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Evolving concepts in the management of patients with neutropenia and fever

ABSTRACT

Much has changed in the treatment of patients with fever and neutropenia, including the patterns of microbial flora and drug resistance and the drugs used. More patients now have indwelling central venous catheters, exposing them to new types of infections. This article reviews the recent treatment guidelines published by the Infectious Diseases Society of America.

KEY POINTS

Rapid and effective empiric therapy with broad-spectrum antibiotics remains vitally important to prevent rapid demise from sepsis.

Gram-positive organisms have overshadowed gram-negative ones as causes of bacteremia.

Symptoms are extremely important in making a diagnosis, as physical signs of inflammation may be blunted in the absence of white blood cells.

Patients who remain febrile despite antibiotic therapy should receive antifungal therapy.

CHEMOTHERAPY PATIENTS with neutropenia and fever need prompt treatment with powerful, broad-spectrum antibiotics to prevent a rapid deterioration into sepsis and possibly death. But what agents should be used? The patterns of microbial flora and antibiotic resistance have shifted over time and vary from hospital to hospital. What evaluation is needed, when focal signs of infection may be lacking in neutropenic patients? What are the pitfalls?

This review summarizes the key issues in evaluating and treating neutropenia and fever for the internist, and summarizes updated treatment guidelines recently published by the Infectious Diseases Society of America.

NEUTROPENIC FEVER: THEN AND NOW

In the 1960s, physicians started to recognize that when patients receive chemotherapy the risk of infection increases with the duration and degree of neutropenia. The threat of rapidly fatal gram-negative sepsis led to universal acceptance of empiric antibiotic therapy for febrile neutropenic patients, even without a localizing source or positive culture.[1–8]

In those days, the principal organisms isolated from blood cultures were aerobic gram-negative bacilli such as *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*. Combinations of extended-spectrum beta-lactam penicillins (eg, carbenicillin) with aminoglycosides (eg, gentamicin) provided synergistic coverage, became popular, and reduced the mortality rate considerably.[8]

These patterns are changing. Gram-positive organisms such as coagulase-negative

staphylococci, *Staphylococcus aureus*, and viridans streptococci now overshadow gram-negative organisms.[1–7,9] Indeed, in a study of 550 febrile neutropenic episodes at the National Cancer Institute in the 1980s, 63% of bacterial isolates were gram-positive.[9] Moreover, highly resistant organisms are emerging, such as vancomycin-resistant enterococci (VRE) and multiple-drug-resistant gram-negative bacilli.[10] In view of these changes, the Infectious Diseases Society of America (IDSA) published updated treatment guidelines in 1997 for the management of neutropenic fever.[4]

DEFINING FEVER, NEUTROPENIA

Definitions of fever and neutropenia, and therefore the threshold for giving antibiotics, differ from one institution to another. Because it is crucial to start therapy quickly, the IDSA guidelines define these terms as follows.

Fever—a single oral temperature higher than 38.3°C (100.9°F) without an obvious environmental cause, or a temperature of 38°C (100.4°F) or greater lasting at least 1 hour.

Neutropenia—a neutrophil count less than 500/μL, or less than 1,000/μL when a decline to less than 500/μL is predicted.

Start broad-spectrum antibiotics right away

WHO IS AT RISK?

Patients at high risk for infection may require different treatment strategies than patients at low risk for infection (see below).[7] In general, patients at high risk often:

- Have received chemotherapy for leukemia (as opposed to a solid tumor), or have undergone bone marrow transplantation
- Have protracted neutropenia (ie, longer than 7 days).

EVALUATION AND MANAGEMENT

The number-one priority in a febrile neutropenic patient is to begin broad-spectrum, high-dose antibacterial therapy right away. A thorough history and physical examination are also important but should not delay treatment. None of the following information should be used as a criterion for giving antibiotics. The only diagnostic test that needs to be done before antibiotics are started is to obtain two blood samples for culture. Draw these immediately, start the antibiotic infusion, and then finish the evaluation.

Key questions

Key questions to ask in the history are:

- What type of cancer does the patient have?
- What chemotherapy has he or she received, and when?
- How long has neutropenia lasted?
- Has the patient had previous bouts of neutropenia?
- Does he or she take other immunosuppressive medications such as long-term steroids?
- Has he or she had prior infections?
- Does he or she have an indwelling vascular catheter or other foreign body?
- Has the patient recently travelled?
- Are any family members or other contacts ill?
- Has the patient otherwise been exposed to any infectious diseases?

Many possible symptoms, few signs

In your history and physical examination, pay particular attention to the sinuses, nose, pharynx, lymph nodes, chest, heart, abdomen, external perianal area, skin, and vascular catheter sites, and include a focused neurologic examination.

Symptoms are extremely important, since physical signs of inflammation may be blunted in the absence of white blood cells. For example:

A nonproductive cough or shortness of breath is very worrisome, because it might reflect a pulmonary process that may herald respiratory failure. Purulent sputum or evidence of lobar consolidation on examination is often absent in neutropenic patients with pneumonia, and a high index of suspicion is essential.

Shortness of breath, tachypnea, or unexplained tachycardia may be the only sign of impending sepsis.

Abdominal pain may signal a serious process such as typhlitis (cecitis, which may progress to necrosis and gangrene of the right colon), appendicitis, or diverticulitis with rupture, in the absence of peritoneal signs or a "surgical" abdomen on examination.

Odynophagia should prompt consideration of candidal or herpetic esophagitis.

Perianal pain may represent the neutropenic equivalent of a perianal abscess, even in absence of frank signs of inflammation. Inspect the perianal area, but do not do a rectal examination or take the temperature rectally: doing so might cause bacteremia with organisms from the colon or rectum. In unusual cases, a colorectal surgeon may need to perform a drainage procedure under antibiotic coverage.

Diarrhea may be due to *Clostridium difficile* or to less-likely enteric bacterial pathogens or parasites. However, most frequently it reflects chemotherapy-induced gastrointestinal mucositis, which in itself predisposes to bacteremia with gut organisms.

Urinary tract infections. The urinary tract may be a source of infection, especially in a patient who has been previously catheterized. Pyuria is often absent.

A new skin lesion may be a clue to a disseminated bacterial or fungal process. The exit sites of all vascular access catheters should be carefully and aseptically examined for tenderness and drainage. Frank erythema and inflammation may be absent.

Chemotherapy-induced oral mucositis is a possible portal of entry for oral organisms such as streptococci and orally colonizing gram-negative bacilli and yeast.

Pain in the nose, sinuses, or face may represent bacterial sinusitis, but it also raises the specter of rapidly progressive necrotizing faciocranial fungal infection due to *Mucor* or *Aspergillus* species.

Focal neurologic signs of any sort are of extreme concern, and may signify a variety of serious conditions, from intracerebral hemorrhage due to thrombocytopenia, to fungal, bacterial, or nocardial space-occupying lesions.

Laboratory studies

Essential laboratory studies include:

- A complete blood count and differential
- Serum electrolyte levels
- Renal and liver function tests (which help in the choice and dosing of antibiotics)

Cultures. As mentioned above, draw at least two blood cultures. If the patient has a vascular access catheter, culture blood via each lumen of the catheter as well. Urine culture is also recommended. Drainage from any exit sites of vascular catheters or other foreign bodies should be cultured for bacteria, fungi, and in some areas (particularly the southeastern United States) nontuberculous mycobacteria.

Lumbar puncture is *not* generally part of the initial evaluation, because bacterial meningitis is an uncommon cause of fever in this population, and also because thrombocytopenia may make such a procedure hazardous. However, if headache, photophobia, or focal neurologic signs are present, proceed with an urgent evaluation for a possible central nervous system (CNS) infection. This should include imaging studies such as a computed tomographic (CT) scan and magnetic resonance imaging (MRI) to rule out hemorrhage or focal infection. In addition, the patient should receive a regimen including antibiotics with excellent CNS penetration, such as third-generation cephalosporins.

Tests for cytomegalovirus. Although most patients who are neutropenic after standard chemotherapy do not have cytomegalovirus (CMV) infection as a source of fever, this virus is a major source of morbidity after allogeneic bone marrow transplantation, especially in the presence of graft-vs-host disease. Specialized laboratory tests such as the CMV buffy coat or CMV-DNA detection assay may be ordered as befits the individual patient's situation.

Stool samples. If a patient presents with diarrhea, the evaluation may include a stool sample to look for *C difficile* toxin, bacterial pathogens, and ova and parasites if the history suggests exposure to these pathogens.

Culture blood from all lumens of the central venous catheter as well as peripheral blood

Radiographic studies

Obtain a **chest radiograph** and, if you suspect a pulmonary source of infection, a **chest CT scan** may be helpful as well. Radiographic findings in a neutropenic host may be extremely subtle, and a CT scan can detect nodules and infiltrates not evident on a standard chest radiograph, possibly leading to earlier bronchoscopic evaluation and diagnosis.

A CT scan of the abdomen may be very helpful in detecting typhlitis, abscess, hemorrhage, or another focal process if a patient has abdominal pain.

A CT scan of the sinuses may be helpful in patients with appropriate symptoms, with attention to the orbits if an invasive bacterial or fungal process is suspected.

A CT scan or MRI of the brain is indicated in any patient with headache, altered mental status, or focal neurologic signs. Again, the major concerns are intracranial bleeding or focal lesions due to bacterial or fungal infection or metastases.

WHAT ANTIBIOTICS TO USE INITIALLY

Febrile neutropenic patients may not have localizing signs and symptoms that point to a particular site or type of infection. Even if such a localizing feature is present, never restrict antibiotic coverage to common community-acquired pathogens for that site. For example, for an infiltrate on the chest radiograph, do not give only a macrolide or second-generation cephalosporin. Broad-spectrum gram-negative coverage is an essential part of the initial regimen, whether localizing signs are present or not.

Do not restrict antibiotics to common community acquired pathogens

Classically, the initial empiric regimen included an antipseudomonal beta-lactam in combination with an aminoglycoside.[2–8,11] Many centers still use such regimens, though the potential for aminoglycoside toxicity and the decline in *Pseudomonas* bloodstream isolates have prompted other strategies. Today, the choice depends on the microbial flora at your own hospital and the antibiotic resistance patterns of the most commonly seen organisms there.[4]

Monotherapy with a broad-spectrum agent such as ceftazidime, imipenem-cilastatin, or other newer agent has gained favor at some hospitals, including the National Cancer Institute.[3,5,12] However, single-agent empiric therapy may become less effective as gram-negative bacteria become resistant to more agents.[13]

Combinations include:

- An aminoglycoside plus an antipseudomonal cephalosporin (eg, amikacin plus ceftazidime[11])
- An aminoglycoside plus an antipseudomonal beta-lactam such as ticarcillin or piperacillin
- Two beta-lactams such as imipenem plus ceftazidime (although cost and the potential for development of resistance may limit this strategy)
- Vancomycin plus ceftazidime (see below).

Is vancomycin needed?

Whether to include vancomycin in the initial regimen is controversial.[3–6,9,10,14,15] Some clinicians favor giving vancomycin if the patient has a central venous catheter, especially at hospitals with high rates of infection due to methicillin-resistant staphylococci, because the rise in gram-positive isolates has paralleled the widespread use of these catheters. On the other hand, some studies[9] suggested that a viable strategy might be to wait to diagnose a gram-positive infection and then add vancomycin (unlike the situation with a gram-negative infection, in which a delay in empiric therapy can be fatal).

With the rise in vancomycin-resistant gram-positive organisms, especially vancomycin-resistant enterococci (VRE), clinical practice may change with regard to inclusion of vancomycin.[10] In the VRE era, many hospitals are attempting to restrict the use of vancomycin.

We favor using vancomycin in the initial regimen in critically ill patients with hemodynamic instability and no apparent source of infection, and also in patients with clinical evidence of catheter-related infection.

SHOULD YOU REMOVE THE VASCULAR CATHETER?

If a patient has a catheter-related infection, the catheter may need to be removed. However, the decision depends on the organism involved and the anatomic site of infection.

Catheter-related infection has been well reviewed elsewhere.[16,17] In general, gram-positive organisms such as coagulase-negative staphylococci and *S aureus* are the most common causes, although gram-negative bacilli, yeast, enterococci, diphtheroids, and other organisms or polymicrobial combinations sometimes occur.

Catheter removal is usually necessary in tunnel infections or septic thrombophlebitis,

along with appropriate antimicrobial therapy, even in non-neutropenic patients. However, exit-site infection or bacteremia without localizing physical signs may be managed with the catheter in place for certain organisms such as coagulase-negative staphylococci, whereas other organisms such as *Candida* species generally mandate removal of the catheter.

If you do remove the indwelling catheter, do not put in another one right away. Rather, wait until cultures are sterile while giving antibiotics through a peripheral line or a temporary central venous line.

Such recommendations, however, may be difficult to follow when the patient is neutropenic or thrombocytopenic or has a history of multiple thromboses at previous indwelling catheter sites, particularly in the early phases of a bone marrow transplant. Management in such cases must be individualized, preferably with the assistance of an infectious disease specialist.

WHEN TO CHANGE OR STOP ANTIBIOTIC THERAPY

In general, empiric antibiotic therapy can often be safely stopped once the patient is afebrile and has an absolute neutrophil count (ANC) higher than 1,000/μL, unless a definite infection has been diagnosed or complications of infection have occurred. The IDSA guidelines recommend stopping after 7 days if the patient becomes afebrile by the third day and has an ANC of 500 or greater by the seventh day. If a positive culture or defined source of infection has been identified, such as catheter-associated bacteremia, antibiotics are continued to complete an appropriate course of therapy. Some carefully selected patients may be able to finish their therapy at home with oral antibiotics.[4] Some clinicians feel it is safe to discontinue antibiotics earlier in low-risk patients, but this approach has yet to become widespread.[5]

What if the neutrophil count remains low?

For patients afebrile for 5 to 7 days but with persistently low neutrophil counts on the seventh day, clinical practice has varied. The IDSA guidelines say to consider continuing antibiotic therapy, especially for high-risk patients such as those with an ANC less than 100/μL, mucosal lesions of the mouth or gastrointestinal tract, or unstable vital signs.[4] We agree with these recommendations. If you do stop antibiotic therapy in a low-risk neutropenic patient who has been afebrile for 5 to 7 days, it is essential to maintain close monitoring and to resume broad-spectrum antibiotics if any fever or evidence of infection recurs.[4]

What if fever persists?

If the patient remains febrile, the initial regimen can be modified by adding vancomycin, changing the gram-negative agent or agents while maintaining broad-spectrum coverage, or adding anti-anaerobic therapy especially in patients who have developed any abdominal or perianal signs or symptoms or with severe oral mucositis. Continue to search for a source of fever, and obtain studies such as CT scans of the chest and abdomen if not originally obtained.

Start antifungal therapy with amphotericin B if the fever persists for 4 to 7 days, as the incidence of invasive mycoses rises precipitously during this period in febrile neutropenic patients receiving broad-spectrum antibacterial agents.[2–6,18] In fact, some clinicians add amphotericin B earlier if the patient has a history of fungal infection or protracted neutropenia. Although fluconazole can be used prophylactically, particularly in leukemic patients, it does not cover *Aspergillus* species or other filamentous fungi. For patients with renal insufficiency, liposomal amphotericin preparations are an option, but are much more costly. Liposomal preparations appear to be comparable in efficacy to standard amphotericin B, but are less nephrotoxic.

Add antifungal therapy after 4 to 7 days of fever if cultures remain negative

IF LOCALIZING SIGNS DEVELOP

If localizing signs of infection develop, further evaluation should be undertaken urgently.

Pulmonary infiltrates in a febrile neutropenic patient are highly worrisome. Consider bronchoscopy early on, with a full set of microbial stains and cultures performed on the bronchoscopic lavage specimen. This

TABLE 1

Differential diagnosis of abdominal pain in a febrile neutropenic patient

DIAGNOSES	COMMENTS
Conditions that may have altered manifestations in a neutropenic host Appendicitis Diverticulitis Cholecystitis Gastric or duodenal ulcer Intra-abdominal abscess Perirectal abscess Perforated viscus	Peritoneal signs may be absent, and pain with or without fever and hypotension may be the presenting sign. In some cases, rapid surgical evaluation may be lifesaving
Neutropenic colitis/typhlitis	Inflammation of the right colon is often due to *Pseudomonas* or other gram-negative bacilli May progress to necrosis or gangrene
Gastrointestinal graft-vs-host disease	Occurs in allogeneic bone marrow transplant recipients. Carries an attendant risk of secondary bacteremia due to enteric flora
***Clostridium difficile* colitis**	Carries an attendant risk of secondary bacteremia due to enteric flora
Other infections with bacterial enteric pathogens	Eg, *Salmonella* enterocolitis
Cytomegalovirus colitis, gastritis, or esophagitis	Especially in allogeneic bone marrow transplant recipients
Hepatosplenic candidiasis	Especially when the WBC count rises May be associated with right upper quadrant pain, elevated alkaline phosphatase, and CT findings

Pulmonary infiltrates in a neutropenic patient are very worrisome

"infectious disease bronchoscopy panel" may include cultures and stains for routine bacteria, *Legionella* species, fungi, acid-fast bacilli, *Pneumocystis carinii*, *Nocardia* species, cytomegalovirus, and respiratory viruses including influenza, respiratory syncytial virus, parainfluenza virus, and adenovirus.

Abdominal or perianal pain may signal the onset of a serious infectious condition (TABLE 1), and signs and symptoms of peritonitis or inflammation may be masked by the lack of white blood cells. Occasionally, surgical consultation and management may be necessary, as in acute appendicitis, perforated viscus, and some cases of diverticulitis, acute cholecystitis, perianal abscess, and typhlitis. Although a surgical procedure in a neutropenic patient may appear risky, such procedures can successfully be performed with careful attention to ongoing antibiotic coverage and cultures, and may be lifesaving. In many cases, an abdominal CT scan can help define the nature and extent of the process and the indications for surgery, since the physical exam may be misleading.

FEVER AFTER RESOLUTION OF NEUTROPENIA

Fever occasionally recurs after recovery from neutropenia (TABLE 2).

Partially treated or untreated bacterial or fungal infection must be suspected. However, consider the following as well.

Persistent mucositis (oral or gastrointestinal) from prior chemotherapy can contribute to persistent fever.

Hepatosplenic candidiasis can present with concomitant fever, right upper quadrant tenderness, alkaline phosphatase elevation, and characteristic lesions on a CT scan. This condition is more common in patients who have had protracted neutropenia, and less common after early and aggressive empiric antifungal therapy.

Drug fever is always a consideration, especially when protracted fever and neutropenia have necessitated giving a variety of broad-spectrum antibiotics. Rash may or may not be present.

Residual or recrudescent leukemia or lymphoma can be a cause of fever, even after intensive chemotherapy.

"Engraftment syndrome." Some patients (particularly recipients of autologous bone marrow or stem cell transplants) have fevers without an identified source and with negative cultures, which may persist for a week or more after engraftment. This may be a prolonged version of the engraftment syndrome,[19] or may represent resolving occult infection. In such patients, a search for uncommon causes such as cytomegalovirus viremia should be undertaken, and CT scans of the abdomen, chest, sinuses, or head may be performed in search of an unsuspected fungal or other infection.

Catheter-related infection sometimes persists despite negative cultures. Removing the indwelling central venous catheter may lead to resolution of fever. In most cases, however, the fever ultimately resolves without a definite diagnosis and without sequelae.

TABLE 2

Causes of fever after recovery from neutropenia

Partially treated infection (bacterial, fungal; often culture-negative), or new infection
Catheter-related infection
Drug fever (vancomycin, beta-lactam antibiotics, sulfonamides, etc)
Persistent mucositis after chemotherapy
C difficile colitis
Hepatosplenic candidiasis
"Engraftment syndrome" (autologous stem cell and bone marrow transplant recipients)
Persistence of underlying disease (lymphoma, leukemia, etc)
Infections related to graft-versus-host disease in allogeneic bone marrow transplant recipients (eg, bacteremia from gastrointestinal mucosal source)
Cytomegalovirus or other viral infection (especially allogeneic bone marrow transplant recipients)

TOPICS OF RESEARCH

Antibiotic prophylaxis

The prevention of infection in afebrile neutropenic patients has been the subject of considerable research. Low-risk patients, that is, those without localizing signs of infection and with short expected durations of neutropenia, are frequently observed and immediately evaluated if any fever occurs. For patients with a longer expected duration of neutropenia, antibiotic prophylaxis directed principally against gram-negative pathogens may be considered. The objective of this strategy is to decrease the gastrointestinal bacterial load of aerobic gram-negative bacilli, but to leave the anaerobic flora as intact as possible to preserve the phenomenon of colonization resistance, which helps to prevent overgrowth of potentially pathogenic organisms.

Early studies evaluated the role of trimethoprim-sulfamethoxazole (TMP-SMX) for this purpose, but the rise of resistance to TMP-SMX even among common enteric bacteria such as *E coli* makes this strategy potentially less useful today. The early quinolones, particularly ciprofloxacin, have been appealing for this purpose because of their powerful broad-spectrum activity against aerobic gram-negative bacilli without anti-anaerobic activity. Several studies have shown ciprofloxacin to be effective in preventing gram-negative infection in certain groups of neutropenic patients; however, disadvantages include the rise of gram-positive infections in this population, and the alarming potential for development of resistance to quinolones both in the individual patient and in general.[4]

Abdominal or perianal pain may signal a serious infection

The decision to use such antibiotic prophylaxis or not is up to the individual clinician and program, but many clinicians feel that this strategy should be reserved for high-risk patients. The IDSA guidelines recommend TMP-SMX prophylaxis only for patients at risk for *P carinii* pneumonia; routine quinolone prophylaxis is not recommended except in certain patients with "profound and prolonged neutropenia," and then only for short courses with awareness of the risks of developing antibiotic resistance.[4] On the other hand, allogeneic bone marrow transplant recipients who remain neutropenic after transplant are at high risk of bacterial,

fungal, and viral infection and generally require continuous prophylaxis in all three categories.

Other topics of research

Other topics in the field of neutropenic fever that are undergoing research include the following.

- Use of vascular catheters impregnated with antimicrobial substances such as minocycline and rifampin,[20] or silver sulfadiazine.[21]
- Hematopoietic growth factors and immunomodulators such as G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-monocyte colony-stimulating factor), which may shorten the duration of neutropenia, thereby decreasing the risk of infection.[22,23]
- How to manage the special problems of patients undergoing autologous stem cell transplantation or bone marrow transplantation.[24]
- Whether some patients can be discharged from the hospital early and complete their antibiotic therapy at home.[7,25] (We have concerns about the safety of this strategy, and do not recommend it at this time outside of specialized centers where this practice has been established and validated.)

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REFERENCES

1. **Bodey GP, Buckley M, Sathe YS, Freireich EJ.** Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966; 64:328–340.
2. **Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG.** Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982; 72:101–111.
3. **Pizzo PA.** Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993; 328:1323–1332.
4. **Hughes WT, Armstrong D, Bodey GP, et al.** 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Clin Infect Dis 1997; 25:551–573.
5. **Chanock SJ, Pizzo PA.** Fever in the neutropenic host. Infect Dis Clinics North Am 1996; 10:777–796.
6. **Hathorn JW, Lyke K.** Empirical treatment of febrile neutropenia: evolution of current therapeutic approaches. Clin Infect Dis 1997; 24(Suppl 2):S256–265.
7. **Rolston KVI, Rubenstein EB, Freifeld A.** Early empiric antibiotic therapy for febrile neutropenia patients at low risk. Infect Dis Clinics North Am 1996; 10:223–237.
8. **Schimpff S, Satterlee W, Young VM, Serpick A.** Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 1971; 284:1061–1065.
9. **Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg S, Pizzo PA.** Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. Ann Intern Med 1988; 108:30–35.
10. **Shlaes DM, Binczewski B, Rice LB.** Emerging antimicrobial resistance and the immunocompromised host. Clin Infect Dis 1993; 17(suppl 2):S527–S536.
11. **EORTC International Antimicrobial Therapy Cooperative Group.** Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. N Engl J Med 1987; 317:1692–1698.
12. **Liang R, Yung R, Chiu E, et al.** Ceftazidime versus imipenem-cilastatin as initial monotherapy for febrile neutropenic patients. Antimicrob Agents Chemother 1990; 34:1336–1341.
13. **Johnson MP, Ramphal R.** β-lactam resistant Enterobacter bacteremia in febrile neutropenic patients receiving monotherapy. J Infect Dis 1990; 162:981–983.
14. **Karp JE, Dick JD, Angelopulos C, et al.** Empiric use of vancomycin during prolonged treatment-induced granulocytopenia: randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. Am J Med 1986; 81:237–242.
15. **Shenep JL, Hughes WT, Roberson PK, et al.** Vancomycin, ticarcillin, and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile, neutropenic children with cancer. N Engl J Med 1988; 319:1053–1058.
16. **Raad I.** Intravascular catheter-related infections. Lancet 1998; 351:893–898.
17. **Elishoov H, Or R, Strauss N, Engelhard D.** Nosocomial colonization, septicemia, and Hickman/Broviac catheter-related infections in bone marrow transplant recipients. A 5-year prospective study. Medicine (Baltimore) 1998; 77:83–101.
18. **Sugar AM.** Empiric treatment of fungal infections in the neutropenic host. Review of the literature and guidelines for use. Arch Intern Med 1990; 150:2258–2264.
19. **Lee CK, Gingrich RD, Hohl RJ, Ajram KA.** Engraftment syndrome in autologous bone marrow and peripheral stem cell transplantation. Bone Marrow Transplant 1995; 16:175–182.
20. **Raad I, Darouiche R, Dupuis J, et al.** Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. Ann Intern Med 1997, 127:267–274.
21. **Maki DG, Stolz SM, Wheeler S, Mermel LA.** Prevention of central venous catheter-related blood stream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. Ann Intern Med 1997; 127:257–266.
22. **Dale DC, Liles WC, Summer WR, Nelson S.** Review: granulocyte colony-stimulating factor—role and relationships in infectious diseases. J Infect Dis 1995; 172:1061–1075.
23. **Liles WC, Huang JE, van Burik JA, Bowden RA, Dale DC.** Granulocyte colony-stimulating factor administered in vivo augments neutrophil-mediated activity against opportunistic fungal pathogens. J Infect Dis 1997; 175:1012–1015.
24. **Mossad SB, Longworth DL, Goormastic M, Serkey JM, Keys TF, Bolwell BJ.** Early infectious complications in autologous bone marrow transplantation; a review of 219 patients. Bone Marrow Transplant 1996; 18:265–271.
25. **Aquino VM, Tkaczewski I, Buchanan GR.** Early discharge of low-risk febrile neutropenic children and adolescents with cancer. Clin Infect Dis 1997; 25:74–78.

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