“Challenging Cases in the Diagnosis and Management of Invasive Fungal Infections”

Posttest Rationale

1. Which one of the following statements regarding the use of voriconazole is INCORRECT?

A. Adverse reactions associated with voriconazole include transient visual disturbances.
B. The recommended loading dose is 4 milligrams per kilogram intravenously every 12 hours on day 1.***
C. Toxicities have been observed with trough levels >5.5 mcg/mL.
D. Voriconazole dose adjustment is recommended in patients with mild-to-moderate hepatic impairment (Child Pugh A/B).

The correct answer is: B. The recommended dosing regimen for voriconazole is 6 milligrams per kilogram intravenously every 12 hours as a loading dose on day 1 followed by 4 milligrams per kilogram IV every 12 hours thereafter.

Adverse reactions associated with voriconazole include visual disturbances (including flashes of white vision).

Trough levels above 5.5 micrograms per milliliter has been associated with increased toxicities.

Voriconazole has not been studied in Child Pugh A/B.

2. Which one of the following statements regarding the use of diagnostics for invasive aspergillosis (IA) is CORRECT?

A. The beta-D-glucan assay is not specific for *Aspergillus* species and can be positive in patients with a variety of invasive fungal infections.***
B. Beta-D-glucan can interfere with galactomannan assessment.
C. Any *Aspergillus* infection in the body will produce a positive galactomannan serum assay.
D. GMA assay values can be falsely elevated in patients on concurrent aminoglycoside therapy.

The correct answer is: A. The beta-D-glucan assay is not specific for *Aspergillus* species and can be positive in patients with a variety of invasive fungal infections, including candidiasis and *Pneumocystis jirovecii*.

3. Which one of the following statements regarding antifungal therapy for invasive aspergillosis is CORRECT?

A. Non-inferiority trials demonstrated that isavuconazole is superior to voriconazole in patients with proven or probable IA.
B. Posaconazole is FDA-approved for primary treatment of invasive aspergillosis.
C. Combination therapy with voriconazole and an echinocandin is an emerging trend in the treatment of invasive aspergillosis.***

The correct answer is: C. Since 2008, voriconazole has been recommended as the drug of choice for invasive aspergillosis and has been endorsed by the IDSA guidelines. However, recent publications and current expert opinion do favor combination therapy with voriconazole plus an echinocandin. Combination therapy with voriconazole and an echinocandin is an emerging trend in the treatment of invasive aspergillosis.

Isavuconazole was compared to voriconazole in a non-inferiority trial design. In the group of patients with proven or probable invasive aspergillosis, the overall success rate at the end of treatment was seen as 35 percent in those who received isavuconazole compared to 38.9 percent in voriconazole-treated patients.

The FDA has only approved posaconazole for prevention and prophylaxis of invasive aspergillosis.
4. Which one of the following factors is NOT typically a major consideration when choosing empiric antifungal therapy?

A. A history of prolonged exposure to antifungal agents.
B. Typical antifungal susceptibility patterns at the medical center or community.
C. A history and assessment of degree of immunosuppression.
D. A history of chronic kidney disease.
E. A history of cardiovascular disease.

The correct answer is: E. A history of cardiovascular disease is not mentioned in the literature as a major consideration when choosing empiric antifungal therapy. Throughout the literature, answers A, B, C, D are mentioned and should be taken into consideration when choosing empiric antifungal therapy. Supporting literature excerpts are below:

When choosing an antifungal agent in patients with known or suspected candidemia, please consider the following factors: prior history of azole exposure, prevalence of different Candida species and current antifungal susceptibility data in your clinical unit medical center, the severity of illness, comorbidities, such as neutropenia. Also, consider evidence of involvement of the central nervous system, cardiac valves, eyes, or visceral organs, intolerance to an antifungal agent in the past.

Surgical units, especially those caring for trauma and burn patients, along with neonatal units, have the highest rates in the hospital for Candida infections.

Due to the rising prevalence of azole-resistant Candida, empiric treatment with an echinocandin is often recommended. The duration of therapy and the most appropriate antifungal therapy must be tailored once factors, including the patient’s degree of immune suppression, history of azole exposure, local resistance patterns, and severity of infection are considered.

Invasive aspergillosis: This infection remains a serious cause of morbidity and mortality in the immunocompromised patient populations. Luckily, new diagnostics and additional antifungal therapies have significantly added to our toolbox. Such patients remain at high risk and some should get antifungal prophylaxis, as well as clinicians being able to properly suspect patients who may have such infections such that rapid implementation of empiric treatment is instituted, and remains critical to improving patient outcomes.

Invasive Candidiasis: Immunocompromised patients who are at special risk include those with hematologic malignancies, solid organ transplants, or hematopoietic stem cell transplant agents and those receiving chemotherapy agents, especially ones that cause mucositis.

Flucytosine at an oral dose of 100 mg/kg divided in four doses can be added for synergistic activity, but caution must be used to avoid dose-related marrow toxicity or kidney injury. Serum flucytosine levels should be routinely monitored, especially in the setting of renal insufficiency, to keep serum peak concentrations less than 75 mcg per mL.

5. Which one of the following factors is NOT a common risk factor associated with invasive Candida infections?

A. Total parenteral nutrition.
B. Broad spectrum antibiotic therapy.
C. Disruption of the GI mucosa.
D. Anemia with hemoglobin <8 g/dL. ***
E. Prolonged neutropenia.

The correct answer is: D. Slide 3 on Page 12 provides a complete listing of risk factors associated with invasive Candida infections that includes total parenteral nutrition, broad spectrum antibiotic use, GI tract perforation and neutropenia. In addition, immunocompromised patients who are at special risk include those with hematologic malignancies, solid organ transplants, or hematopoietic stem cell transplant agents and those receiving chemotherapy agents, especially ones that cause mucositis. Anemia is not mentioned as a risk factor.
6. Which one of the following statements regarding the use of echinocandins for the treatment of candidemia is INCORRECT?

A. Echinocandins are appropriate for empiric therapy in neutropenic hosts.
B. A lower than customary daily dose of caspofungin (35 mg daily) should be used in patients with Child-Pugh score 7-9.
C. Echinocandins are a recommended choice for empiric antifungal therapy in non-neutropenic hosts with severe illness or recent azole exposure.
D. *Candida krusei* is intrinsically resistant to echinocandins.***

The correct answer is: D. In general, all isolates of *Candida krusei* are intrinsically resistant to fluconazole. Slide 17 indicates that *Candida krusei* is susceptible to echinocandins.

7. Which one of the following epidemiologic and historic factors is not a major consideration when selecting antifungal therapy for candidemia?

A. History of recent azole exposure.
B. Prevalence of different *Candida* species and current antifungal susceptibility data in the clinical unit and medical center.
C. Severity of illness.
D. Evidence of involvement of the central nervous system, cardiac valves, eyes, and/or visceral organs.
E. Use of a proton pump inhibitor.***

The correct answer is: E. Use of a proton pump inhibitor was not mentioned in the literature. When choosing an antifungal agent in patients with known or suspected candidemia, please consider the following factors: prior history of azole exposure, prevalence of different *Candida* species and current antifungal susceptibility data in your clinical unit medical center, the severity of illness, comorbidities, such as neutropenia. Also, consider evidence of involvement of the central nervous system, cardiac valves, eyes, or visceral organs, intolerance to an antifungal agent in the past.

8. Which one of the following statements regarding the management of *Cryptococcus* meningoencephalitis is true?

A. The use of flucytosine during induction therapy is only recommended for patients with HIV infection.
B. Careful management of intracranial pressures has been shown to improve patient outcomes.***
C. The transition to consolidation therapy must always begin on week 2 to limit the toxicities of amphotericin B.
D. Antifungal doses should be reduced in patients who develop Immune Reconstitution Syndrome.

The correct answer is: B. One of the most critical determinants of the outcome for cryptococcal meningoencephalitis is control of CSF pressure, and therefore intracranial pressure. This elevation is associated with increased morbidity and mortality, especially early in the treatment course.

9. Which one of the following statements regarding cryptococcal infections is INCORRECT?

A. The leading risk factor for cryptococcal infection is HIV/AIDS.
B. *C. neoformans* is only isolated from patients with documented immunodeficiencies.***
C. *C. gattii* has been associated with a recent outbreak of cryptococcal infections in the northwest United States.
D. *C. gattii* infections can be more aggressive and progress more rapidly than infections with *C. neoformans*.

The correct answer is: B. While *Cryptococcus neoformans* has a clear predilection for causing disease in immunocompromised people, it should be noted, however, that not all patients with *Cryptococcus* have a demonstrable immune defect, host issue or iatrogenic explanation.

Cryptococcal infection is the fourth most common opportunistic infection identified in patients with AIDS.
**Cryptococcus gattii**, a more recently categorized organism seen primarily in Australia, Western Canada and in the northwestern United States, specifically in the states of Washington and Oregon.

**Cryptococcus gattii**, unlike **Cryptococcus neoformans**, is mostly seen in normal hosts, has a relatively reduced susceptibility to fluconazole, and appears to be more virulent. Early data suggests that **Cryptococcus gattii** may behave differently and have different susceptibilities to antifungal agents, and perhaps require more aggressive or lengthier antifungal therapy.

10. Which one of the following statements regarding **Cryptococcus** infections is INCORRECT?

A. Severe **C. gattii** have been observed in persons with no identified immunodeficiency or immunosuppression.
B. CSF cryptococcal antigen assays can routinely detect **C. gattii**.
C. CSF fungal cultures routinely grow **Cryptococcus** if present.
D. **C. neoformans** cryptococcal infections are more resistant to azole therapies such as fluconazole compared to **C. gattii**.

**The correct answer is:** D. **Cryptococcus gattii**, unlike **Cryptococcus neoformans**, is mostly seen in normal hosts, has a relatively reduced susceptibility to fluconazole, and appears to be more virulent.

**Cryptococcus gattii** is associated with causing illness in immunocompetent people.

Detection of the cryptococcal capsular polysaccharide antigen in the serum or CSF is a compelling test if found to be positive. A lateral flow assay is an alternative approach to detecting the cryptococcal antigen, which utilizes a simple dipstick test and is inexpensive to perform and can be used in either urine, serum, CSF, or plasma samples.