

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

“eCase Challenge #1 – Aspergillosis”

Hello and welcome to this eCase, “Challenging Cases in the Diagnosis and Management of Invasive Fungal Infections.” I am Dr. Paul Auwaerter, the Sherrilyn and Ken Fisher Professor of Medicine and Clinical Director of the Division of Infectious Diseases at the Johns Hopkins University School of Medicine here in Baltimore, Maryland. We will start with Case Study number one, the first of three cases included in this continuing medical education program. The topic for this case will center upon an evaluation of a patient with an *Aspergillus* infection. Let’s begin.

Patient History

- 39 year-old Caucasian female
- Previous episode of bronchitis, treated with azithromycin and methylprednisolone
- Four days later presents to ER with worsening symptoms and new onset blurred vision

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Our first patient is a 39-year-old Caucasian woman who has only had a past medical history of depression. She presented to her primary care physician in mid-November for an acute care visit with the following symptoms: a low grade fever, malaise, poor appetite, dyspnea and a persistent non-productive cough for the past 2 weeks. She was diagnosed with bronchitis versus pertussis and started on azithromycin and methylprednisolone. These medications had little effect, and now she presents to the hospital emergency room four days later with worsening shortness of breath, dizziness and new onset blurry vision. Her laboratories are notable for the following: a white blood cell count of 49,000 with 86% blasts, a hemoglobin of only 5.1 grams per deciliter, and platelets of 17,000 and her INR was elevated at 1.7. Chest x-ray

is unremarkable but a head CT scan demonstrated findings concerning for a left anterior parietal hemorrhage. Further physical examination is notable for a heart rate of 105 beats per minute, a blood pressure of 125 over 80, a respiratory rate that was normal at 16 and a peripheral capillary oxygen saturation of 93% on 2 liters of supplemental oxygen by nasal cannula. She is alert and oriented but her head and neck exam included the findings of pale conjunctiva. Her lung exam is normal and her cardiac exam does display tachycardia but with no murmur. Bone marrow studies that were performed do confirm AML or acute myelogenous leukemia. Subsequent induction chemotherapy with seven days of cytarabine plus three days of doxorubicin, typically referred to as the ‘seven plus three regimen’ was instituted. In keeping with the guidelines from the Infectious Diseases Society of America, commonly known in shorthand as IDSA, for management of neutropenia in cancer patients, moxifloxacin, a fluoroquinolone, was started for antibacterial prophylaxis as the patient is expected to experience neutropenia for more than seven days.

Now let’s pose our first clinical question.

How would you classify this patient’s risk of developing the leading severe fungal infection in hematologic patients, invasive aspergillosis infection?

- A. High risk
- B. Intermediate risk
- C. Low risk
- D. At same risk as the average population

Diagnosis

- Acute Myelogenous Leukemia (AML)
- Treated with 7+3 regimen
- Moxifloxacin initiated prophylactically to address anticipated neutropenia

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Aspergillosis: Common Pathogens

- *Aspergillus fumigatus*
- *Aspergillus flavus*
- *Aspergillus niger*
- *Aspergillus terreus*

Walsh TJ. *Curr Opin Investig Drugs*. 2001;2(10):1366-7.

Slide 3

Aspergillosis refers to diseases caused by any *Aspergillus* species. The most commonly identified pathogens with invasive infections are *Aspergillus fumigatus* complex, *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus*. These organisms cause a range of diseases from allergic to saprophytic to invasive illnesses in both immunocompetent and immunocompromised patients. *Aspergillus* species are ubiquitous in the environment and inhalation of these infectious conidia occur frequently. Despite frequent exposure, tissue invasion is actually quite uncommon and mostly occurs in the setting of immune suppression associated with therapies for hematologic malignancies or potentially organ transplantation. Historically, the highest risk for invasive infections have been seen in two types of

severely immunosuppressed patients. First, those who have had allogeneic hematopoietic stem cell transplants, also known in shorthand as HSCT patients. The second, are solid organ transplant patients, especially those who have had lung, heart-lung, or liver transplants, as well as patients who experience any bout of prolonged neutropenia. In patients with AML, the incidence of *Aspergillus* infection invasive type, sometimes known in shorthand as IA, ranges between five to ten percent.

Risk Factors for Aspergillosis

High-Risk	Intermediate-Risk	Low-Risk
Prolonged neutropenia	Prolonged corticosteroid therapy	Severe burn
Hematologic malignancy	COPD	Cardiac surgery
Allogeneic HSCT	Autologous HSCT	Corticosteroid therapy <7 days
Solid organ transplant	Prolonged ICU stay	Malnutrition
	Cirrhosis with duration of stay >7 days	Other solid organ transplant
	Solid-organ cancer	
	HIV infection	

Walsh TJ. *Clin Infect Dis*. 2008 Feb 1;46(3):327-60.

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The IDSA published guidelines for the treatment of invasive aspergillosis in 2008, and in 2011 the American Thoracic Society also issued their own guidelines. The IDSA guidelines suggest that patients can be classified into high, intermediate and low risk IA infections based on the presence of certain epidemiologic factors, illnesses and use of immunosuppressive therapies. In HSCT recipients, persistent neutropenia, severe graft-versus-host disease, cytomegalovirus infection are additional risks factors. Invasive aspergillosis can also occur in less immunosuppressed hosts, particularly those who have chronic obstructive lung disease and those who receive longer-term glucocorticoid therapies. Because our patient has AML, she is considered high-risk so the correct answer is A.

Let's continue with our case. Your colleagues request your opinion on whether the patient should be started on prophylaxis against fungi and molds, including *Aspergillus* infections in addition to antibacterial prophylaxis.

This question about starting prophylaxis presents our next clinical question.

Which of the following statements regarding prophylaxis against IA infection is correct?

- A. Prophylaxis against IA infection is only recommended for patients with a prior history of *Aspergillus spp.* infection.
- B. Patients undergoing intensive chemotherapy for conditions such as AML should receive prophylaxis with an antifungal agent active against *Candida* and mold infections.
- C. Antifungal prophylaxis is recommended for all patients who experience neutropenia of any duration.
- D. Primary prophylaxis against invasive mold infections has no proven benefit.

The correct answer is B and let me explain why.

Primary prophylaxis refers to the administration of an antimicrobial agent to prevent infection in patients at increased risk who have not previously had the type of infection being targeted. As our patient did not have any known prior history of *Aspergillus* infection, the benefits of primary prophylaxis for invasive aspergillosis should be considered when formulating our opinion.

Prophylaxis against invasive *Aspergillus* has been demonstrated to improve patient outcomes. A 2012 meta-analysis of twenty randomized trials comparing mold-active prophylaxis to fluconazole-only prophylaxis in patients with hematologic malignancies receiving chemotherapy and showed that mold-active prophylaxis reduced the number of proven or probable invasive fungal infections in this high-risk population. In fact, a reduction in the risk of invasive *Aspergillus* infections and related mortality had a relative risk of 0.53 and 0.67 respectively, a rather significant reduction.

Rationale for PRIMARY Prophylaxis

- Rising incidence of life threatening infections
- Difficulty of establishing a diagnosis
- Poor outcomes with later therapeutic intervention

Ethier MC, Br J Cancer. 2012 May;106(10):1626-37. Slide 5

The rationale for primary prophylaxis in our patient rests on three main arguments: the rising incidence of life-threatening invasive fungal infections among cancer patients, the difficulty of establishing a diagnosis of invasive *aspergillus* early in the course of such an infection, and third, that poor outcomes especially with later initiation of directed antifungal therapy do occur. The recommended approach to primary prophylaxis can be summarized as follows:

PRIMARY Prophylaxis Should Be Given To:

- Patients with acute leukemia undergoing induction or salvage chemotherapy
- Patients undergoing intensive chemotherapy for AML or MDS
- Patients in whom neutropenia is expected to last >7 days

Freifeld AG, Clin Infect Dis. 2011;52(4):e56-93. doi: 10.1093/cid/cir073. Slide 6

- Patients with acute leukemia undergoing induction or salvage chemotherapy, or who are expected to develop mucositis should at a minimum receive antifungal agents with activity against *Candida spp.*
- Patients undergoing intensive chemotherapy for AML or myelodysplastic syndrome should receive antifungal agents with activity not only against *Candida*, but also against invasive molds.
- Antifungal prophylaxis is **not** recommended for patients in whom the anticipated duration of neutropenia is less than 7 days.

Let's review the secondary prophylaxis. Patients who have had a prior history of invasive fungal infection, especially *Aspergillus spp.*, are at high-risk for recurrence with further chemotherapy and therefore antifungal prophylaxis with a mold-active agent is recommended. This approach of secondary prophylaxis should be summarized in the following way:

- Patients with a history of prior aspergillosis receiving myelosuppressive chemotherapy with an anticipated and prolonged neutropenic period of at least two weeks should receive antifungal prophylaxis with a mold-active agent.
- The duration of antifungal prophylaxis will need to be individualized based on the patient's clinical status and prior history of fungal infections. For example:
 - In a patient with acute leukemia, primary prophylaxis against *Candida spp.* is typically continued until the myeloid reconstitution occurs.
 - In patients receiving secondary prophylaxis during a period of myelosuppression, prophylaxis is usually considered at least until the myeloid reconstitution has occurred.

SECONDARY Prophylaxis Should Be Given To:

- Patients with a history of prior invasive aspergillosis receiving myelosuppressive chemotherapy, and
- Anticipated neutropenia of at least two weeks

Marr KA. *Clin Infect Dis.* 2002;34(7):909-17.

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Now – as our case continues, the patient was indeed placed on a mold-active agent, that is posaconazole, for prophylaxis against invasive aspergillosis. After receiving induction chemotherapy, the patient was aplastic for three weeks. On day 23, her peripheral white blood cell count began to recover and on day 28 the patient was ultimately discharged with an absolute neutrophil count of more than 500 cells on moxifloxacin and valacyclovir prophylaxis. The antifungal prophylaxis was stopped as the neutropenia has resolved.

The patient returns three weeks later and receives an uncomplicated course of consolidation chemotherapy. However, on day ten after this consolidation chemotherapy she does develop a temperature to 101 degrees Fahrenheit and also requires supplemental oxygen four liters by nasal cannula. As part of her evaluation, the patient undergoes a CT scan of her chest which demonstrates a nodular infiltrate pattern without clear halo or crescent sign. A serum galactomannan assay or GMA is sent and does return with a value just above the reference range. A (1→3) β-D glucan assay is performed and returns at 100 pg/mL, whereby anything higher than 80 is judged as positive.

Now let's pose our next clinical question.

Which one of the following options is an appropriate next step in the management of this patient?

- A. Await results of pending cultures - do not initiate any therapy.
- B. Repeat the serum GMA assay and initiate an antifungal agent only if it has increased.
- C. Initiate high dose steroids for a GVH flare.
- D. Draw blood cultures and initiate antifungal therapy for probable pulmonary aspergillosis.
- E. Draw blood cultures and initiate an antifungal agent only if positive.

Well the correct answer is D because we suspect our patient has pulmonary aspergillosis.

Patients with pulmonary aspergillosis may have a number of signs and symptoms, including: fever, chest pain, shortness of breath, cough, and/or hemoptysis. The classic triad has been described in neutropenic patients with fever, and that is pleuritic chest pain, fever and hemoptysis; however, this is both non-specific and insensitive. Chest X-ray is insensitive alone for detecting the earliest stages of pulmonary disease, but CT scanning typically demonstrates nodules with or without cavitation, patchy or segmental consolidation, or peribronchial infiltrates sometimes in tree-in-bud patterns. The radiographic progression of disease has been best studied in such neutropenic patients, in whom the initial findings typically include macronodules that are larger than one centimeter in diameter that have been surrounded by ground glass infiltrates, also known as the halo sign, reflecting hemorrhage in the area surrounding the fungal infection.

Signs and Symptoms of Aspergillosis


- Fever
- Chest pain
- Shortness of breath
- Cough, with or without hemoptysis

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These nodules typically enlarge, even with appropriate therapy, and may eventually cavitate, producing the so-called air-crescent sign. Without adequate therapy in these patients, invasive pulmonary aspergillosis will almost always progress to a life-threatening pneumonia, and be associated with spread to the central nervous system as well as other intrathoracic structures. With a history of severe immunosuppression, evidence of pulmonary disease and a positive galactomannan assay as well as a (1→3) β-D glucan assays, this patient meets criterion for probable invasive aspergillosis. Early administration of antifungal therapy while diagnostic evaluation that is ongoing is critical.

1,3-beta-D-glucan is a cell wall component of many fungi and can be detected by the (1→3) β-D glucan assay. This assay has been cleared by the Food and Drug Administration (FDA) as an aid to the diagnosis of invasive fungal infections. This assay measures the activity of Factor G, using the same principal as serum endotoxin assays. The output of the serum assay currently available in the United States is based on spectrophotometer readings, in which optical density is converted to beta-D-glucan concentrations. The results are interpreted as either a negative, with less than 60 picograms per milliliter, indeterminate

Radiologic Findings in Pulmonary Aspergillosis



Wedge-shaped consolidation

Nodules may be surrounded by a halo of ground-glass attenuation ("halo sign")
• Most reliable in neutropenic patients

Separation of necrotic lung from adjacent parenchyma results in air crescents

Similar appearance has been described in infection by *Mucorales* and *Candida*

Slide 9

Franquet T. *Radiographics*. 2001;21(4):825.

60 to 79 picograms per milliliter, or positive if levels are more than 80 picograms per milliliter. In two meta-analyses of studies evaluating this assay for the diagnosis of invasive infections reported in 2011 and 2012, the sensitivity ranged from 50-95% while the specificity was higher even, at 85-99%. Despite the heterogeneity among these different studies, the beta-D-glucan assay has a good accuracy for distinguishing patients with proven or probable invasive fungal infections from patients without invasive fungal infection. One major caveat is that 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*. Additionally, the following have been associated with some false positives of the beta-D-glucan assay: hemodialysis using cellulose membrane filters, administration of albumin or intravenous immunoglobulins, the use of cellulose filters for any intravenous administration of products, and gauze packing on serosal surfaces. Of note, certain fungi such as the *Cryptococcus* and members of the *Mucor* family are not detected by this test. *Aspergillus spp.* grow well on standard media, however blood cultures are of limited value and are often negative even in disseminated infections. So therefore, choice E is incorrect.

So now our case continues. The patient was started on the antibacterial cefepime as well as liposomal amphotericin. Forty-eight hours later the patient is still feverish and has no improvement in oxygen requirement. Blood cultures remain negative at 48 hours, and the patient undergoes a bronchoscopy and bronchoalveolar lavage, sometimes known in shorthand as a BAL. Tissue biopsy was deferred due to risk of bleeding. The results of the lavage culture are pending. However, the gram stain returns with mixed respiratory flora and heavy gram positive cocci. The results of acid-fast bacillus stains are negative and the BAL galactomannan assay returns with a value of 1.0.

This does bring us to our next clinical question.

How does this patient's history of recent posaconazole use influence your treatment decision for this patient?

- A. Stop antifungal treatment, start vancomycin and continue cefepime as respiratory samples suggest that primary etiology is bacterial.
- B. Change fungal treatment to fluconazole, add vancomycin and continue cefepime as blood culture fails to show evidence of IA.
- C. The patient has evidence of probable aspergillosis, continue antifungal and antibacterial treatment until cultures return.
- D. Stop antifungal treatment as positive BAL GMA is likely a false positive due to cefepime use.

The correct answer is C. Let me explain why. The patient has evidence of probable pulmonary aspergillosis and antifungals should not be stopped. Posaconazole prophylaxis has been associated with a significant risk reduction in probable or proven invasive fungal disease in such high risk groups. However, infections are still reported so the patient should be treated regardless of her history of prophylaxis.

Galactomannan Assay

- Detects galactomannan, a major constituent of *Aspergillus* cell walls
- 71% sensitivity and 89% specificity for PROVEN IA infection
- 61-86% sensitivity and 91-93% specificity for PROVEN AND PROBABLE IA infection

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Pfeiffer CD. *Clin Infect Dis.* 2006;42(10):1417-27.

Galactomannan is a polysaccharide and a major constituent of *Aspergillus* cell walls and it is released during the growth of hyphae. The galactomannan assay is an ELISA which detects fungal antigens and can provide an indication of potentially invasive disease. A meta-analysis of 27 studies, mainly performed in patients with hematologic malignancies, reported a 71% sensitivity and 89% specificity for galactomannan in patients with proven invasive aspergillosis. Combining proven and probable cases resulted in an overall rate of 61% sensitivity and 93% specificity. The use of a bronchoscopy and lavage galactomannan has been evaluated as a diagnostic tool for the diagnosis of pulmonary infections. In one retrospective study of 251 patients at-risk for invasive aspergillosis and being evaluated

for unexplained nodular lesions or consolidation on lung imaging, the BAL galactomannan optical density of greater than or equal to 0.8 yielded a sensitivity of 86% and a specificity of 91% for diagnosing either proven or probable invasive aspergillosis. It should be noted though, that in this study, more than 35% of these 251 patients were not transplant patients or patients with any known malignancy.

Many centers use this assay on BAL fluid as an adjunct to other diagnostic tests when invasive aspergillosis is so suspected. Currently the GMA assay has been cleared by the FDA for use on either serum or lavage fluid. A result with an optical density or OD index greater than or equal to 0.5 is considered a positive result. While the use of serial galactomannan measurements has been investigated in several institutions, there is currently no conclusive clinical evidence for the use of serial galactomannan antigen levels to gauge the presence or the progress of treatment of invasive aspergillosis infections. It should be noted that false positives and false negatives with the galactomannan assay do occur. For false positives, these can be especially common in the setting of airway colonization with *Aspergillus*, as often occur in lung transplant patients, or when fluid used for lavage washes are contaminated with galactomannan. However, one study performed in lung transplant patients suggested a high specificity of 95%.

Now let's continue with our case. The patient does develop rather severe hypokalemia while on amphotericin B and while you review the patient's antifungal therapy, awaiting culture results and final pathology, this presents us with another clinical question.

Which of the following would be an appropriate choice of antifungal for this patient?

- A. Fluconazole 400 mg IV q 24h.
- B. Voriconazole 4 mg/kg IV every 8h.

- C. Amphotericin B deoxycholate 1-1.5 mg/kilogram IV daily.
- D. Caspofungin 70 mg IV once followed by 50 mg IV daily.
- E. Voriconazole 6 mg/kg every 12h for 2 doses, then 4 mg/kg IV every 12h + caspofungin 70 mg IV once followed by 50 mg IV daily.

Antifungals with Activity Against *Aspergillus*

Triazoles	Echinocandins	Polyenes
Voriconazole	Caspofungin	Amphotericin B Lipid Complex
Posaconazole	Micafungin	Liposomal Amphotericin B
Isavuconazole	Anidulafungin	Amphotericin B Deoxycholate
Itraconazole		

• Monotherapy with echinocandins is not recommended for IA infections

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There are three classes of antifungal agents available for the treatment of aspergillosis: the polyene class, azoles, and echinocandins. It's important to know that fluconazole is the only member of the triazoles that has no activity against *Aspergillus spp.*, and that itraconazole has become a second-line agent, while voriconazole, posaconazole, and isavuconazole all have legitimate and good activities.

Posaconazole

- Indicated for *Aspergillus ssp.* and *Candida* infections; treatment of oropharyngeal candidiasis
- Suspension: 200 mg 3 times per day
- Delayed release tablets and IV therapy: 300 mg 2 times per day, then 300 mg daily
- Indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk patients

Noxafil (posaconazole) package insert. Merck Sharp & Dohme Corp. Revised March 2014.

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Although posaconazole has good *in vitro* activity against *Aspergillus* and the fact that the FDA has only approved this drug for prevention and prophylaxis of invasive aspergillus, its role in treatment of this mold infection is uncertain. The efficacy and safety of oral posaconazole as monotherapy was investigated in an open-label, multicenter trial of patients with invasive aspergillosis or other mycoses that were refractory to conventional antifungal therapy. In this study, the overall success rate was 39% for those who received posaconazole compared to 26% who received other agents which were all collected by retrospective case control. Given its spectrum of activity and treatment success here, but yet it's in uncontrolled trials, it's not yet judged to be a first line therapy for initial treatment of invasive aspergillosis.

Another drug, isavuconazole was recently approved by the Food and Drug Administration in March of 2015 for the treatment of invasive aspergillosis as well as mucormycosis. This drug was compared to voriconazole in a non-inferiority trial design in patients with proven, probable, or possible invasive fungal disease by *Aspergillus*, or other members of filamentous fungal families. In the group of patients with proven or probable invasive aspergillosis, the overall success rate at end of treatment was seen as 35 percent in those who received isavuconazole compared to 38.9 percent in voriconazole-treated patients.

Isavuconazole

- Indicated for invasive aspergillosis and mucormycosis infections
- IV or oral therapy, 200 mg every 8h x 6 doses then 200 mg daily

Cresemba (isavuconazonium sulfate) package insert. Astellas Pharma US, Inc. Revised March 2015.

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Voriconazole

- Indicated for invasive aspergillosis, esophageal candidiasis, *Scedosporium apiospermum* and *Fusarium ssp.*
- Intravenous:
 - Loading: 6 mg/kg every 12h for 2 doses
 - Maintenance: 4 mg/kg every 12h
- Oral:
 - Pt <40 kg
 - Loading: 200 mg every 12h for 2 doses
 - Maintenance: 100 mg every 12h; max: 300 mg/day
 - Pt ≥40 kg
 - Loading: 400 mg every 12h for 2 doses
 - Maintenance: 200 mg every 12h; max: 600 mg/day
- Not studied for Child-Pugh C

See reference list

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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. Therefore, answer E is correct. Voriconazole is available in both intravenous and oral formulations. 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. When patients are able to take oral medications, one can consider switching to the oral formulation. In the

echinocandin class, caspofungin is typically dosed at 70 milligrams IV for the first dose followed by 50 milligrams daily thereafter.

Amphotericin B deoxycholate is active against *Aspergillus spp.* and has been used extensively for this infection historically. However, its use can be associated with infusion-related reactions, electrolyte imbalances, nephrotoxicity and poorer treatment outcomes and survival when compared to voriconazole. Less toxic options in the polyene class, now predominantly liposomal amphotericin B, may be used in patients with *Aspergillus* and especially if other mold infections are suspected such as mucormycosis.

Amphotericin

- Indicated for treatment of aspergillosis, cryptococcosis, blastomycosis, coccidiomycosis, histoplasmosis, zygomycosis, visceral leishmaniasis, and empiric therapy in febrile, neutropenic patients

Dosing:

Amphotericin B lipid complex – 5 mg/kg IV per day

OR

Liposomal amphotericin B – 3-5 mg/kg IV per day

See reference list

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Echinocandins

- Caspofungin – FDA licensed for probable or proven IA and treatment of *Candida* infections
- Micafungin and anidulafungin – Not FDA licensed for IA infections. However, have shown efficacy against *Aspergillus spp.*

Candidas (caspofungin acetate) package insert. Merck Sharp & Dohme Corp. Revised August 2013. Mycamine (micafungin sodium) for intravenous injection package insert. Shionogi Inc. Revised April 2013.

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Caspofungin has been licensed by the Food and Drug Administration for the treatment of proven or probable invasive aspergillosis in patients who cannot tolerate or who are refractory to standard therapies, which was basically amphotericin products. Other available echinocandins, such as micafungin and anidulafungin, are not FDA-licensed for the treatment of invasive aspergillosis. However, these agents, at least *in vitro*, also have activity against *Aspergillus* and could be considered equivalent for clinical use. Echinocandins are not recommended as initial monotherapy for invasive aspergillosis but are emerging as agents for combination therapy with voriconazole in salvage regimens.

So our case continues and we find that the patient improved and was discharged to a skilled nursing facility after a one-week hospitalization. She continues on the antifungal treatment with voriconazole at 4 milligrams per kilogram dosing every 12 hours PLUS caspofungin given 50 mg IV daily. She comes to your clinic for follow-up one week later with laboratories that had been drawn earlier. She is tolerating the antifungals well with no missed doses. Her exam has no remarkable findings. Her lab results are within normal limits but are important for the following:

Her serum creatinine is now 1.2 mg/dL; her prior baseline was just 1.1. Her INR was in normal range, as was her total bilirubin, albumin, but her transaminases had modest elevations with an AST of 105 IU/mL and an ALT of 100 IU/mL. An alkaline phosphatase level was normal, and a voriconazole trough level returned at 3.5 mcg/mL.

Now that we have all these lab results, we can present our next clinical question.

Dosage Regimens for Echinocandins

Echinocandins	
Caspofungin*	Intravenous: Loading: 70 mg for 1 dose Maintenance: 50 mg every 24h
Micafungin**	Intravenous: 100 mg daily
Anidulafungin**	Intravenous: Loading: 200 mg for 1 dose Maintenance: 100 mg every 24h

*Salvage only for *Aspergillus*
**Off label uses for *Aspergillus*
See reference list

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Which one of the following options would be an appropriate next step?

- A. Continue voriconazole at the current doses, with serial liver enzymes measurement.
- B. Decrease voriconazole to HALF the current dose, with serial liver enzymes measurement.
- C. Stop voriconazole and switch to amphotericin B an alternative first-line agent.
- D. Stop voriconazole and switch to isavuconazole as an alternative first-line agent.

Answer A does happen to be correct and let's proceed with explaining why. Adverse reactions associated with voriconazole include transient visual disturbances (including flashes of white vision), hepatotoxicity, elevated serum bilirubin, alkaline phosphatase and aminotransferase levels, skin rash and even visual hallucinations. Liver enzymes should be monitored at baseline and every one to two weeks thereafter. Although no dose adjustment is necessary for patients with abnormally elevated liver function tests, if they are more than five times normal, the dose may be reduced or a different drug considered. Serum voriconazole troughs should be measured every five to seven days after therapy is started. The preferred goal trough concentration is between 2 and 5.5 micrograms per milliliter. If the trough concentrations are below one microgram per milliliter, poor clinical outcomes have been reported and this might prompt an increase in the dose of voriconazole and subsequent therapeutic drug monitoring. If serum troughs are above 5.5 micrograms per milliliter, this would warrant a reduction in the voriconazole dose because it has been associated with increased toxicities. Thus in this patient, a voriconazole dose adjustment isn't needed because it's in normal range.

The phase 3 clinical trial known as 'SECURE' was a randomized, multicenter, double-blind, non-inferiority study of isavuconazole versus voriconazole for the primary treatment of invasive fungal disease caused by *Aspergillus spp.* or other filamentous fungi. In preliminary data from this study, isavuconazole was non-inferior to voriconazole for all-cause mortality in the intent to treat population at 42 days.

Isavuconazole may cause serious side effects including hepatotoxicity, infusion reactions, and severe allergic and skin reactions, though the most common adverse reactions were nausea, vomiting, diarrhea, headache, elevated liver function tests, low potassium, constipation, shortness of breath, cough, edema, and back pain. Thus a change to this agent doesn't seem to be warranted on the basis of these laboratories.

This concludes our case of a patient with 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.

Definitions of Invasive Aspergillosis

Proven

Requires histopathologic evidence and positive culture from a normally sterile site

Probable

Requires fulfillment of criteria in three categories:

Host Factors:

- Inherited or acquired severe immunodeficiency
- Prolonged neutropenia
- Allogeneic HSCT

Clinical Criteria:

Organ specific signs

Mycologic Criteria:

Direct tests: cytology, direct microscopy, or culture
Indirect tests: GMA in plasma, serum, bronchoalveolar lavage fluid, or CSF, Fungitel® β-D Glucan Assay

Possible

Requires fulfillment of criteria in two categories:

Radiologic Criteria:

eg, for pulmonary disease: dense, well-circumscribed lesions with or without halo sign, air crescent sign or cavity

Mycologic Criteria: and/or positive serum galactomannan, positive Fungitel® β-D Glucan Assay

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Walsh, TJ *Clin Infect Dis.* 2008;46(3):327-60.

CLINICAL PEARL

Invasive *Aspergillus* infections remain a major cause of morbidity and mortality in patients receiving immunosuppressive therapy or chemotherapies for life-threatening conditions including acute leukemia. Any clinician will need to be aware of the severity of such invasive fungal infections and become familiar with the prophylactic strategies to try to help prevent them. Also, existing and newer diagnostic modalities are available which really are geared towards earlier recognition of potential invasive fungal infections so that earlier treatment can begin and better outcomes yielded.

References:

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Slide 12: Noxafil (posaconazole) package insert. Merck Sharp & Dohme Corp. Revised March 2014.

Slide 13: Cresemba (isavuconazonium sulfate) package insert. Astellas Pharma US, Inc. Revised March 2015.

Slide 14: Vfend (voriconazole) package insert. Roerig, Division of Pfizer Inc. Revised February 2015.

Slide 15: Ambisome (amphotericin B) liposome for injection package insert. Astellas Pharma US, Inc. Revised May 2012. Abelcet (amphotericin B lipid complex) injection package insert. Sigma-tau Pharmaceuticals, Inc. Revised March 2013. Amphotericin b injection, powder, lyophilized, for solution package insert. X-Gen Pharmaceuticals, Inc. Revised December 2009.

Slide 16: Cancidas (caspofungin acetate) package insert. Merck Sharp & Dohme Corp. Revised August 2013. Mycamine (micafungin sodium) for intravenous injection package insert. Shionogi Inc. Revised April 2013.

Slide 17: Cancidas (caspofungin acetate) package insert. Merck Sharp & Dohme Corp. Revised August 2013. Mycamine (micafungin sodium) for intravenous injection package insert. Shionogi Inc. Revised April 2013. Eraxis (anidulafungin) for injection package insert. Roerig, Division of Pfizer, Inc. Revised July 2012.

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

“eCase Challenge #2 – Candidiasis”

In this case, we will evaluate a patient who develops an invasive *Candida* infection. Let's begin.

Patient History

- 26 year-old male admitted to ICU
- Splenectomy 1 week previously after being struck by a car
- Non-tunneled central venous catheter for parenteral nutrition
- Placed on piperacillin/tazobactam since surgery
- 102° fever, four days after surgery
- Blood cultures negative

Slide 1

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A 26-year-old patient is admitted to the surgical ICU at your hospital. The patient was previously in good health, but involved in a motor vehicular accident one week ago where he was struck by a car while crossing a street. He had no other medical illnesses at the time of the accident and was admitted to the trauma service, and subsequently underwent emergency laparotomy for control of intraperitoneal bleeding, bowel injury with repair and ultimately required a splenectomy.

The patient's postoperative hemodynamic status has improved such that vasopressors have been stopped. He was started on TPN via a non-tunneled central venous catheter and was initially placed on piperacillin tazobactam perioperatively and has been continued on that drug since his surgery, although he did have a

fever to 102 degrees Fahrenheit four days after surgery.

Blood cultures from that time have remained negative, and now you are asked by the surgical team for a recommendation regarding this fever and use of potential antifungal therapy in this patient. Now let's pose our first clinical question.

What would be an appropriate response?

- A. Surgical patients in ICU who have undergone abdominal surgery are at no additional risk of invasive fungal infections (IFI) compared to elective surgeries, and do not require antifungal prophylaxis.
- B. The patient is immune-competent and therefore at low-risk of IFI and thus does not require prophylaxis.
- C. The patient has sufficient risk factors for invasive candidiasis and prophylaxis should be considered.

Our patient has a number of potential risk factors for invasive fungal infection, or IFI, including history of recent abdominal surgery, placement of a central venous catheter and use of TPN. So the correct answer is, in fact, C.

Candida species are among the most common cause of invasive fungal disease in humans, producing problems that range from non-life-threatening mucocutaneous disorders, such as thrush, to deep systemic processes that can involve any organ of the body. Candidemia specifically describes the presence of *Candida* in the blood and is one of the most common manifestations of invasive candidiasis.

***Candida* spp. are the most common invasive fungal infections in humans.**

Wisplinghoff H, et al. *Clin Infect Dis.* 2004;39:309-317.
Shorr AF, et al. *Crit Care Med.* 2009;37:2519-2526.
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Slide 2

Risk Factors for Invasive Candidiasis

High-Risk Factors	Non-specific Risk Factors
APACHE II score >20	Age (young and old)
Broad-spectrum antibiotic therapy	Diabetes mellitus
Burns on >50% body surface area	Multiple transfusions
Candiduria (>105 cfu/mL)	Prolonged ICU stay
Central venous catheter	Recent surgery
Colonization of multiple body sites	Renal failure
Hemodialysis/hemofiltration	Urinary catheter
Immunosuppression	Vascular access
Major abdominal surgery	
Major trauma	
Neutropenia	
Perforation of digestive tract	
Total parenteral nutrition	
Urinary tract surgery in presence of candiduria	

Pappas PG, et al. *Clin Infect Dis.* 2009;48(5):503-35. © All rights reserved - The Johns Hopkins University School of Medicine.

Slide 3

Patients in ICUs and those who are immune compromised are most at risk for candidemia. Surgical units, especially those caring for trauma and burn patients, along with neonatal units, have the highest rates in the hospital for *Candida* infections. Besides the risks associated with the extremes of age, trauma or burns, other factors that are notable include: any presence of central venous catheters, use of TPN, broad-spectrum antibiotic employment, high Apache scores, presence of

acute renal failure, especially if requiring hemodialysis, any prior surgery, but specifically gastrointestinal surgery, and especially in that subset people who have perforations of the GI tract or anastomotic leaks.

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.

Due to the high mortality in patients with candidemia, the role of antifungal prophylaxis has been explored. However, to date, an optimal approach remains unclear and subject to some debate.

Currently, there are no uniform recommendations for antifungal prophylaxis in ICU patients. Fluconazole has been indicated for prophylaxis to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation or those who receive chemotherapy or radiation therapy.

Some centers do use fluconazole off label routinely in ICU patients, especially in patients with the risk factors, specifically, central venous catheters, TPN, hemodialysis, trauma, broad-spectrum antibiotic use, recent surgery, and particularly abdominal surgery.

Prophylaxis Against *Candida*

- Prophylaxis should be considered in:
 - High-risk patients in ICUs where incidence of invasive candidiasis is >5%.
 - Neutropenic patients undergoing profound immunosuppression for HSCT or treatment of leukemia or lymphoma.
 - Central venous catheters, parenteral nutrition, hemodialysis, trauma, broad-spectrum antibiotic use, and recent surgery.

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Slide 4

IDSA Recommendations for Invasive Candidiasis

Use empiric antifungal therapy in critically ill patients at high-risk, and who have persistent fever despite antibacterial therapy.

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Slide 5

The Infectious Diseases Society of America, also known as IDSA, last published updated clinical practice guidelines for the management of candidiasis in 2009. These guidelines recommend empiric antifungal therapy in critically ill patients who are at risk for invasive candidiasis and for those who have persistent fever, despite earlier antibacterial therapy.

Now let's continue with our case.

The patient was, indeed, started on intravenous fluconazole at a dose of 400 mg daily, which was considered as prophylaxis against invasive fungal infections. Although with the onset of fever, this could also be viewed potentially as empiric therapy.

Abdominal imaging did show collections in the splenic bed and around several loops of bowel judged to be postoperative findings. Unfortunately, he continued to have low-grade fevers on a daily basis and had an elevated white blood cell count which rose from 15 to 24,000, associated with elevated liver enzymes rising to as high as three times normal.

Vasopressor support had to be reinstated. With each febrile episode, additional blood cultures were drawn to evaluate for potential bloodstream infection. On the seventh day of admission, one bottle from the two blood culture sets drawn earlier returned with a preliminary result indicating a yeast form that was growing. This does bring us to our next clinical question.

What would be the appropriate management at this time?

- A. Continue fluconazole, yeast is likely a contaminant.
- B. Continue fluconazole, start a second antifungal.
- C. Either switch fluconazole IV to 800 mg or change to an echinocandin class agent.
- D. Discontinue fluconazole due to likely drug-induced fever and hepatitis.

Candida species account for approximately 10% of all bloodstream infections in ICUs and are associated with a crude in-hospital mortality rate of up to 30%. Yeast, including *Candida* in the blood, should never be viewed as a contaminant. Such a finding requires a search for the source of the bloodstream infection.

For many, candidemia is a manifestation of invasion that could have originated in an organ, a surgical site, or if there's an infected indwelling intravenous catheter. *Candida* species are the most frequently identified yeast in blood cultures and appropriate coverage should be implemented.

So a switch to an alternative agent until susceptibilities can be determined would be a reasonable approach. For these reasons, answer C is correct.

As we will be discussing later in this case, there are very limited situations of invasive candidiasis that require multiple fungal agents, and this is not routinely indicated in this kind of patient.

So now our case continues, and you make the decision to change from fluconazole to another antifungal agent while awaiting further microbiology results. This decision brings about our next clinical question.

Candidemia

- *Candida spp.* = 10% of bloodstream infections in ICUs.
- Do not view as a contaminant in blood cultures
- Identify source of infection

Wisplinghoff H, et al. *Clin Infect Dis*. 2004;39:309-317.
Shorr AF, et al. *Crit Care Med*. 2009;37:2519-2526.
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Slide 6

Antifungals FDA-licensed for Candidemia

- Polyenes: amphotericin deoxycholate, liposomal amphotericin B
- Azoles: fluconazole, voriconazole
- Echinocandins: caspofungin, micafungin, anidulafungin

Slide 7

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Which of the following antifungals would be the least appropriate choice in this patient's management?

- A. Itraconazole
- B. Micafungin
- C. Voriconazole
- D. Liposomal amphotericin B

Therapeutic antifungal agents for the treatment of candidiasis include polyenes, azoles and echinocandins. Among the azole class, fluconazole has been used most extensively. Azoles tend to inhibit certain cytochromes, including the P450-dependent enzyme, lanosterol 14 alpha-demethylase, which happens to be necessary for conversion of lanosterol to ergosterol, which is a key component of the fungal cell membrane.

Fluconazole has an excellent safety profile, and it's available in both intravenous and oral formulations.

The drug is highly bioavailable in oral formulation, meaning that it can be used via this route in place of intravenous therapy in appropriate patients. For treatment of candidemia, fluconazole can be dosed as follows: at 800 mg or 12 mg/kg as a loading dose, and then 400 mg or 6 mg/kg given either orally or intravenously.

Voriconazole is also active against *Candida* species, often with a lower mean inhibitory concentration. Although in vitro cross-resistance has been described between fluconazole and voriconazole in some *Candida* isolates, making this a less

appropriate choice at this time without knowing the susceptibility profile.

Itraconazole nowadays is only available as an oral formulation, so in the septic patient with a bowel injury it would be an inappropriate choice. So answer A is correct.

While posaconazole is available as an oral extended-release tablet and is also present as an intravenous formulation, the FDA has only indicated its use as a prophylactic agent for fungal infections in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease and in patients who have prolonged neutropenia due to chemotherapy for hematologic malignancies.

Azoles for Treatment of Candidemia

- **Voriconazole:**
 - Active against *Candida* species with lower MICs
 - Cross-resistance with fluconazole observed
- **Itraconazole:**
 - Oral only in US
 - Not used for systemic *Candida* infections
- **Posaconazole:**
 - Not FDA-indicated for systemic candidemia
 - Indications include prophylaxis of IFI in at-risk patients, esophageal candidiasis

Voriconazole package insert. Roerig, Division of Pfizer Inc. Revised February 2011.
Itraconazole package insert. Hospira. March 2009.
Posaconazole package insert. Merck Sharp & Dohme Corp. Revised March 2014.
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Posaconazole is also indicated for esophageal candidiasis, but not for systemic candidiasis, although some clinicians do use it off label, as this drug does have activity against many *Candida* species.

Fluconazole for Candidemia

- Extensive use and history
- Excellent safety profile
- Available IV and oral
- Typical dosing for candidemia:
 - 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) orally or IV daily.

Fluconazole package insert. Roerig, Division of Pfizer Inc. Revised March 2014.
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Polyenes for Treatment of Candidemia

- Liposomal amphotericin B formulations preferred given more favorable side effect profile

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Amphotericin B is a prototype polyene antifungal agent, which is known to disrupt fungal cell wall synthesis by binding to sterols and inducing formation of pores in the fungal cell wall. Amphotericin B deoxycholate is associated with significant nephrotoxicity, so nowadays liposomal amphotericin B formulations are almost used exclusively, given their more favorable side effect profile.

Echinocandins inhibit non-competitively (1-3) Beta-D-Glucan, which is an integral component of the fungal cell wall. They have excellent activity against most *Candida* species with low toxicity profiles and

Echinocandins for Treatment of Candidemia

- Excellent activity against most *Candida* species
- Low toxicity profiles
- FDA-licensed for treatment of candidemia and other forms of invasive candidiasis

Pappas PG, et al. *Clin Infect Dis.* 2009;48(5):503-35.
 Denning DW. *Lancet.* 2003 Oct 4;362(9390):1142-51.
 Mora-Duarte J, et al. *N Engl J Med.* 2002 Dec 19;347(25):2020-9.
 Reboli AC, et al. *N Engl J Med.* 2007 Jun 14;356(24):2472-82.
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are indicated for the treatment of candidemia and other forms of invasive candidiasis. Several trials that have been randomized compared the activity of echinocandins with either amphotericin B formulation or fluconazole among patients with invasive candidiasis.

The echinocandins appear to be as effective and better tolerated than amphotericin B formulations, and in one study more effective than fluconazole, as illustrated by the following observations.

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.

The echinocandins are preferred over azoles for the initial treatment of candidemia if *Candida glabrata* or *Candida krusei* is identified or suspected, or if the patient has been previously treated extensively with an azole agent.

So now let's get on with our case. Treatment with fluconazole was stopped, and the patient was initiated on micafungin at 100 mg total IV daily dose.

Within hours, several other blood culture bottles drawn on the same day as the initial positive culture also turned positive. Ultimately, the organism was speciated as *Candida glabrata*, and you expect sensitivity data to be available in the next 48 to 72 hours.

Once again, this new information about our patient presents us with our next clinical question.

Candidemia: Considerations for Choosing Antifungal Therapy

- History of recent azole exposure
- Prevalence of different *Candida* species/ current antifungal susceptibility data
- Severity of illness
- Relevant comorbidities, eg, neutropenia
- Evidence of involvement of the CNS, cardiac valves, eyes, and/or visceral organs
- History of intolerance to antifungal agent

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In addition to changing antifungals, which of the following management steps is indicated?

Management of Candidemia in Patients with Central Venous Catheters

- Whenever possible the catheter should be removed
- Catheter removal alone without antifungal agents is associated with poor outcomes

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- A. The double lumen central catheter should remain to deliver TPN and micafungin.
- B. Ophthalmology consultation should be obtained in the next few days to evaluate for endophthalmitis.
- C. Blood cultures should be drawn daily for the remainder of the hospitalization.
- D. A baseline serum galactomannan should be obtained to assist in long-term follow-up.

In all cases, candidemia requires treatment with an antifungal agent, and it should never be assumed that removal of a catheter

alone is adequate therapy for candidemia.

Several studies have noted the high mortality rates associated with candidemia. And these same studies have shown that mortality is highest in patients who never received an antifungal drug. Whenever possible, the catheter should be removed, or at a minimum, exchanged over a guided wire.

The appropriate duration of therapy for candidemia has not been well studied. A minimum of two weeks of therapy after blood cultures become negative is a recommendation from the 2009 IDSA Clinical Practice Guidelines for *Candida*.

Daily blood cultures should be performed after initiating therapy in order to determine the date of blood sterilization. Thereafter, routine culturing can be discontinued. If blood cultures remain positive, then a search for a metastatic focus should be performed with considerations of an abscess or endocarditis as leading considerations.

In addition, all patients should have resolution of symptoms attributable to the candidemia, and for neutropenic patients, they should have demonstration of resolution of their neutropenia, which means that their cell count should be more than 500 per milliliter.

All patients who have candidemia, whether they have ocular symptoms or not, should undergo a formal ophthalmologic examination to look for evidence of endophthalmitis as recommended by these same 2009 IDSA guidelines. So answer B is correct.

Duration of Antifungal Therapy for Candidemia

- IDSA recommends minimum of 2 weeks after sterilization of blood cultures, AND/OR
- Resolution of all attributable symptoms
- Neutropenic patients should demonstrate resolution of neutropenia

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Endophthalmitis Caused by *Candida*

- All patients with candidemia should undergo an ophthalmologic examination – regardless of symptoms
- Amphotericin B, liposomal Amphotericin B or azoles are the preferred initial agents as echinocandins have poor ocular penetration

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Typically, this may not be immediate, as retinal findings may take 3 to 5 days to develop once positive blood cultures are identified. In some patients, galactomannan antigen can be detected in the serum before the presence of clinical signs or symptoms of invasive aspergillosis. Many fungi contain galactomannans on their cell walls, thus positive results of the aspergillus galactomannan EIA can be seen with other organisms, including ascomycetes, penicillium and histoplasmosis, for examples, that seem to share cross-reacting antigens.

Before we go on with our case, we learn that the organism was *Candida glabrata*. This organism does warrant a bit more discussion. For starters, let me present our next clinical question.

Which of the following statements regarding *Candida glabrata* is incorrect?

- A. Incidence of *C. glabrata* infection has increased and accounts for a significant percentage of candidemia.
- B. *C. glabrata* is universally resistant to azoles.
- C. *C. glabrata* isolates can display cross-resistance among azoles.
- D. The echinocandins have generally retained excellent activity against *C. glabrata*, although isolated cases of resistance have been reported.

Candida albicans is the most common cause of candidemia, however the incidence of candidemia from non-*albicans* species has increased in recent years. For example, one multicenter surveillance study performed in the United States between 2004 and 2008, found that 54% of bloodstream isolates were non-*albicans* species. So, knowledge of your local prevalence of non-*albicans* species is important to any clinician because susceptibility to antifungal agents does vary among the species. In general, all isolates of *Candida krusei* are intrinsically resistant to fluconazole, and a significant portion of *Candida glabrata* are also fluconazole resistant.

A small but variable portion of *Candida albicans* display resistance to fluconazole usually under 5%. Resistance to fluconazole has been found though in other species, such as *Candida parapsilosis* and *Candida tropicalis*.

In addition, the mean inhibitory concentration for *Candida parapsilosis* among the echinocandin class is higher than for other *Candida* species, though this is not generally believed to be significant in actual clinical use.

Causes of Candidemia

- *C. albicans* – most common fungus
- However, non-*C. albicans* infections are growing
- Fluconazole resistance seen with *C. krusei*, *C. glabrata*, *C. albicans*, *C. parapsilosis* and *C. tropicalis*

Hachem R, et al. *Cancer*. 2008;112(11):2493-2499.
Pappas PG, et al. *Clin Infect Dis*. 2009;48(5):503-35.
Cuenca-Estrella M, et al. *J Antimicrob Chemother*. 2005 Feb;55(2):194-9. Epub 2004 Dec 23.
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Antifungal Resistance Patterns

General Patterns of Susceptibility of *Candida* species
I=Intermediate susceptible; R=resistant; S=susceptible; S-DD=dose dependent susceptibility

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Echinocandins
<i>C. albicans</i>	S	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S	S
<i>C. parapsilosis</i>	S to R	S	S	S	S	S	S to R
<i>C. glabrata</i>	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
<i>C. krusei</i>	R	S-DD to R	S	S	I to R	S to I	S
<i>C. lusitanae</i>	S	S	S	S	S	S to R	S

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General patterns of susceptibility of common *Candida* species are provided in the 2009 IDSA Clinical Practice Guidelines. Risk factors for fluconazole-resistant *Candida* species include neutropenia and prior azole use.

Candida glabrata

- Many isolates are resistant to azoles
- Cross-resistance among the azoles is common
- Isolates resistant to fluconazole are generally resistant to voriconazole as well
- For severe infections and critically ill patients an echinocandin should be used for empiric therapy until susceptibilities can be confirmed

Spellberg BJ, et al. *Clin Infect Dis*. 2006;42(2):244-251.
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Historically, *Candida glabrata* has been considered a relatively nonpathogenic saprophyte of the normal flora of healthy individuals and rarely a serious cause of infection.

However, with the increased and widespread use of immunosuppressive therapies, as well as broad-spectrum antibacterial therapies, the frequency of both mucosal and systemic infections by *Candida glabrata* has increased. Many of the *Candida glabrata* isolates found resistant to azoles seem to be due to changes in drug efflux mechanisms.

This type of resistance can be overcome somewhat by using higher doses of fluconazole. Cross resistance among the azoles is common for *Candida glabrata*. Among *Candida* species, the

MICs for voriconazole are the highest with *Candida glabrata*. Isolates that are resistant to fluconazole are

generally resistant to voriconazole as well. So this does mean that answer B is correct.

So let's get back to our case. The patient's condition stabilizes and his blood cultures are negative starting on the third day after the central catheter is removed. He remains on micafungin and appears to be tolerating the drug with no adverse events. He is ultimately discharged to an inpatient rehabilitation facility and completes three additional days of antifungals, which consists of a 14-day course of total therapy and continues with physical rehabilitation.

Ophthalmologic consultation was not requested, and the patient never had any visual complaints. One week after completing antifungals, he complains of severe shortness of breath, sweats, and pain at the tips of several fingers. He is taken to your emergency room department, where it is noted that he has a fever to 39 degrees Celsius. He also has a new onset murmur of aortic regurgitation in addition to a previously-determined mitral regurgitant murmur in several nodules on his fingers. A transthoracic echocardiogram is ordered and demonstrates a large mobile vegetation on his aortic valve.

Due to the patient's recent history, you suspect *Candida* endocarditis. This does lead us to our next clinical question.

Which of the following statements regarding *Candida* endocarditis is correct?

- A. *Candida spp.* are uncommon causes of fungal endocarditis.
- B. Diagnostic criteria are different for endocarditis from *Candida* when compared to bacterial endocarditis.
- C. Risk factors for *Candida* endocarditis in adults include prosthetic heart valves or other valvular disease, intravenous drug use and indwelling central venous catheters.
- D. Recent studies have demonstrated superior outcomes with medical management without surgical intervention.

Candida endocarditis is the most common form of fungal endocarditis, accounting for greater than half of all cases, and is among the most serious manifestations of candidiasis with mortality rates of 30% to 50%. Clinical manifestations of *Candida* endocarditis include traditional signs and symptoms of valvular involvement, including shortness of breath, pulmonary edema, chest pain, new or changing murmurs on exam, embolic phenomena and systemic symptoms, which might include fever, night sweats, malaise, and weight loss.

Specifically, for *Candida*, risk factors for endocarditic involvement includes presence of prosthetic heart valves or other valvular abnormalities, intravenous drug use, presence of indwelling central venous catheters, in neonates very low birth weights. So the answer, therefore, is C.

Endocarditis Caused by *Candida*

- Most common form of fungal endocarditis
- Mortality rate of 30-50%
- Symptoms include: dyspnea, edema, chest pain, and new or changing murmurs, embolic phenomena and systemic symptoms

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Risk-Factors for *Candida* Endocarditis

- Prosthetic heart valves or other valvular disease
- Intravenous drug use
- Indwelling central venous catheters
- Low-birth weight in neonates

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The diagnostic criteria for *Candida* endocarditis are similar to those for bacterial infections, though much less common, accounting for less than 2% to 3% in most series. Blood cultures usually show persistent *Candida* infection and echocardiography frequently reveals large vegetations.

A combined medical and surgical approach is recommended for the treatment of either native or prosthetic valve *Candida* endocarditis, according to the 2009 IDSA document. The therapeutic regimen most frequently used historically was amphotericin B, with or without 5-flucytosine. While most of the reported experience is with amphotericin B deoxycholate, using a dose of 0.7 to 1 mg/kg IV daily, now lipid formulations are preferred, and most patients are now treated with lipid formulations dosed somewhere between 3 to 5 mg/kg daily, usually the liposomal product.

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.

Resection of the affected valve and any associated abscesses is viewed as essential for cure in most but not all patients. Following surgery, antifungal therapy should be continued for a minimum of six weeks. Although the preferred regimen is amphotericin B with or without flucytosine, after the patient's condition is stabilized and blood cultures remain negative, therapy can be changed to oral fluconazole with dosings of between 400 to 800 mg, or 6 to 12 mg/kg daily if the organism is found to be susceptible to complete the course of therapy.

If the Patient Cannot Undergo Surgery

- Use amphotericin B formulation plus flucytosine followed by lifelong suppression with oral fluconazole (400 to 800 mg [6-12 mg/kg] daily) is recommended

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Because of the significant rates of relapse, many clinicians opt for longer courses, especially if valve replacement is not undertaken. For patients who cannot undergo valve resection, initial treatment with amphotericin B products plus flucytosine, followed by lifelong suppression with oral fluconazole, usually in doses of between 400 to 800 mg a day is recommended.

In patients with *Candida glabrata* endocarditis, voriconazole should be used for chronic suppressive therapy if the organism is susceptible, and an echinocandin could be used if the organism is resistant to typical oral agents. *Candida* has long been associated with significant morbidity and mortality. Such a fungemia should always prompt investigation for the source of bloodstream infection.

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.

Species identification and in vitro resistant testing will further help identify the best path to achieve a durable cure.

Management of *Candida* Endocarditis

- IDSA guidelines recommend combined medical and surgical approach
- Liposomal amphotericin B, 3-5 mg/kg daily + oral flucytosine 100 mg/kg daily in four divided doses is recommended
- Removal/replacement of the affected valve and tissue
- Continue antifungal therapy for at least six weeks following surgery
- Switch to oral fluconazole 400 to 800 mg (6-12 mg/kg) daily to complete course of therapy

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Endocarditis Caused by *C. glabrata*

- Use voriconazole for chronic suppressive therapy, if susceptible
- Use echinocandin if resistant to oral agents

Pappas PG, et al. *Clin Infect Dis.* 2009;48(5):503-35.
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CLINICAL PEARL

Management of invasive candidiasis has changed in the past decade. Both epidemiology and the emergence of resistance in both the triazoles and echinocandins means that clinicians now should take some important historical information to determine if risk factors are present that would help inform the best treatment for their patients.

So-called combination clinical prediction rules, as well as early treatment now often using an echinocandin for our most severely-ill patients, seems to be the best course of action, although once patients are stabilized, stepdown therapy to oral azoles can certainly be considered.

Familiarity with these changes among clinicians will lead to declining mortality in patients with candida.

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

“eCase Challenge #3 – Cryptococcosis”

In this, we'll evaluate a patient who develops an invasive cryptococcal infection.

Patient History

- 28-year-old male presents to ER
- Febrile
- Nuchal rigidity
- Photophobia
- Molluscum-like lesion on chest wall
- Lumbar puncture shows elevated opening pressure, WBCs, and protein
- Gram stain shows moderate PMNs
- Serum *Cryptococcus* antigen positive

Slide 1

You are seeing a 28-year-old man in your emergency room in Southern California in midsummer. His level of alertness is waxing and waning and he's unable to provide any additional history. On exam, he is febrile with nuchal rigidity and photophobia. He has no focal neurological deficits identified.

Pulmonary, cardiac and abdominal exams are unremarkable. However, you do make note of a molluscum-like lesion on his chest wall. A head CT was unremarkable, as was a fingerstick blood glucose measurement.

You suspect meningitis and perform a lumbar puncture. The preliminary results show the opening pressure to be 35 cmH₂O, which is elevated, a white blood cell count in the CSF of

300 cells/mm³ (90% L). Red blood cells are absent, but the CSF protein is high at 150 mg/dL, but CSF glucose is in normal range at 55.

Gram stain does not show any organisms present. The serum cryptococcal antigen returns positive. So now let's pose the first clinical question.

Which of the following options is an appropriate next step in the management of this patient?

- No further management, await culture results.
- Start vancomycin + ceftriaxone at meningitis treatment doses, await culture results.
- Start vancomycin + ceftriaxone at meningitis treatment doses. Perform a rapid HIV test, start amphotericin only if positive.
- Start vancomycin + ceftriaxone at meningitis treatment doses. Start amphotericin B + flucytosine for empiric treatment of *Cryptococcus* meningitis.

Cryptococcus species are yeast-like round fungi found worldwide in soil. Cryptococcosis in humans is caused predominantly by two species, *Cryptococcus neoformans* and *Cryptococcus gattii*. These species have been further subdivided into several genotypes. Only in rare circumstances are other cryptococcal species found to cause human infection.

Patient Evaluation

- Lumbar puncture consistent with meningitis
- Empiric therapy recommended while awaiting microbiology results

Slide 3

CSF lymphocytosis may also typically trigger concern for either viral or tubercular infections if the CSF cryptococcal antigen had, in fact, been negative.

Cryptococcal infection is the fourth most common opportunistic infection identified in patients with AIDS. Humans likely become infected with *Cryptococcus neoformans* by inhaling spores, which following can cause a focal pneumonitis that may or may not be causing symptoms.

This pneumonitis may resolve and therefore be self-limited, or the organism can then disseminate to other sites. Lumbar

Cryptococcus Infections

- Caused primarily by *Cryptococcus neoformans* and *Cryptococcus gattii*
- Fourth most common opportunistic infection in patients with AIDS
- Inhalation likely route of infection

Velagapudi R, et al. *Infect Immun*. 2009;77(10):4345-4355.
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Slide 2

puncture results in this patient are consistent with meningitis, and so empiric therapy for bacterial and fungal infections should be started while awaiting results of cultures.

Despite the lack of information regarding risk factors for cryptococcal meningitis, the high opening pressure should raise suspicion also for this particular infection. Therefore, the correct answer is D.

Serum cryptococcal antibody testing is not particularly helpful in diagnosing active infection, and therefore not used clinically. Detection of the cryptococcal capsular polysaccharide antigen in the serum or CSF is a compelling test if found to be positive. Commercially, there are primarily two types of tests, either the latex agglutination or the ELISA test. Both are rapid, and their sensitivity and specificities range between 80% to 95% for meningitis and 20% to 50% in non-meningeal presentations.

Diagnosing *Cryptococcus* Infections

- **Rapid testing available**
 - Detection of cryptococcal capsular polysaccharide antigen
 - Serum or CSF
- **Latex agglutination and ELISA systems available**
 - Sensitivity and specificity:
 - Meningoencephalitis: 80-95%
 - Non-meningeal presentations: 20-50%

Perfect JR, et al. *Clin Infect Dis.* 2010;50(3):291-322.
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Slide 4

***Cryptococcus* Lateral Flow Assay**

- Simple, inexpensive dipstick test
- Urine, serum, CSF or plasma samples
- Provides rapid results
- Potential use at “point-of-care”

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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. This lateral flow assay compares favorably to the older tests, which are the latex agglutination and the ELISA.

Especially in low resource settings, the lateral flow assay does offer advantages, including rapid turnaround time and minimal requirements for specialized laboratory with potential use as a point-of-care test with low cost.

Before we present more of this clinical case, we do have another question to ask.

Which of the following conditions does not increase the patient's risk for cryptococcal infection?

- A. AIDS.
- B. Organ transplantation.
- C. Cystic Fibrosis.
- D. Prolonged treatment with glucocorticoids.

The vast majority of patients with cryptococcosis are immune compromised. So patients with cystic fibrosis are not at increased risk for infection, making answer C the correct one.

In higher income countries, the burden of patients with cryptococcal disease largely consists of those with HIV infection or patients who receive high-dose corticosteroids or other immunosuppressive agents, which do include TNF inhibitor biologics, such as alemtuzumab and infliximab.

It should be noted, however, that not all patients with *Cryptococcus* have a demonstrable immune

Risk Factors for Cryptococcosis

- **AIDS: particularly with CD4 <100 cells/mm³**
- **Prolonged treatment with glucocorticoids**
- **Organ transplantation**
- **Malignancy**
- **Sarcoidosis**
- **Diabetes**
- **Idiopathic CD4 lymphopenia**
- **Anti-TNF inhibitor therapy**

Perfect JR, et al. *Clin Infect Dis.* 2010;50(3):291-322.
Pappas PG, et al. *Clin Infect Dis.* 2001;33(5):690-9.
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defect, host issue or iatrogenic explanation. In fact, if HIV-infected patients were excluded, approximately 20% to 30% of patients with disseminated cryptococcosis will present with no apparent underlying risk factors or diseases.

Case Continued

- Patient started on liposomal amphotericin B plus flucytosine
- Repeat lumbar puncture shows continued elevated opening pressure

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It's now time to get on with the case. You start the patient on broad-spectrum antibacterials, as well as liposomal amphotericin B plus flucytosine for presumed cryptococcal meningitis. His symptoms continue and a lumbar puncture repeated after 48 hours of antifungal therapy shows an opening pressure that's even higher at 40 cmH₂O.

This does bring us to the next clinical question.

How should the intracranial hypertension, which is now quite significant, be managed?

- A. Start mannitol to reduce intracranial pressures.
- B. Repeat LP to remove fluid, remove volume until headache resolves.
- C. Reduce the opening pressure by 50% or to a normal pressure of 20 cmH₂O by high volume lumbar puncture.
- D. Placement of CSF lumbar drain.

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. Mannitol has no demonstrable benefit and is not routinely recommended for management.

Management of Intracranial Hypertension

- Increased CSF pressure = increased morbidity and mortality
- Relieve by CSF drainage
 - If CSF pressure is ≥ 25 cmH₂O **PLUS**
 - Symptoms of increased intracranial pressure
- Method: usually serial lumbar punctures

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Management of Intracranial Hypertension

- Refractory elevation intracranial pressures:
 - Temporary percutaneous lumbar drains
 - Ventriculostomy
- Permanent CSF shunts
 - Place only if more conservative measures fail
 - Can place with active infection, without CNS sterilization

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Perfect JR, et al. Clin Infect Dis. 2010;50(3):291-322.
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If intracranial pressures are greater than or equal to 25 cmH₂O and there are symptoms of increased intracranial pressure during early induction therapy, relief by repeated CSF drainage is recommended. Therefore, the correct answer is C. Temporary percutaneous lumbar drains or even a ventriculostomy may be considered in persons who required repeated daily lumbar punctures. Permanent ventriculoperitoneal shunts should only be placed if more conservative measures fail to control increased intracranial pressures.

Such a more permanent shunt can be placed during active infection though, without completely sterilizing the cerebrospinal fluid. Now let's get back to our case.

Case Continued

- CSF sample grows *Cryptococcus spp.*
- Bacterial cultures remain negative
 - Patient tests negative for HIV infection
 - Patient has normal renal and liver function

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The CSF fluid cultures do yield *Cryptococcus species* after 72 hours of incubation, thereby absolutely confirming the diagnosis of cryptococcal meningitis. Bacterial cultures are negative and therefore the antibacterial drugs are stopped.

HIV 1 and 2 antigen and antibody tests return negative, as does an RT-PCR for HIV virus. The patient's absolute CD4 cell count is 1,005 cells/mm³, which falls well within range of this T-cell value. Also, the patient appears to have normal renal and liver function.

This presents us with another clinical question.

What length of induction therapy is generally recommended in the non-HIV-infected, non-solid organ transplant patients with cryptococcal meningoencephalitis?

- A. Continue until CSF Cryptococcal antigen is negative.
- B. 4 weeks.
- C. 8 weeks.
- D. Undefined, continue until resolution of headaches.

Treatment of cryptococcal neoformans meningoencephalitis consists of antifungal therapy, management of intracranial pressure, and reducing immunosuppressive therapies, if present. The 2010 guidelines for the management of cryptococcal disease from the Infectious Diseases Society of America, or IDSA,

Treatment of *Cryptococcus neoformans* Meningoencephalitis

- Administer antifungal therapy
- Manage intracranial pressure
- Reduce immunosuppressive therapy

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Principles of Antifungal Treatment for Cryptococcal Meningoencephalitis

- Treatment is divided into 3 phases
 - Induction
 - Consolidation
 - Maintenance

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provides guidance on this topic. However, in brief, management is divided into three phases. These are referred to as the induction phase, the consolidation phase, and then the maintenance phase. Three patient groups are recognized with individualized recommendations: HIV-infected hosts, organ transplant recipients, and then all others.

In the non-HIV-infected non-transplant host, the polyene antifungal amphotericin B plus flucytosine for at least four weeks is recommended as induction therapy in persons without neurologic complications in whom the CSF yeast culture results are negative at the two-week treatment mark. Therefore, the correct answer is B.

Cryptococcal Meningoencephalitis Treatment in Non-HIV, Non-transplant Patients

- **Induction:**
 - AmBd + flucytosine **≥4 weeks**
- **Consolidation:**
 - Fluconazole 400-800 mg/day x **8 weeks**
- **Maintenance:**
 - Fluconazole 200-400 mg/day x **6-12 months**

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Amphotericin B Deoxycholate for Cryptococcal Meningoencephalitis

- Drug of choice for *C. neoformans*
- Acetaminophen and diphenhydramine can reduce infusion-related reactions
- Monitor for nephrotoxicity, hypokalemia and hypomagnesemia
- Lipid preparations have reduced nephrotoxicity and infusion-related reactions

Perfect JR, et al. *Clin Infect Dis.* 2010;50(3):291-322.
Amphotericin b injection, powder, lyophilized for solution. Ben Venue Laboratories. Revised September 2009.
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In HIV-infected people, or in those receiving organ transplants, a shorter induction phase is recommended. Amphotericin B deoxycholate is the standard drug and used with great history in serious infections caused by *Cryptococcus neoformans*, including CNS infections. Cryptococcal meningitis is one of the few routine uses for this drug currently. However, infusion-related reactions can be reduced by pretreating with acetaminophen and diphenhydramine prior to giving the amphotericin B deoxycholate.

Patients should be monitored for nephrotoxicity, as well as electrolyte imbalances, including potassium and magnesium while on therapy. Amphotericin B lipid formulations do have advantages of reduced nephrotoxicity and reduced infusion-related side effects. Hence, many clinicians now favor their use. Fever and rigors can still be produced even with the use of liposomal amphotericin B.

Flucytosine, also known as 5-FC, is a fluorinated pyrimidine analog that interferes with fungal RNA and DNA synthesis. It should not be used as monotherapy due to concern for emergence of resistance. It is usually combined with the polyene products, so that it has additive or synergistic effect in combination. Doses should be reduced if renal function is not in normal ranges.

The main side effects of 5-FC include gastrointestinal intolerance, such as diarrhea, abdominal pain and potential bone marrow suppression. Antifungal therapy should be given that yields rapid sterilization in the CSF, but clinicians should be aware that the cryptococcal antigen will persist for many weeks and does not reflect clinical failure.

Flucytosine for Cryptococcal Meningoencephalitis

- **NOT used as monotherapy**
- Usually combined with polyene products
- Dose adjustment for renal function
- **Main side effects:**
 - GI intolerance
 - Hepatic dysfunction
 - Bone marrow suppression

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Principles of Treatment

- Antifungal therapy should rapidly sterilize CSF
- Lumbar puncture assessment at 2 weeks
- Combination therapy for induction may be needed if patient does not respond

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Lumbar puncture assessment at two weeks with negative cultures is associated with more favorable outcomes. Combination induction therapy may need to be continued if the patient remains comatose, has not improved, or is deteriorating and has persistently elevated intracranial pressures, and if there are still positive CSF cultures at the two-week mark.

In HIV-positive patients, maintenance therapy with oral fluconazole 200 mg daily should be continued for long-term suppression for a minimum of one year, although maintenance therapy can be discontinued if the patient has achieved sufficient immunologic recovery with antiretroviral therapy, such that CD4 counts are greater than 100 cells/mm³.

Treatment of organ transplant recipients generally follows a plan for HIV-infected people, with the exception of a defined course of maintenance therapy that is limited to 6 to 12 months.

For complete treatment recommendations, review Tables 2-4 from: 'Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America'.

Cryptococcal Meningoencephalitis in HIV-infected and Organ Transplant Patients

- AmBd + flucytosine x 2 weeks
- Combination therapy for induction may be needed if patient does not respond
- HIV-infected patients:
 - Maintenance: fluconazole 200-400 mg/day >1 year
 - Discontinue if CD4 counts recover to >100 cells/mm³
- Organ transplant recipients:
 - Maintenance: fluconazole 200-400 mg/day x 6 to 12 months

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Case Continued

- Patient responsive following 6 days of liposomal amphotericin B plus flucytosine
- Recently moved from Seattle
- No past medical history
- Previous STD screening negative

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For patients without central nervous system involvement, but yet still have severe disease, including pulmonary infection, or at least two noncontiguous sites, these patients should be managed just the same as for central nervous system infection, even in the setting of normal findings on CSF exam.

Now the case continues. After six days of antifungal therapy and an additional lumbar puncture to manage the intracranial pressure, the patient is more awake. Your patient provides additional history by telling you that he recently moved to your area from Seattle, where he saw his primary care physician annually. He has no medical history of any significance and was screened for venereal diseases one month ago.

The next question is as follows.

How does this additional information change your management plan?

- A. No change in management is indicated.
- B. Change to fluconazole as the patient likely has *Cryptococcus gattii* infection.
- C. Complete entire treatment with amphotericin B as *Cryptococcus species* from this region tend to be resistant to azoles.

The genus *Cryptococcus* includes over 37 species. There are two species of particular relevance in human infections. The first, *Cryptococcus neoformans*, is divided into four serotypes, A through D, based upon capsular components. Among these four *Cryptococcus neoformans*, *variation neoformans*, and *Cryptococcus neoformans variation grubii*, both cause human disease.

The second species, *Cryptococcus gattii*, is 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. In 2001, public health authorities in southwestern British Columbia noted an increased incidence of human and animal cryptococcosis. *Cryptococcus gattii serotype B* was isolated from human and animal cases associated with recognition of this outbreak.

Cryptococcus ssp.

- *C. neoformans var. neoformans* and *C. neoformans var. grubii* cause human diseases
- *C. neoformans var. grubii* seen in Australia, Western Canada and Pacific Northwest

Datta K, et al. *Emerg Infect Dis*. 2009;15(8):1185-91.
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Treatment Considerations

- Request cryptococcal isolate be speciated
- *C. gattii* more virulent
- Treatment same for *C. gattii* and *C. neoformans*

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The human cases were not associated with immune suppression. Because species identification is not routinely carried out in all commercial or hospital laboratories in the United States, the extent of the impact of cases of *Cryptococcus gattii* infection that were identified in Washington, Oregon, and elsewhere in the United States is not completely known. In patients without risk factors, the treating clinician should request that the cryptococcal isolate be speciated.

Cryptococcus gattii, unlike *Cryptococcus neoformans*, is mostly seen in normal hosts, has a relatively reduced susceptibility to fluconazole, and appears to be more virulent. Despite these attributes, recommendations for the treatment remain the same as for *Cryptococcus neoformans*. Therefore, the correct answer is A.

Cryptococcus has evolved into a major invasive fungal disease of humans. Its primary epidemiology has been focused on three major outbreaks of disease that reflect both the changing environmental exposures and the growth of host risk factors.

Improved understanding of the yeast pathobiology has led to the development of point-of-care simple and cheap testing, which utilizes a lateral flow assay for antigen detection. Treatment of severe infection is accomplished with antifungals, supportive measures, and reversal or control of immune suppression. A clinician does need to be familiar with all aspects of care to help ensure successful outcomes.

Cryptococcosis Management

- Simple, “point-of-care” tests available
- Treatment focused on:
 - Antifungal therapy
 - Supportive measures
 - Reversal of immunosuppression

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CLINICAL PEARL

Cryptococcus is a ubiquitous fungal organism that causes predominately meningitis and pneumonia. The two species of *Cryptococcus* that cause the vast majority of human infections are *Cryptococcus neoformans* and *Cryptococcus gattii*. While *Cryptococcus neoformans* has a clear predilection for causing disease in immunocompromised people, in contrast *Cryptococcus gattii* is associated with causing illness in immunocompetent people, many of whom live in tropical and subtropical regions, and it is an emerging pathogen in the United States.

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.

Having a heightened suspicion of the changing epidemiology may prove useful to clinicians who might identify patients, such as this case, who are presenting with a meningitis, yet don't have traditional risk factors. This will lead to earlier initiation of treatment and perhaps better outcomes.

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