCR)

- *Candida* spp. and *Aspergillus* spp.

PCR

- PROS:
  - Comparable sensitivities in diagnosing candidemia
  - Comparable to GM testing for IA
  - Allow detection of very low copy number of target DNA
  - Not influenced by the addition of antifungal therapy
- CONS:
  - Difficulty determining colonisation versus infection
  - Using too early may decrease sensitivity
  - Infectious Diseases Society of America recommends cautious use

Source: Paramythiotou E et al. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014 Jan 17. Accessed November 15, 2023

Knowledge Check 2

True or false: Diabetes mellitus is considered to be a risk factor for invasive fungal infections in the ICU

Knowledge Check 2: Correct Response

True or false: Diabetes mellitus is considered to be a risk factor for invasive fungal infections in the ICU

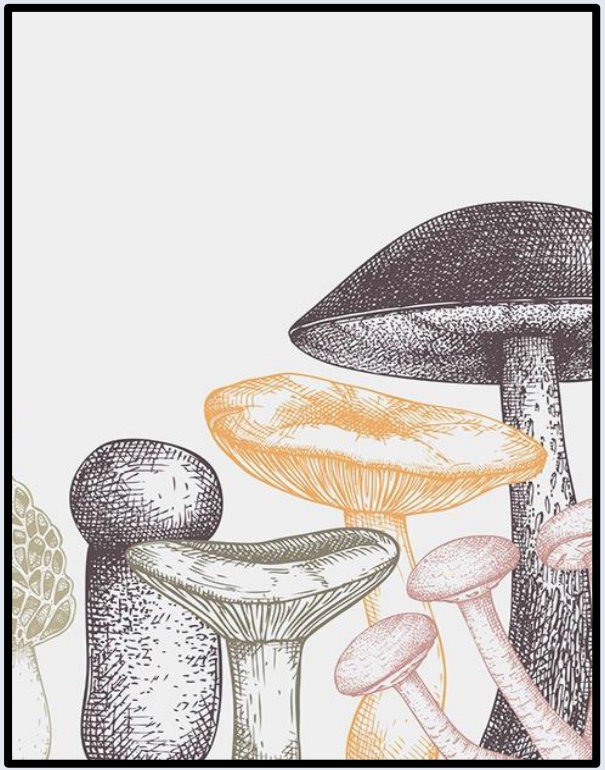
Treatment

Antifungal agents:

- Azole antifungals
- Echinocandins
- Amphotericin B
- Flucytosine

Treatment considerations:

- Local resistance patterns
- Patient risk factors
- Prior fluconazole use
- Site of infection
- Presence of haemodynamic instability



Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 Feb 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 Aug 2016

Treatment Guidelines

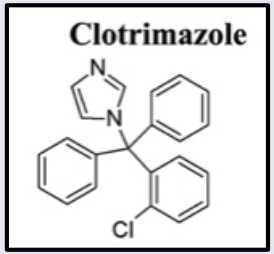
Infectious Diseases Society of America (IDSA)

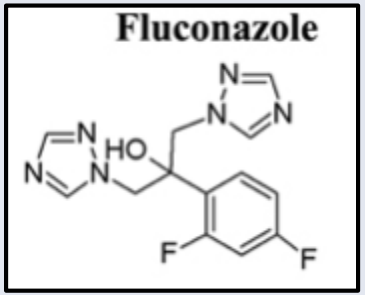
- **Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America**
  - Mucosal *Candida* infections – NOT considered to be invasive disease; however, they are included in these guidelines
  - Updated from the 2009 guidelines

- **Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America**
  - Updated from the 2008 guidelines

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 Feb 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 Aug 2016

Azole Antifungals





Imidazoles (2 nitrogen molecules)
- Clotrimazole, Miconazole, Ketoconazole

Triazoles (3 nitrogen molecules)
- Fluconazole, Itraconazole, Voriconazole, Posaconazole, Isavuconazole

Mechanism of action: Decrease ergosterol synthesis and membrane formation

Spectrum: Azole class: most *Candida* species
Fluconazole: limited yeast and endemic fungi activity
Itraconazole: broad spectrum covering endemic fungi, *Aspergillus* spp., some molds
Voriconazole: enhanced activity against Aspergillus

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Azole Antifungals

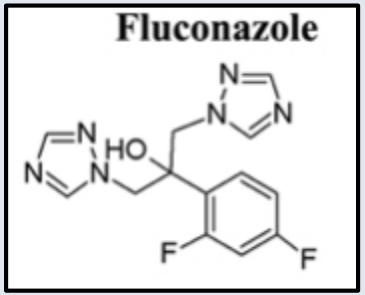
Class adverse effects:
- Hepatic toxicity
- QT prolongation
- Dermatologic reactions
- Nausea, vomiting

Drug interactions: immunosuppressants, anticoagulants, antiepileptic medications
- Cytochrome P450 interactions (CYP3A4, 2C19, 2C9 inhibition)

Treatment considerations:
- Less nephrotoxicity than other agents

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Azole Antifungals



Fluconazole

Dosing weight: actual body weight

Dose adjustments:
- CrCl ≤ 50 mL/minute: reduce dose by 50%

Monitoring:
- Hepatic function (AST, ALT, alkaline phosphatase) periodically during therapy
- Renal function tests, potassium

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Azole Antifungals

Itraconazole

Black Box Warning: itraconazole can cause or exacerbate congestive heart failure

Dose adjustments: No adjustments necessary

Additional adverse effects: hypokalemia/pseudoaldosteronism, peripheral neuropathy

Monitoring:
- Hepatic function (AST, ALT, alkaline phosphatase) in patients with preexisting hepatic dysfunction
- Renal function tests, potassium
- Signs/symptoms of heart failure or neuropathy
- For invasive aspergillosis (IA): serum trough concentrations
    - Obtain a trough after steady state (4-7 days)
    - Goal range: >0.5 to 1 mcg/mL
    - Toxicity range: >3 mcg/mL

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Azole Antifungals

Voriconazole

Dosing weight: actual body weight; adjusted body weight if BMI ≥30 kg/m^2

Dose adjustments: No adjustments necessary

Additional adverse effects: neurotoxicity, renal toxicity, photosensitivity

Monitoring:
- Hepatic function at initiation, weekly during the first month, and then monthly
- Renal function, baseline and periodically during therapy
- Serum electrolytes prior to initiation (Ca, Mg, K)
- Visual function
- For invasive aspergillosis (IA): serum trough concentrations
    - Obtain a trough after steady state (4-7 days)
    - Goal range: >1 to 1.5 mcg/mL
    - Toxicity range: >5 mcg/mL

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Azole Antifungals

Posaconazole

Dose adjustments: No adjustments necessary

Monitoring:

- Hepatic function (AST/ALT, alkaline phosphatase, bilirubin); prior to initiation and during therapy
- Renal function
- Serum electrolytes (Ca, Mg, K); prior to initiation and during therapy
- Serum concentration
    - Obtain a trough after steady state (>5 to 7 days)
    - Goal range: >1 to 1.5 mg/L
    - Toxicity range: >3 to 3.75 mg/L

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Azole Antifungals

Isavuconazole

Dose adjustments: No adjustments necessary

Monitoring:
- Hepatic function (AST/ALT, alkaline phosphatase, bilirubin); prior to initiation and during therapy
- Infusion-related reactions (hypotension, dyspnea, chills, paresthesias)

Source: Images obtained from Frontiers in Cellular and Infection Microbiology 2015. Accessed December 17, 2023. Available at https://www.frontiersin.org/articles/10.3389/fcimb.2015.00057/full; Uptodate. Pharmacology of azoles. Uptodate.com. Accessed December 17, 2023

Echinocandins

Caspofungin, Micafungin, Anidulafungin

Mechanism of action: Inhibit synthesis of 1,3-beta D glucan; weaken fungal cell wall

Spectrum: Most *Candida* spp; *Aspergillus* spp in combination

Class adverse effects: Hepatotoxicity, histamine-mediated symptoms (rash, pruritus, flush)

Drug interactions:

Caspofungin: cyclosporine, tacrolimus, rifampin, phenytoin, carbamazepine
Micafungin: cyclosporine, sirolimus, nifedipine

Source: Uptodate. Pharmacology of echinocandins and other glucan synthesis inhibitors. Uptodate.com. Accessed December 17, 2023

Echinocandins

Caspofungin

Dose adjustments:

- Child-Pugh class B: 70 mg on day 1 (where recommended), followed by a reduced daily dose of 35 mg

Monitoring:

- Hepatic function (AST, ALT, alkaline phosphatase) periodically during therapy
- Signs or symptoms of anaphylaxis
- Skin rash or histamine-related reactions

Source: Uptodate. Pharmacology of echinocandins and other glucan synthesis inhibitors. Uptodate.com. Accessed December 17, 2023

Echinocandins

Micafungin

Dose adjustments: No adjustments necessary

Monitoring:

- Hepatic function (AST, ALT, alkaline phosphatase) periodically during therapy
- Renal function
- Infusion-related reactions (rash, pruritus, facial swelling, and vasodilation)

Source: Uptodate. Pharmacology of echinocandins and other glucan synthesis inhibitors. Uptodate.com. Accessed December 17, 2023

Echinocandins

Anidulafungin

Dose adjustments: No adjustments necessary

Monitoring:

- Hepatic function (AST, ALT, alkaline phosphatase) periodically during therapy
- Infusion-related reactions (rash, pruritus, facial swelling, and vasodilation)

Source: Uptodate. Pharmacology of echinocandins and other glucan synthesis inhibitors. Uptodate.com. Accessed December 17, 2023

Polyene Antifungals

Conventional (deoxycholate)

Lipid complex (ABLC, Abelcet®)

Liposomal (AmBisome®)

Amphotericin B

Mechanism of action: Binds to ergosterol and alters cell membrane permeability

Spectrum: Broad spectrum of activity (yeasts, molds, dimorphic fungi)

Class adverse effects: Hepatotoxicity, nephrotoxicity, phlebitis, bone marrow suppression, electrolyte abnormalities

Drug interactions: Hypotensive agents, nephrotoxic agents

Source: Uptodate. Pharmacology of amphotericin B. Uptodate.com. Accessed December 17, 2023

Polyene Antifungals

Conventional (deoxycholate)

Black Box Warning: Dose should not exceed 1.5 mg/kg

Dosing weight: Actual body weight; adjusted body weight if BMI $\geq$30 kg/m^2

Dose adjustments: No adjustments necessary

- If nephrotoxicity occurs, interrupt therapy for 24-48 hours, then resume at one-half the usual daily dose

Monitoring:

- Renal function (BUN, SCr) every other day when therapy is increased, then weekly
- Serum electrolytes, hepatic function, temperature, intake/output

Source: Uptodate. Pharmacology of amphotericin B. Uptodate.com. Accessed December 17, 2023

Polyene Antifungals

Lipid complex (ABLC, Abelcet®)

Dosing weight: Actual body weight

Dose adjustments: No adjustments necessary

Monitoring:

- Renal function (BUN, SCr) every other day when therapy is increased, then weekly
- Serum electrolytes, hepatic function, temperature, intake/output

Source: Uptodate. Pharmacology of amphotericin B. Uptodate.com. Accessed December 17, 2023

Polyene Antifungals

Liposomal (AmBisome®)

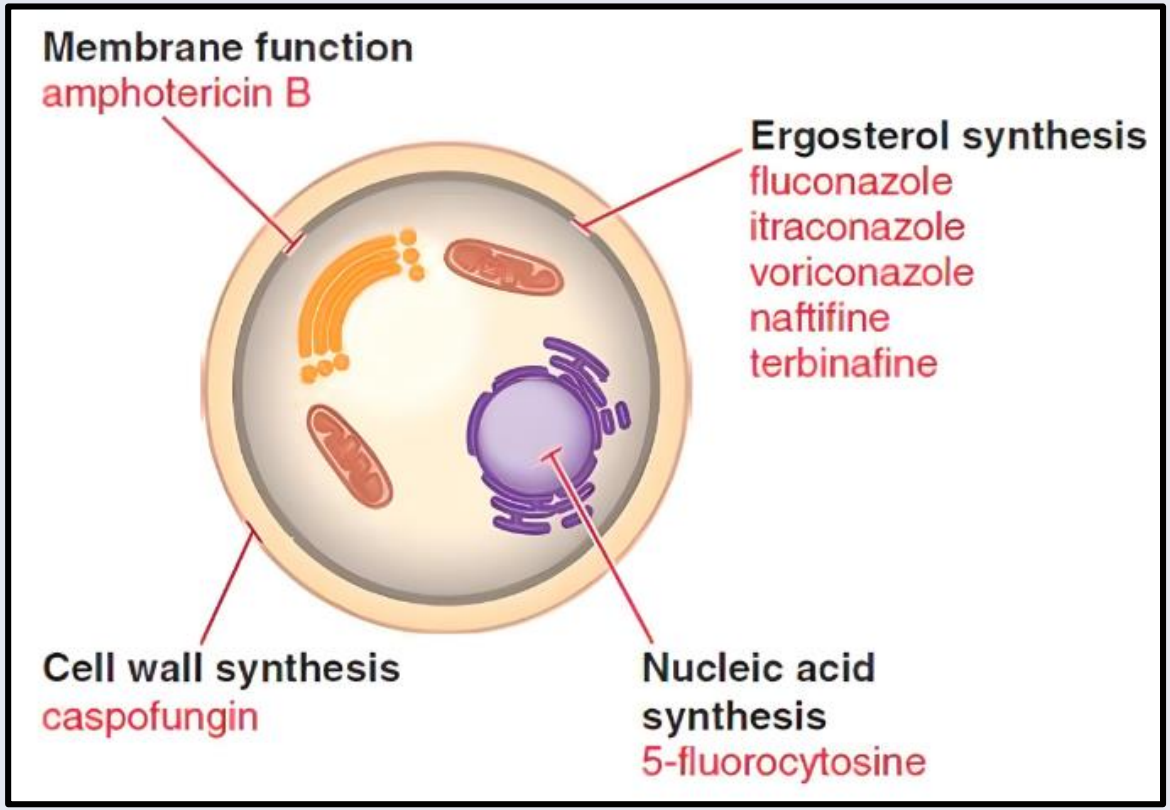
Dosing weight: Actual body weight
Maximum daily dose: 600 mg

Dose adjustments: No adjustments necessary

Monitoring:

- Renal function (BUN, SCr) every other day when therapy is increased, then weekly
- Serum electrolytes, hepatic function, temperature, intake/output

Source: Uptodate. Pharmacology of amphotericin B. Uptodate.com. Accessed December 17, 2023



Source: Image obtained from BasicmedicalKey. Accessed on December 17, 2023. Available at: https://basicmedicalkey.com/antifungal-agents-4/

Knowledge Check 3

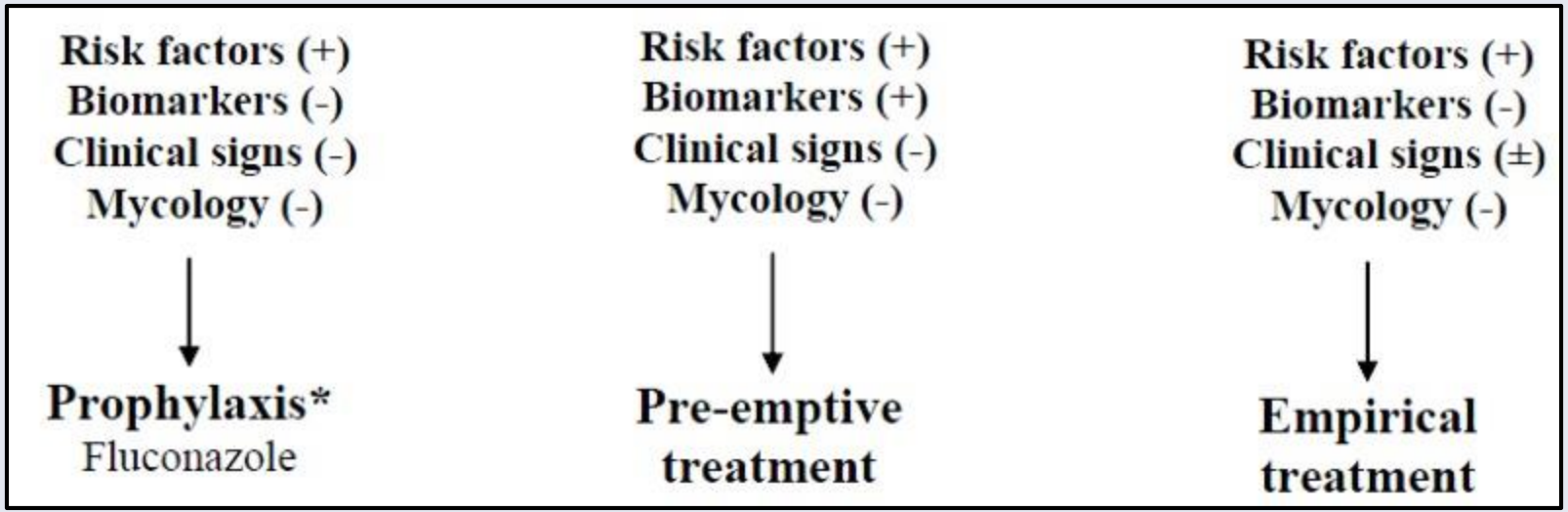
Which type of treatment is given to a patient with clinical signs of infection (e.g. persistent fever not responding to antimicrobials) and several risk factors for candidemia without proof of invasive candidiasis?

A. Prophylactic treatment
B. Pre-emptive treatment
C. Empiric treatment
D. Definitive treatment

Knowledge Check 3: Correct Response

Which type of treatment is given to a patient with clinical signs of infection (e.g. persistent fever not responding to antimicrobials) and several risk factors for candidemia without proof of invasive candidiasis?

A. Prophylactic treatment
B. Pre-emptive treatment
C. Empiric treatment
D. Definitive treatment



Source: Image obtained from: Paramythiotou E et al. Invasive fungal infections in the ICU: how to approach, how to treat. Molecules. 2014 Jan 17. Accessed November 15, 2023

Prophylactic Treatment

Administration of antifungal agents to high-risk patients **without** signs/symptoms of infection.

IDSA Recommendations:

Candidiasis

- Hospitals with a reported high incidence of invasive candidiasis

Aspergillosis

- High-risk patients during prolonged neutropenia
- Previous history of invasive aspergillosis (IA) infection

Considerations:

- Potential to increase drug-resistance

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Prophylactic Treatment

IDSA Recommendations:

Candidiasis

- Fluconazole
- Echinocandin

Aspergillosis

- Posaconazole
- Voriconazole
- And/or micafungin

Considerations:

- Toxic levels with concurrent triazole coadministration with certain chemotherapies

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Prophylactic Treatment

Typical regimens:

Azoles

- Fluconazole: 800 mg (or 12 mg/kg) loading dose, then 400 mg (or 6 mg/kg) daily
- Posaconazole: 300 mg twice daily for 2 doses, then 300 mg once daily
- Voriconazole: 4 mg/kg twice daily

Echinocandins

- Caspofungin: 70 mg loading dose, then 50 mg daily
- Anidulafungin: 200 mg loading dose, then 100 mg daily
- Micafungin: 100 mg daily

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Pre-emptive Treatment

Utilization of **diagnostic markers** to screen high-risk patients before or just as symptoms begin to develop.

IDSA Recommendations:

- Fluconazole
- Echinocandin

Considerations:

- Helpful to limit the number of patient exposed to drug therapy
- Potential to catch patients earlier in the course of disease

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Pre-emptive Treatment

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Azoles

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Empiric Treatment

Antifungal treatment is given to a patient with **clinical signs of infection** and **several risk factors** for fungal infection without definitive proof of invasive organism.

IDSA Recommendations:

Candidiasis

- High-risk patients with risk factors and no other known cause of fever
- Clinical signs of septic shock

Aspergillosis

- High-risk patients during prolonged neutropenia who remain febrile despite broad-spectrum antibiotics

Considerations:

- Utilize risk factors, surrogate markers, and/or culture data from nonsterile sites

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Clinical Signs and Symptoms of IFI	
Infection that is not responding to usual antibiotics	
Systemic symptoms:	**Site-specific symptoms:**
Belly pain	**CNS**: Confusion Headaches Memory loss
Chills	
Fever	
Muscle aches	**Eyes**: Blurriness Vision changes Sensitivity to light
Skin rash	
Weakness or fatigue	

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Empiric Treatment

IDSA Recommendations:

★ Duration: 2 weeks

Candidiasis

- Echinocandin (preferred)
- Fluconazole
- Lipid formulation of AmB

Aspergillosis

- Lipid formulation of AmB
- Echinocandin
- Voriconazole

Considerations:

- For patients who have no clinical response at 4-5 days and do not have evidence of an invasive infection, consideration should be given to stopping antifungal therapy

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Empiric Treatment

Typical regimens:

Amphotericin B

- Lipid formulation AmB: 3-5 mg/kg daily (actual body weight)

Azoles

- Fluconazole: 12 mg/kg loading dose, then 6 mg/kg daily
- Voriconazole: 4 mg/kg twice daily

Echinocandins

- Caspofungin: 70 mg loading dose, then 50 mg daily
- Anidulafungin: 200 mg loading dose, then 100 mg daily
- Micafungin: 100 mg daily

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Definitive Treatment

Definitive diagnosis is established when either *Candida* spp. or *Aspergillus* spp. are identified in tissue specimens from normally sterile body sites or if culture of a normally sterile fluid yields the organism.

Considerations:

- Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant *Candida* isolates
- Echinocandin susceptibility should be considered if:
  - Prior echinocandin treatment
  - Previous infection with *C. glabrata* or *C. parapsilosis*

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Definitive Treatment

Candidemia

(Nonneutropenic)

Primary treatment:

- Echinocandin
  - Caspofungin: loading dose 70 mg, then 50 mg daily
  - Micafungin: 100 mg daily
  - Anidulafungin: loading dose 200 mg, then 100 mg daily

Alternative therapies:

- Fluconazole: IV or PO; 800 mg (12 mg/kg) loading dose, then 400 (6 mg/kg) daily

Duration of therapy: 2 weeks after documented negative blood cultures

Clinical pearl:

- Azole susceptibility testing is recommended for all bloodstream infections
- Recommended step down therapy to fluconazole within 5-7 days in patients who are stable, fluconazole-susceptible isolates, and negative repeat blood cultures
- Infection with *C. glabrata*: recommended higher-dose fluconazole daily or voriconazole 3 to 4 mg/kg twice daily

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016

Definitive Treatment

Candidemia

(Neutropenic)

Primary treatment:

- Echinocandin
  - Caspofungin: loading dose 70 mg, then 50 mg daily
  - Micafungin: 100 mg daily
  - Anidulafungin: loading dose 200 mg, then 100 mg daily

Alternative therapies:

- Lipid formulation AmB: 3 to 5 mg/kg daily
- Fluconazole: IV or PO; 800 mg (12 mg/kg) loading dose, then 400 (6 mg/kg) daily
- Voriconazole: 400 mg (6 mg/kg) twice daily x2 doses, then 200-300 (3 to 4 mg/kg) twice daily; additional mold coverage

Duration of therapy: 2 weeks after documented negative blood cultures

Clinical pearl:

- Recommended step down therapy to fluconazole or voriconazole
- Infection with *C. krusei*: recommended echinocandin, lipid formulation AmB, or voriconazole

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016

Definitive Treatment

Chronic Disseminated (Hepatosplenic) Candidiasis

Primary treatment:

- Lipid formulation AmB: 3 to 5 mg/kg daily
- Echinocandin
  - Caspofungin: loading dose 70 mg, then 50 mg daily
  - Micafungin: 100 mg daily
  - Anidulafungin: loading dose 200 mg, then 100 mg daily

Followed by: PO fluconazole; 400 mg (6 mg/kg) daily

Duration of therapy: Several months; continued until lesions resolve on repeat imaging

Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016

Definitive Treatment

Invasive Pulmonary Aspergillosis (IPA)

Primary treatment: Voriconazole

Alternative therapies:

- Liposomal AmB
- Isavuconazole

Duration of therapy: minimum of 6-12 weeks

Clinical pearl:

- Secondary prophylaxis is recommended in patients with successfully treated IPA who require subsequent immunosuppression
- Reducing doses of immunosuppressive agents is advised when feasible

Source: Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Definitive Treatment

Invasive Aspergillosis (IA)

- **Primary therapy**: Voriconazole IV 6 mg/kg twice daily x2 doses, then 4 mg/kg twice daily
  PO 200 mg twice daily; may increase to 300 mg twice daily
- **Refractory**: Lipid formulations of AmB; minimum of 6-12 weeks
  - Abelcet IV 5 mg/kg once daily
  - AmBisome IV 3 to 5 mg/kg once daily; up to 7.5 mg/kg

Aspergillus Endocarditis, Pericarditis, and Myocarditis

- Surgical intervention + antifungal therapy (voriconazole, lipid formulations of AmB)
- Lifelong antifungal therapy

Aspergillus Osteomyelitis and Septic Arthritis

- Surgical intervention where feasible + voriconazole

Source: Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

Which Situations May Not Constitute Treatment?

- Isolation of *Candida spp*. from the respiratory tract/respiratory secretions
  - Usually indicates colonization

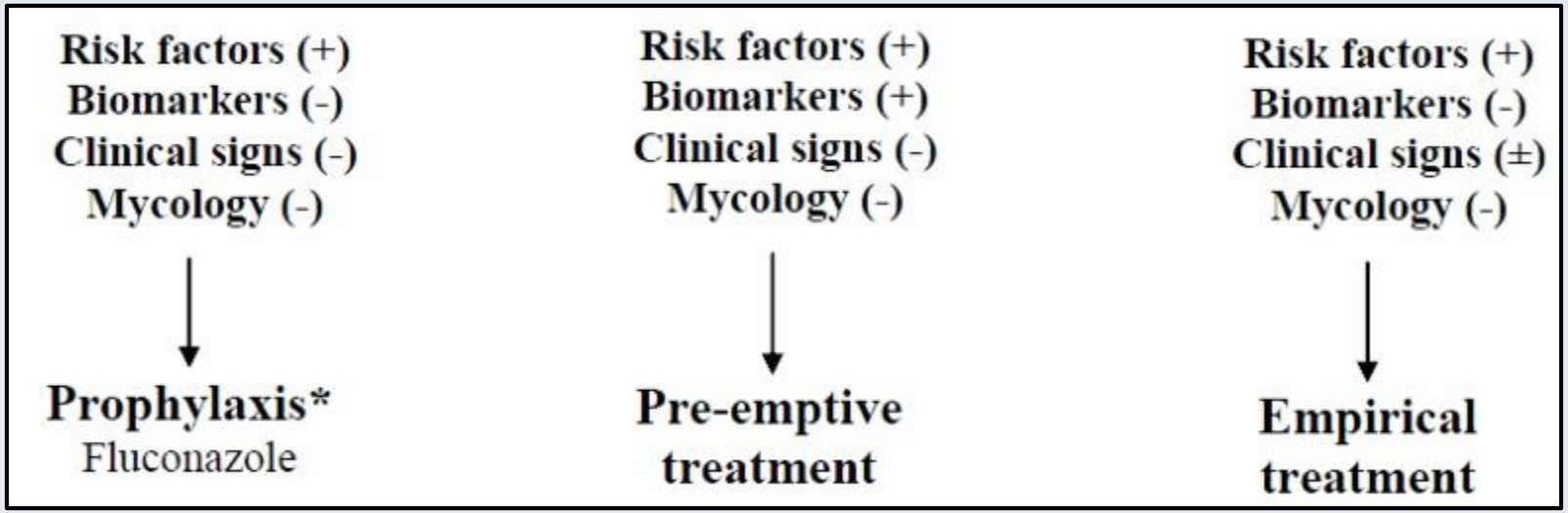
- Asymptomatic Candiduria
  - Treatment NOT recommended unless at high risk for dissemination
    - Neutropenic patients
    - Patients who will undergo urologic manipulation

- Airway aspergillosis (TBA)
  - Saprophytic forms of TBA do not require antifungal treatment except for:
    - Symptomatic patients
    - Immunosuppressed patients

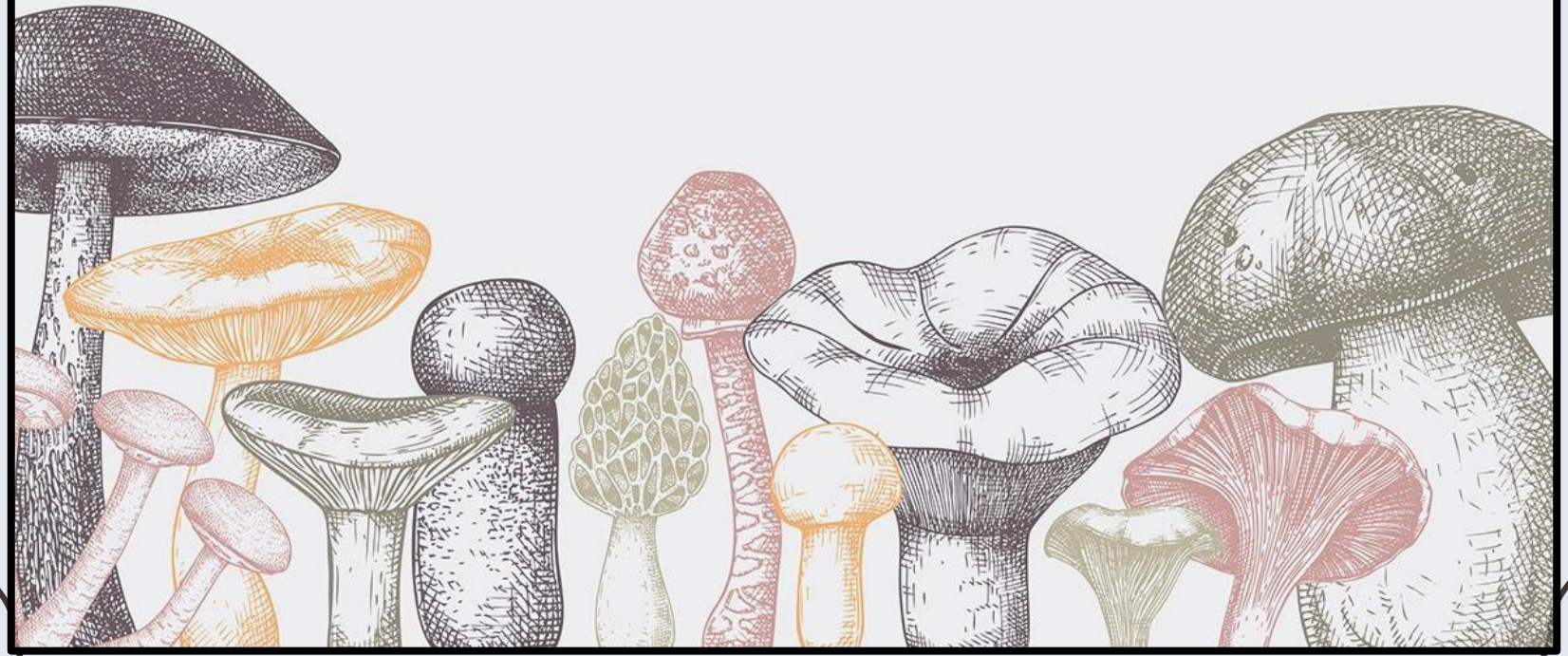
Source: Pappas, PG et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the IDSA. Clinical Infectious Diseases.5 February 2016,; Patterson TF. et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the IDSA, Clinical Infectious Diseases, 15 August 2016

How can I incorporate this into practice?

- Be aware of patient risk factors, diagnostic markers, clinical signs of infection
- Be aware of institutional biomarker testing availability



Let’s Review



Source: Image obtained from Shelton J. The Future is Fungal. The Imperial Medicine Blog. April 2021. Accessed December 17, 2023. Available at: https://blogs.imperial.ac.uk/imperial-medicine/2021/04/28/the-future-is-fungal/

Key Take Home Points

- Invasive infections caused by *Candida* and *Aspergillus* species are the most prevalent invasive fungal infections in the ICU
- Risk factors for IFIs include immunosuppression, severe illness, increased risk for infection, and comorbidities
- Utilizing diagnostic markers and clinical signs of infection can help to determine if antifungal treatment is necessary

Source: Image obtained from Martonicz TW. Candida auris Rapidly Recontaminates Surfaces Around Patients' Beds Despite Cleaning and Disinfection. Infection Control Today. 2022. Accessed December 17, 2023.

Resources

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Thank you!

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