Antifungal Management: Individualizing Therapy for Susceptible Patient Groups

Learning Objectives
1. Describe the epidemiology, risk factors, and morbidity and mortality associated with infections caused by Aspergillus and Candida species;
2. Describe methods utilized to identify invasive fungal pathogens;
3. Compare and contrast the mechanism of action, adverse effects, and drug interactions of currently available antifungal agents; and
4. Describe guideline recommendations and best practices for the treatment and management of patients with invasive fungal infections.

Post-test/Rationale
1. According the most recent (2009) Infectious Diseases Society of America (IDSA) guidelines for the treatment of candidemia, which of the following statements regarding EMPIRIC THERAPY for patients with candidemia and the use of azoles and echinocandins is MOST correct:

   A. Amphotericin B is preferred for patients with mild illness but recent echinocandin exposure
   B. Amphotericin B is preferred for patients with no azole exposure
   C. Patients who are clinically unstable can be transitioned to fluconazole after 24 hours of therapy
   D. Echinocandins are preferred as initial therapy for patients with previous azole exposure or who are severely ill

   Correct Answer: D

   For empiric therapy in adults without neutropenia, current IDSA guidelines recommend use of an echinocandin or fluconazole as initial therapy. Echinocandins are recommended for patients with moderately severe to severe illness and patients with recent azole exposure.

2. Which one of the following statements regarding the treatment of candidemia is INCORRECT:

   A. Patients should receive intravenous (IV) therapy for the entire duration of antifungal therapy
   B. IV catheters should be removed whenever possible
   C. The duration of therapy for candidemia in patients whose symptoms have resolved and who have no metastatic complications is 2 weeks after documented Candida clearance from the blood
   D. All patients with Candida should have an ophthalmological exam

   Correct Answer: D
Correct Answer: A
IDSA guidelines state that therapy should be continued for 2 weeks after documented clearance of blood cultures, with resolution of all signs and symptoms of infection. All patients should have a dilated funduscopic exam within the first week of therapy. Most consensus recommendations urge that, if feasible, initial nonmedical management should include removal of all existing tunneled central venous catheters (CVCs) and implantable devices. Patients may be transitioned to oral fluconazole if their Candida isolates are known/likely to be susceptible to fluconazole.

3. Which one of the following statements regarding RESISTANCE to antifungals is INCORRECT:

A. Of commonly isolated Candida species, resistance to fluconazole is most common for Candida glabrata
B. Of commonly isolated Candida species, resistance to fluconazole is most common for Candida albicans***
C. Resistance to echinocandins, while less common than for azoles, is increasing
D. Risk factors for echinocandin resistance include prior echinocandin therapy

Correct Answer: B
Fluconazole resistance is observed most frequently in the treatment of Candida glabrata. With the increase in echinocandin use, there has been an increase in the number of reports of echinocandin-resistant isolates from patients failing therapy. Echinocandin exposure and previous episode of C glabrata are predictors of FKS mutations.

4. Candida blood cultures when tested by traditional methodology (i.e., without the use of rapid diagnostic tests)

A. Are usually reported as positive within 2 hours after obtaining a blood culture so empiric therapy can be initiated on the same day
B. Are not usually reported as positive until 7 to 10 days after obtaining a blood culture, making the selection of empiric therapy difficult
C. Are usually reported as positive within about 2.5 days after obtaining a blood culture; however, speciation and antifungal susceptibility testing generally require an additional 2 to 3 days***
D. Are not usually reported as positive

Correct Answer: C
Isolation of yeast from blood cultures generally requires approximately 2.5 days after obtaining a blood culture. An additional 2.5 days is needed for speciation of the yeast and there is another 0.5 to 1 day before results of antifungal susceptibility testing is available.
5. **Plasma level monitoring of antifungals**

A. Is rarely necessary unless toxicity is observed
B. May be necessary for patients receiving voriconazole therapy because of its *variable* metabolism***
C. Is required for patients undergoing treatment with fluconazole, voriconazole, and caspofungin because the efficacy of these agents correlates with peak levels
D. Is only necessary for patients receiving fluconazole therapy for central nervous system infections

**Correct Answer: B**

For patients being treated with voriconazole, therapeutic drug monitoring is recommended because of its variable metabolism, which is the result of nonlinear pharmacokinetic and genetic variability in CYP2C19 and unpredictable dose-exposure relationship—low concentrations are associated with poor outcome; high concentrations are associated with adverse effects.

6. **Which one of the following statements about Candida bloodstream infections (BSIs) is MOST correct:** *Candida* BSIs

A. Should always be treated with fluconazole because it is cheap (generic) and has a good safety profile
B. Are associated with a low mortality rate, unless the patient is immunocompromised; thus, antifungal therapy is generally not necessary
C. Are most often caused by *Candida krusei*
D. Are associated with poor outcomes when initiation of antifungal therapy is delayed***

**Correct Answer: D**

Delays in the initiation of antifungal therapy significantly increase mortality.

7. **As compared with the oral suspension formulation, the delayed-release tablet formulation of posaconazole**

A. Must be administered with a high-fat meal or a nutritional supplement
B. Requires less frequent dosing***
C. Has lower bioavailability when coadministered with medications that raise the gastric pH, such as antacids
D. At recommended dosages, has a lower bioavailability than the suspension formulation

**Correct Answer: B**

The development of intravenous and delayed-release tablet formulations of posaconazole have circumvented these absorption issues. The tablet formulation allows once daily oral administration of posaconazole.
8. Rapid diagnostic testing methods for *Candida* or *Aspergillus* can be performed in most hospitals, using

A. Polymerase chain reaction (PCR)-based testing of urine for *Candida*
B. Detection of galactomannan, an antigen released from *Candida* spores
C. A test for 1,3-β,D-glucan that can be detected in blood and bronchoalveolar lavage specimens
D. Matrix-assisted laser desorption ionization mass spectrometry–time-of-flight (MALDI-TOF), Peptide Nucleic Acid in Situ Hybridization (PNA-FISH), PCR, galactomannan, and T2 Magnetic Resonance Assays***

Correct Answer: D
PCR-based testing of Aspergillus is being performed in some centers and appears promising; however, no U.S. Food and Drug Administration (FDA)-approved method is commercially available. Several rapid, accurate diagnostic laboratory tests, including matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), Peptide Nucleic Acid in Situ Hybridization (PNA-FISH), PCR, galactomannan, and T2 Magnetic Resonance Assays, have been developed which have the potential to enhance sensitivity and speed of diagnosis of invasive fungal infections.

9. In which of the following patients would it be most appropriate to use an echinocandin to manage/prevent invasive candidiasis:

A. A patient with invasive candidiasis and endophthalmitis
B. A patient who previously received fluconazole who is hemodynamically unstable***
C. A patient with invasive candidiasis and candiduria
D. A patient with meningeal candidiasis

Correct Answer: B
For empiric therapy in adults without neutropenia, current IDSA guidelines recommend use of an echinocandin or fluconazole as initial therapy. Echinocandins are recommended for the treatment of patients with moderately severe to severe illness and patients with recent azole exposure.

10. Which of the following is correct regarding treatment of Aspergillosis:
A. Voriconazole is currently the agent of choice for the primary treatment of *Aspergillus***
B. Should always be treated with a combination of antifungal agents
C. Is generally treated with fluconazole
D. Has low mortality, therefore, is usually not treated except in severely ill patients

Correct Answer: A
Voriconazole is currently the agent of choice for the primary treatment of *Aspergillus*. There are as yet no firm recommendations regarding the use of such combinations in humans.