**Clinical Case Segment**

Vignette: A 35-year-old Caucasian woman with acute lymphocytic leukemia (ALL) underwent total body irradiation and allogeneic bone marrow transplantation 2 weeks ago. She is currently in the intensive care unit because of an increased severity of illness while awaiting stem cell engraftment. She developed *Acinetobacter* pneumonia and is on day 7 of piperacillin/tazobactam and tobramycin. Because of high fevers (temperatures as high as 40.6°C), decreasing mental status, decreased urine output, increased sputum production, and worsening respiratory function over the past 48 hours, she has been intubated and placed on a mechanical ventilator. Chest radiography and computed tomography scan reveal a left lower lobe infiltrate with a halo sign. A sputum sample is sent to the laboratory for culture.

Past Medical History: ALL, hypertension, anemia, atrial fibrillation

Social History: Noncontributory, no alcohol, occasional marijuana use

Current Medications: Piperacillin/tazobactam 4.5 g every 6 hours, tobramycin 7 mg/kg every 24 hours, oxycodone 5–10 mg every 4 hours as needed, furosemide 20 mg twice daily, simvastatin 40 mg daily, cyclosporine 200 mg twice daily, prednisone 20 mg daily, and filgrastim 300 mcg every 24 hours

Allergies: No known drug allergies

Vital Signs: Temperature 40.1°C; heart rate 100 beats/minute; respiratory rate 23–48 breaths/minute; weight 72.1 kg; height 168 cm; blood pressure 94/50 mm Hg

Laboratory Values: White blood cell count 3 x 103 cells/mm3(3/ x109 cells/L) platelet count 390,000/mm3 (3.9 x109/L) sodium 136 mmol/L; potassium 4.3 mmol/L; chloride 99 mmol/L; bicarbonate 18 mmol/L; glucose 196 mg/dL (10.8 mmol/L); blood urea nitrogen 38 mg/dL (13.6 mmol/L); serum creatinine 1.8 mg/dL (159.2 micromoles/L); INR 1.6

Procedure Data: Blood and sputum cultures: Pending

Microscopic evaluation of sputum reveals filamentous fungi (mold), likely *Aspergillus* spp. (species identification to follow)

Galactomannan enzyme-linked immunoassay was positive at 1.8 (normal range 0–0.8).

Other Data: Intravenous lines: 2 peripherals, 1 arterial line, 1 triple lumen peripherally inserted central catheter

**Question 1**

What risk factor is **least** likely to be contributing to this patient’s susceptibility to an invasive mold infection?

1. Age
2. Allogeneic bone marrow transplantation
3. Broad-spectrum antibiotics
4. Cyclosporine

Answer: 1. Age

Rationale: Common risk factors for invasive mold infection are immunosuppression, hematologic malignancy, bone marrow transplantation, neutropenia, and broad-spectrum antibiotics.

Citation: Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327-60.

**Question 2**

What is the most appropriate antifungal regimen to treat this patient’s invasive *Aspergillus* infection?

1. Amphotericin B deoxycholate intravenously
2. Caspofungin intravenously
3. Posaconazole oral suspension
4. Voriconazole intravenously

Answer: 4. Voriconazole intravenously

Rationale: Voriconazole is the treatment of choice for a patient with an invasive *Aspergillus* infection, according to the guidelines. Amphotericin is considered an alternative, but the deoxycholate product should not be used in this patient with renal insufficiency. Caspofungin is approved for salvage therapy only or can be added as a combination agent with weak evidence. Posaconazole is an alternative, but it is not preferred because of the lack of data compared with voriconazole, and intravenous therapy is preferred because of erratic suspension bioavailability.

Citation: Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327-60.

**Question 3**

A major drug interaction with voriconazole requires a dose reduction for which of the patient’s current medications?

1. Cyclosporine
2. Filgrastim
3. Furosemide
4. Prednisone

Answer: 1. Cyclosporine

Rationale: Voriconazole is a major inhibitor of the cytochrome P450 (CYP) enzyme system and will significantly increase the cyclosporine concentration, requiring a dose reduction. No interaction is present with voriconazole and filgrastim or furosemide. The interaction with prednisone is not major and requires no empiric dose adjustment, just additional monitoring.

Citation: Romero AJ, Le Pogamp P, Nilsson LG, et al. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther 2002;71:226-34.

**Question 4**

A voriconazole trough concentration in this patient is 0.4 mg/L. A genetic polymorphism in what enzyme might be responsible for the subtherapeutic voriconazole concentration in this patient?

1. CYP2C19
2. CYP2D6
3. CYP3A4
4. UDP-glucuronosyltransferase

Answer: 1. CYP2C19

Rationale: Two common polymorphisms present in Caucasians (*CYP2C19\*2* and *CYP2C19\*17*) are associated with decreased or increased CYP2C19 activity, resulting in altered voriconazole concentrations.

Citation: Lamoureux F, Duflot T, Woillard JB, et al. Impact of *CYP2C19* genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. Int J Antimicrob Agents 2016;47:124-31.

**Question 5**

Which of the patient’s medications could cause a false-positive galactomannan assay result in this patient?

1. Cyclosporine
2. Oxycodone
3. Piperacillin/tazobactam
4. Tobramycin

Answer: 3. Piperacillin/tazobactam

Rationale: Semisynthetic antibiotics such as piperacillin, amoxicillin, and amoxicillin/clavulanate, which are based on natural compounds derived from the genus *Penicillium*, cross-react with the rat EBA-2 monoclonal antibody used in the assay. The occurrence of false-positive galactomannan assay results because of treatment with piperacillin/tazobactam should be considered in patients who have no clinical findings associated with invasive *Aspergillus* infection.

Citation: Adam O, Aupérin A, Wilquin F, et al. Treatment with piperacillin-tazobactam and false-positive *Aspergillus* galactomannan antigen test results for patients with hematological malignancies. Clin Infect Dis 2004;38:917-20.