

Management of Febrile Neutropenia: Review Questions

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QUESTIONS

Choose the single best answer for each question.

1. A 38-year-old man with relapsed acute myelogenous leukemia (AML) recently received induction chemotherapy that included high-dose cytosine arabinoside. He is receiving antimicrobial prophylaxis with ciprofloxacin and fluconazole. On hospitalization, he has high fever, oral mucositis, and profound neutropenia. Soon after, he develops hypotension, rash, and acute respiratory distress syndrome. Which of the following is the most likely pathogen responsible for this patient's clinical condition?
 - (A) Viridans streptococci
 - (B) *Pseudomonas aeruginosa*
 - (C) *Candida albicans*
 - (D) *Staphylococcus aureus*
 - (E) Herpes simplex virus (HSV)
2. A 54-year-old woman who is undergoing chemotherapy for multiple myeloma is hospitalized with a temperature of 101°F (38.3°C) and neutropenia. Clinical examination reveals pallor. Her tunneled Hickman catheter site appears normal. The rest of her examination is unremarkable. Blood cultures are obtained, and empiric therapy is started with intravenous cefepime and vancomycin. She remains febrile over the next 3 days with no change in her clinical status. Her blood cultures remain negative, and she remains neutropenic. What is the most appropriate management at this time?
 - (A) Stop all antibiotics
 - (B) Stop vancomycin
 - (C) Stop cefepime
 - (D) Continue current therapy
 - (E) Add amphotericin B
3. A 36-year-old man with AML receives an allogeneic stem cell transplantation. His post-transplantation course is complicated by prolonged neutropenia and fevers. He is started on empiric cefepime, and his fever slowly resolves over the next 6 days. All blood cultures remain negative. Engraftment occurs on day 21 post-transplant. Upon resolution of neutropenia, he develops sudden pain and diminished vision in his left eye. Ophthalmologic examination reveals chorioretinitis of the left eye. What is the most likely pathogen responsible for this patient's symptoms?
 - (A) Cytomegalovirus
 - (B) HSV
 - (C) Methicillin-resistant *Staphylococcus aureus*
 - (D) *Candida* species
 - (E) *Toxoplasma gondii*
4. A 42-year-old man undergoing chemotherapy for non-Hodgkin's lymphoma is hospitalized with fever and chills. He appears clinically stable. Examination reveals no signs of mucositis or infection. His absolute neutrophil count (ANC) is 200 cells/mm³. Blood cultures are obtained, and empiric therapy with imipenem is begun. His fevers subside over the next 2 days. He remains clinically stable, his chest radiograph is normal, and all cultures remain negative. A week after admission, his ANC is 300 cells/mm³ and he is afebrile. What is the next most appropriate course of management?
 - (A) Stop imipenem
 - (B) Continue imipenem until ANC > 500 cells/mm³
 - (C) Add amphotericin B
 - (D) Add granulocyte colony stimulating factor (G-CSF)

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ANSWERS AND EXPLANATIONS

1. (A) **Viridans streptococci.** Viridans streptococci are an increasing cause of blood stream infections in neutropenic patients with cancer.¹ Risk factors include high-dose cytosine arabinoside, antimicrobial prophylaxis with fluoroquinolones or trimethoprim-sulfamethoxazole, severe neutropenia, and oral mucositis. In some patients, a toxic shock-like syndrome (eg, hypotension, rash, palmar desquamation) and rapid progression to acute respiratory distress syndrome can occur. Moreover, there is increasing resistance of viridans streptococci to penicillin and a variety of other antibiotics; hence, vancomycin is the preferred agent for empiric therapy in these situations. Although all of the other pathogens can cause serious infections, viridans streptococci is the most likely pathogen given this clinical scenario.
2. (B) **Stop vancomycin.** Due to an increase in the emergence of vancomycin-resistant organisms (ie, vancomycin-resistant enterococci), the use of vancomycin should be restricted to specific indications. In the febrile patient with neutropenia, the recommended indications for the initial empiric use of vancomycin are: (1) suspected/confirmed catheter-related or skin-soft tissue infections (generally caused by gram-positive organisms), (2) blood culture positive for gram-positive bacteria at initiation of empiric therapy, (3) known colonization with methicillin-resistant *Staphylococcus aureus* or drug-resistant *Streptococcus pneumoniae*, and (4) septic shock.² Because this patient is stable without any of the above-noted features, empiric vancomycin can be safely discontinued at this point. Antimicrobial therapy with cefepime should be continued, and if fever and neutropenia persist beyond 5 to 7 days, consideration should be given to initiating empiric antifungal therapy.
3. (D) **Candida species.** Candidemia can occur in patients receiving cytotoxic chemotherapy with prolonged neutropenia. Disseminated candidiasis, as with other infections, may go undetected owing to the muted inflammatory reaction in the absence of neutrophils. These infections become clinically apparent only after recovery from neutropenia.³ Hepatosplenic infection and retinitis are some of the manifestations of disseminated candidiasis. Cytomegalovirus disease in stem cell transplant recipients generally causes viremia, pneumonia, and gastrointestinal disease;

often, this occurs in the setting of graft-versus-host disease. Acute retinal necrosis caused by HSV generally has been described in immunocompetent persons. Left-sided endocarditis caused by *Staphylococcus aureus* can result in retinal emboli but is unlikely in this patient who has no features of endocarditis and negative blood cultures. Reactivation of toxoplasma infection is rare in stem cell transplantation recipients and occurs in patients with graft-versus-host disease. It can be disseminated and generally affects the brain, heart, and lungs.

4. (A) **Stop imipenem.** The patient is stable without mucositis or signs of infection and has been afebrile for at least 5 to 7 days. Antibiotic therapy can be discontinued and the patient should be monitored. The duration of empiric antibiotic therapy in a febrile patient with neutropenia is determined by the recovery of the neutrophil count ($ANC > 500$ cells/mm³).² If a patient is afebrile with $ANC \geq 500$ cells/mm³ for at least 2 days and if no infection has been identified, empiric antibiotic therapy can be discontinued. If the patient is afebrile by days 3 to 5 but remains neutropenic, the decision to continue treatment with antibiotics is based upon clinical status and risk of infection. In unstable patients with profound neutropenia (ie, $ANC < 100$ cells/mm³) or mucositis, antibiotic therapy generally should be continued during the neutropenic period. If fever and neutropenia persist, consideration should be given to empiric antifungal therapy such as amphotericin B. The role of colony-stimulating factors, such as G-CSF, in the management of patients with fever and neutropenia is limited. They may be considered in severely neutropenic patients with infections unresponsive to appropriate antimicrobial therapy.

REFERENCES

1. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis* 2002;34:1524–9.
2. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–51.
3. Walsh TJ, Hiemenz JW, Anaissie E. Recent progress and current problems in the treatment of invasive fungal infections in neutropenic patients. *Infect Dis Clin North Am* 1996;10:365–400.