Management of Fever in Neutropenic Cancer Patients: Review Questions

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QUESTIONS

Choose the single best answer for each question.

Questions 1 through 3 refer to the following case study.

A 66-year-old woman presents to her physician with fever, malaise, sore throat, and easy bruisability. She is diagnosed to have acute myeloid leukemia. Following induction chemotherapy, the patient becomes profoundly neutropenic (absolute neutrophil count ≤ 100/mm^3). She is asymptomatic but develops a fever on the third day of neutropenia. Her physical examination, which includes the oral mucosa, indwelling vascular catheter site, heart, lungs, abdomen, and perianal region, is normal except for an oral temperature of 102°F. A chest radiograph is normal, and blood cultures are obtained.

1. Which one of the following measures is most appropriate?

A) Obtain additional tests including sputum, throat, and urine cultures; then initiate treatment with appropriate empiric antimicrobial therapy
B) Await results of blood cultures and initiate empiric antimicrobial therapy if clinical deterioration occurs
C) Initiate empiric therapy with imipenem and vancomycin
D) Initiate empiric therapy with cefepime
E) Initiate empiric therapy with ceftazidime and tobramycin

2. Two sets of blood cultures grow gram-positive cocci in clusters. The patient appears clinically stable except for continued fever. What is the most appropriate next step?

A) Await identification and antibiotic susceptibility of the organism before modifying antimicrobial therapy
B) Remove the indwelling intravascular catheter
C) Initiate therapy with vancomycin
D) Obtain additional blood cultures via catheter and peripheral vein

3. The gram-positive cocci in the patient's blood are identified as methicillin-resistant coagulase-negative staphylococci. Despite appropriate management for the next 6 days, fever persists. Again, the patient appears stable with no other symptoms or signs of infection. Repeat blood cultures and chest and sinus radiographs are negative. Which of the following is the best next step?

A) Change the patient's antibacterial regimen
B) Continue the same antimicrobial therapy
C) Test for *Clostridium difficile* toxin in stool and perform urinalysis and urine culture
D) Administer empiric antifungal therapy

4. All of the following statements are true EXCEPT:

A) Transfusion of granulocytes is beneficial in the routine management of febrile neutropenia.
B) Acyclovir prophylaxis is appropriate during chemotherapy in patients with a history of severe herpetic infection with prior cycles of chemotherapy.
C) Administration of colony stimulating factors (eg, granulocyte colony–stimulating factor [G-CSF], granulocyte-macrophage colony–stimulating factor [GM-CSF]) is not recommended as adjuvant therapy for neutropenic patients with fever of unknown origin.
D) Antibiotic prophylaxis with a quinolone or trimethoprim-sulfamethoxazole during neutropenia significantly reduces documented gram-negative infection.
E) Both conventional and lipid formulations of amphotericin B have similar success rates in the empiric management of fever unresponsive to antibiotics.

(turn page for answers)

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EXPLANATION OF ANSWERS

1. **(D) Initiate empiric therapy with cefepime.** Fever during neutropenia must be treated as a medical emergency. Generally, presence of infection is assumed, and after a careful examination to exclude a source of fever, empiric therapy with antibiotics is instituted immediately. Failure to do so may result in serious morbidity and mortality. Tests other than blood cultures and a chest radiograph are not necessary prior to therapy, unless clinically indicated. The empiric antibiotics used must be highly active against gram-negative bacteria, particularly *Pseudomonas aeruginosa*, which is believed to originate from the gastrointestinal tract. Imipenem, cefepime, and ceftazidime are effective, and recent data show that monotherapy with these agents is as effective as the traditional combination of an anti-pseudomonal β-lactam plus an aminoglycoside in the treatment of uncomplicated febrile neutropenia. Empiric coverage against gram-positive bacteria with vancomycin is unwarranted unless positive bacterial cultures or clinical findings indicate catheter infection or critical illness in the patient. However, empiric vancomycin may be justified in institutions with a high prevalence of infections caused by methicillin-resistant *Staphylococcus aureus* or *Streptococcus viridans*.
2. **(C) Initiate therapy with vancomycin.** Because blood cultures grew gram-positive cocci in clusters that suggest staphylococci, therapy with vancomycin is appropriate until identification of the organism and its antibiotic susceptibility data become available. There is no reason to wait for further identification of the organism or data from additional blood cultures. The gram-positive cocci are likely to be methicillin-resistant staphylococci (most commonly, coagulase-negative), and, because empiric monotherapy has no reliable activity against the organism, vancomycin must be added to the regimen. Routine vascular catheter removal under such circumstances is not necessary. In most cases, even bacteremias associated with catheter infection may be treated successfully without catheter removal. Vascular catheter malfunction, vascular thrombosis, tunnel infection, or persistent bacteremia are indications for removal of the catheter.
3. **(D) Administer empiric antifungal therapy.** Defervescence after initial antibiotic therapy usually occurs in approximately 3 to 5 days. In the present case, fever persisted despite clearance of bacteremia, suggesting a noninfectious etiology or another source of infection. Among the noninfectious etiologies of fever, drugs and transfusions must be considered. Common infections include herpes simplex or candidal oral mucositis and *Clostridium difficile* colitis. Such infections are usually symptomatic and easily diagnosed and treated. In patients with persistent fever without any other symptoms or signs of infection, an occult systemic fungal infection must be considered. Blood cultures may be negative, and thus empiric antifungal therapy is justified. Failure to use empiric antifungal therapy in neutropenic patients with fever refractory to antibiotics may result in high mortality because of undiagnosed fungal infection. *Candida* is the most common fungus in such cases. Amphotericin B has been the standard empiric antifungal agent. More recently, less toxic fluconazole has been shown to be equally effective. However, if the patient was receiving fluconazole as prophylaxis or if *Aspergillus* is suspected, then amphotericin B must be used for empiric therapy.
4. **(A) Transfusion of granulocytes is beneficial in the routine management of febrile neutropenia (FALSE).** Granulocyte transfusions may be administered to profoundly neutropenic patients with refractory infections. However, no role exists for granulocyte transfusion in the routine management of febrile neutropenia. Acyclovir prophylaxis is effective in the prevention of herpes reactivation during neutropenia. Colony-stimulating factors may be indicated during neutropenia when worsening of the clinical course is predicted and a long delay in marrow recovery is expected. Also, therapy with G-CSF may be justified in patients with severe neutropenia and refractory bacterial or fungal infection. However, these expensive agents are not routinely indicated. Both quinolones (eg, ciprofloxacin, norfloxacin) and trimethoprim-sulfamethoxazole have been shown to reduce gut colonization and decrease infections caused by aerobic gram-negative bacteria. Frequency of gram-positive bacterial and fungal infections is not altered by this strategy. Lipid formulations of amphotericin B and conventional amphotericin B are equally effective in the management of febrile neutropenia. Although the lipid formulation is less nephrotoxic, its cost is prohibitive, and conventional amphotericin B is preferred.