Cancer Management: A Multidisciplinary Approach, 12th Edition (2009).
Chapter 40

Infectious complications

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Infections are among the most common, potentially serious complications of cancer and its treatment. This chapter discusses infections from a syndromic approach: that is, infections present as a complex of signs and symptoms to the clinician. The syndromes addressed include febrile neutropenia, pneumonia, catheter-associated infections, and gastrointestinal infections (*Clostridium difficile*-associated diarrhea and typhlitis). Special sections focus on fungal and viral infections.

INFECTION DURING FEBRILE NEUTROPENIA

It has long been recognized that the incidence of infection is high in patients who develop a fever during neutropenia and that empiric antimicrobial therapy is warranted in such patients.

Definitions

Fever is usually defined as a temperature 38.3°C.

Neutropenia is defined as a neutrophil count of < 500/L, although patients with a neutrophil count between 500 and 1,000/L in whom a decrease is anticipated are considered to be neutropenic. Patients with a neutrophil count < 100/L are at greatest risk for infection, as are those with a rapid decrease in neutrophil count and those with protracted neutropenia.

Etiology

Bacteria Infections occurring during episodes of febrile neutropenia are caused predominantly by aerobic gram-negative bacilli (especially *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) and gram-positive cocci (coagulase-negative staphylococci, -hemolytic streptococci, viridans streptococci, enterococci, and *Staphylococcus aureus*). In recent years, multidrug-resistant organisms have become more prominent.

Fungi Fungal infections usually occur after a patient has received broad-spectrum antimicrobial therapy and/or steroids. The most common fungal pathogens are *Candida* species (predominantly C *albicans* and C *tropicalis*) and *Aspergillus* species. Less common are *Fusarium*, *Scedosporium*, and *Zygomycetes* infections (see also section on “Fungal infections”).

Viruses Viral infections occurring during neutropenia are caused predominantly by herpesviruses and respiratory viruses. The herpesviruses include herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). The respiratory viruses include adenovirus, respiratory syncytial virus, parainfluenza virus, influenza A and B viruses, metapneumovirus, and rhinovirus (see also section on “Viral infections”).

Signs and symptoms

The most remarkable aspect of the febrile, neutropenic patient is the lack of physical findings. This is due to the neutropenia and the absence of an inflammatory response at the infection site. The patient may have only a fever with or without chills or rigors. Even if the patient has pneumonia, there may be few respiratory symptoms. Likewise, a perirectal abscess may be relatively asymptomatic.

Diagnosis

An initial evaluation and diagnostic work-up of any fever in a neutropenic patient should begin immediately but should not delay the initiation of empiric therapy (see below). A complete history (exposures, past infections, rashes, cough, abdominal pain, diarrhea) should be taken and a physical examination (skin lesions, exit site and tunnel of right atrial catheter, oropharynx, abdomen, perineum) should be performed.

Diagnostic workup should include:

• at least two sets of blood cultures: one from a peripheral vein and one from each port of a central venous catheter. If fever persists in the face of negative cultures, blood cultures for fungi and acid-fast bacilli should be considered.

• culture of any drainage from a catheter exit site

• stool examination for *Clostridium difficile* and other bacterial/protozoal agents

• urine culture and urinalysis

• chest radiograph

• aspiration or biopsy of any skin lesions.

CT If indicated by signs or symptoms, CT scans of the brain (followed by lumbar puncture), chest, abdomen, and pelvis can be performed.

Laboratory tests Determination of serum transaminases, CBC, and serum creatinine is also recommended. Other useful serologies include *Aspergillus galactomannan*, beta-D-glucan, *Coccidioides* antibody panel, and histoplasmosis antigen, depending on the region.

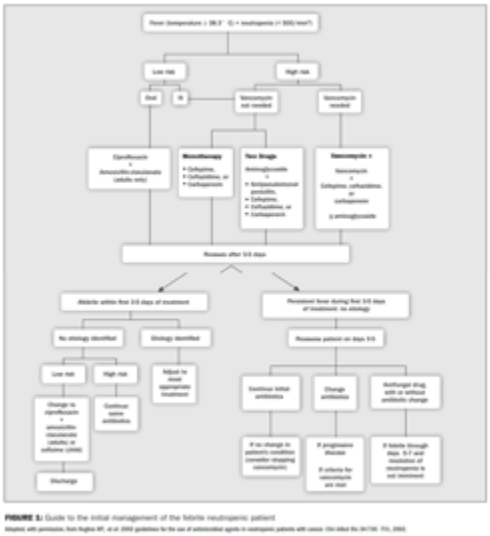
Treatment

initial empiric antibiotic therapy

Initial antibacterial therapy in the febrile, neutropenic patient should be broad-spectrum and should be based on the prevalence and susceptibility of bacterial isolates seen in the individual hospital setting (Figure 1). When choosing an antibiotic, the clinician also should take into consideration the patient’s

allergies, renal and hepatic function, and other drugs he or she is receiving that may interact with the empiric antimicrobial agent.

The choice of initial empiric antibiotic therapy for the febrile, neutropenic patient is dictated in part by the susceptibility pattern of blood isolates seen at a particular cancer center. If the prevalence of extended-spectrum beta-lactamase (ESBL) gram-negative bacteria is high, for example, one probably would not want to use a third-generation cephalosporin such as ceftazidime as initial empiric monotherapy. Some data suggest that prolonged use of ceftazidime monotherapy in this setting promotes the emergence of ESBL bacteria. City of Hope has been using ceftazidime as initial monotherapy for the past 15 years, however, without a significant rise in the incidence of resistant gram-negative infections, and this experience has been shared by other centers. Finally, any special circumstance, such as the suspicion of an indwelling IV catheter-associated infection, may influence the antibiotic choice.



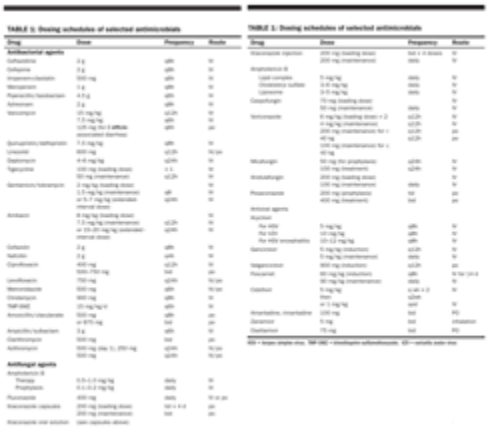
Either single antibiotics or antibiotic combinations can be used for initial empiric therapy (see Table 1 for dosage regimens).

Monotherapy

Ceftazidime, cefepime (Maxipime), imipenem-cilastatin (Primaxin), or meropenem (Merrem), when used as monotherapy, avoids the potential for nephrotoxicity. However, none of these antibiotics covers coagulase-negative staphylococci, methicillin-resistant *S aureus* (MRSA), vancomycin-resistant or vancomycin-susceptible enterococci, some strains of penicillin-resistant *Streptococcus pneumoniae*, and viridans streptococci. Also, ceftazidime does not cover anaerobes well, and imipenem-cilastatin may have CNS toxicity at high doses.

Duotherapy

Aminoglycoside plus antipseudomonal -lactam The aminoglycoside could be gentamicin, tobramycin, or amikacin (Amikin). The -lactam could be ticarcillin (Ticar) or piperacillin (Pipracil), either alone or with a -lactamase inhibitor (piperacillin/tazobactam [Zosyn]); ceftazidime; cefepime; or a carbapenem.



Advantages of the combination of an aminoglycoside and an antipseudomonal -lactam include possible synergistic effects against gram-negative bacilli and decreased emergence of resistant strains. The major disadvantages of the combination are potential nephrotoxicity, ototoxicity, hypokalemia, and the need to monitor drug levels of the aminoglycoside. Also, gram-positive coverage is not ideal.

Vancomycin plus one or two drugs The use of vancomycin as part of the initial regimen is controversial. Certainly, a majority of documented bacteremias in neutropenic febrile patients are caused by gram-positive organisms, and most of them are due to coagulase-negative staphylococci. Also, vancomycin is probably the preferred drug for viridans streptococcal sepsis and the drug of choice for MRSA and *Corynebacterium* infections. On the other hand, there is concern for the overuse of vancomycin and the emergence of vancomycin-resistant enterococci (and now S aureus). A study by the EORTC and the NCIC did not support the use of vancomycin in initial empiric therapy.

It should be noted that the CDC advises against the use of vancomycin in initial empiric therapy for a febrile, neutropenic patient "unless initial evidence indicates that the patient has an infection caused by gram-positive micro-organisms (eg, at an inflamed exit site of a Hickman catheter) and the prevalence of infections caused by MRSA in the hospital is substantial."

Thus, it is recommended (in the 2002 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever developed by the Infectious Diseases Society of America [IDSA]) that vancomycin be added to the initial regimen (eg, with ceftazidime) in selected patients, including:

• patients with clinically obvious, serious catheter-related infections

• patients undergoing intensive chemotherapy that produces substantial mucosal damage (ie, high-dose cytarabine [Ara-C], which increases the risk of penicillin-resistant streptococcal infections, particularly those due to viridans streptococci)

• patients receiving prophylaxis with quinolones before the onset of the febrile episode

• patients who have known colonization with pneumococci that are resistant to penicillin and cephalosporins or MRSA

• patients with a blood culture positive for gram-positive bacteria before final identification and susceptibility testing

• patients with hypotension or other evidence of cardiovascular impairment

Double -lactam therapy usually consists of a third-generation cephalosporin (ceftazidime or cefoperazone [Cefobid]) and a ureidopenicillin (piperacillin, ticarcillin, or mezlocillin [Mezlin]). The advantages of this regimen are low toxicity (mainly renal) and theoretical synergism. However, it is more costly (compared with monotherapy) and has the possibility of antagonism.

Changes in initial therapy

Defervescence If the fever subsides after 3 days of empiric therapy and a specific organism is identified, broad-spectrum antibiotic coverage can be modified to provide optimal treatment. Antibiotics can be discontinued after 7 days if all evidence of infection has been eradicated and if neutropenia has resolved.

If no organism is isolated, treatment with the initial regimen should be continued for a minimum of 7 days. If the patient is clinically well, the regimen can be switched to an oral antibiotic, such as cefixime (Suprax) or a quinolone.

Persistent, unresponsive fever If the fever persists after 3–5 days of antibiotic therapy, reassessment is recommended. If no infectious etiology is determined, a change in or addition to the antibiotic regimen is recommended.

If vancomycin was not part of the initial empiric regimen, many physicians would consider adding it. However, because of the recommendation by the CDC against empiric vancomycin use, it probably should not be added unless there is a strong clinical or microbiologic reason to do so. Instead, cefazolin or nafcillin could be added for better gram-positive coverage. If the initial regimen did not provide anaerobic coverage, metronidazole could be added. Finally, if fever and neutropenia persist despite 4 days of antibiotic therapy, an antifungal agent

(caspofungin [Cancidas], liposomal amphotericin B [AmBisome], amphotericin B lipid complex [Abelcet], itraconazole [Sporanox], voriconazole [Vfend]), or even fluconazole (if the risk of mold infection is low) should be added. If the patient is already on antifungal prophylaxis with an azole or echinocandin, a polyene (an amphotericin B lipid formulation) should be started. If the patient is receiving a polyene as prophylaxis, the dose should be escalated, or, alternatively, a change can be made to an extended-spectrum azole (eg, voriconazole). Another alternative is to add an echinocandin (caspofungin) to the increased dosage of the polyene.

Duration of antimicrobial therapy The most important determinant of the duration of therapy is the absolute neutrophil count (Figure 2).

Prevention

Attempts to prevent infection in the neutropenic host focus on two broad areas: preventing acquisition of pathogenic organisms and suppressing or eradicating endogenous microbial flora.

Hygienic measures
The simplest, most effective, and least expensive way to prevent acquisition of potential pathogens is to institute strict hand-washing precautions.

A cooked diet with elimination of fresh fruit and vegetables is also recommended.

Water purification systems (to eliminate *Legionella* organisms) and high-efficiency particulate air (HEPA) filtration systems (to eliminate fungal spores) can decrease rates of acquisition of these pathogens.

The use of more “protective” environments for neutropenic patients is controversial. The total protective environment, which consists of a totally sterile environment and an aggressive antimicrobial regimen, can reduce the rate of infection but does not contribute to increased survival and is also costly.

Antibacterial prophylaxis
Prophylactic antibacterial therapy generally falls into three categories: oral nonabsorbable antibiotics, selective decontamination regimens, and systemic prophylaxis.

Nonabsorbable antibiotics Although the use of oral nonabsorbable antibiotics has demonstrated some reduction in infection rates, this option has become less popular due to its cost, side effects, unpalatability, poor compliance, and selection of resistant organisms.

Selective decontamination with trimethoprim-sulfamethoxazole (TMP-SMZ), ie, establishment of “colonization resistance” by preserving anaerobic flora while reducing aerobic bacteria, has not resulted in clear-cut reductions in infection rates. Moreover, the disadvantages of prolonged neutropenia and emergence of resistant organisms make this regimen less desirable than others.

Systemic prophylaxis More recently, many studies have touted the value of antibacterial prophylaxis with fluoroquinolones (eg, ciprofloxacin [Cipro], ofloxacin [Floxin], and levofloxacin [Levaquin]) in neutropenic patients. However, no single study (except for a meta-analysis of 52 trials) has demonstrated a survival advantage. Thus, neither the NCCN nor the Infectious Diseases Society of America (IDSA) guidelines recommend using antibacterial prophylaxis in neutropenic patients. The NCCN guideline recommends that bacterial prophylaxis (fluoroquinolones) be considered for high-risk

patients (neutropenia < 100 L for > 7 days). Despite this lack of a strong recommendation, fluoroquinolone (mainly levofloxacin) prophylaxis is widely used at many cancer centers; the obvious downside of this trend is the emergence of resistant bacteria, which has already been observed in many institutions. Levofloxacin use has also been associated with the emergence of hypervirulent C *difficile* enterocolitis.

***Pneumocystis jirovecii* pneumonia** In patients at risk for *P jirovecii* pneumonia (patients undergoing allogeneic hematopoietic cell transplantation [HCT], those with lymphoma, or those receiving steroids), TMP-SMZ, administered for only 2 or 3 days per week, can reduce the incidence of infection.

Antifungal prophylaxis
Fluconazole, itraconazole, micafungin (Mycamine), and posaconazole (Noxafil) have all been shown to lower the incidence of invasive fungal infection when used as prophylaxis in the HCT setting. In a retrospective study, low-dose conventional amphotericin B has also been associated with a lower incidence of infection. Fluconazole, however, has no activity against molds. Itraconazole is limited by its gastrointestinal and hepatic toxicities. Posaconazole has been shown to prevent both *Candida* and *Aspergillus* infections in both neutropenic AML (acute myelogenous leukemia) and MDS (myelodysplastic syndrome) patients and the high-risk allogeneic HCT recipient with graft vs host disease (GVHD). Antifungal prophylaxis should be reserved for those patients at highest risk for invasive fungal infection—ie, HCT and high-risk leukemia patients undergoing high-dose chemotherapy (see also “Prevention” section under “Fungal infections”).

Antiviral prophylaxis
Acyclovir Patients at risk for mucositis (ie, those undergoing induction therapy for leukemia or lymphoma or HCT) who have evidence of prior HSV infection (positive serology) can receive prophylaxis with twice-daily IV acyclovir (see Table 1 for dose).

The promise of maribavir as an effective prophylactic agent against cytomegalovirus in the setting of HCT did not prove beneficial in a larger randomized study (*Bone Marrow Transplant 43 [Suppl 1]: abstract 321, 2009*).

Ganciclovir has been shown to be an effective “preemptive” antiviral in preventing CMV interstitial pneumonia in allogeneic HCT recipients who demonstrate evidence of viremia by polymerase chain reaction (PCR), antigen testing, or positive blood cultures (see section on “Viral infections”).

PNEUMONIA

A significant number of infections in cancer patients are due to pneumonia. For example, 25% of documented infections in patients with nonlymphocytic leukemia are caused by pneumonia. Also, 50% of allogeneic HCT recipients will develop pneumonia.

Etiology and risk factors

Some of the risk factors that predispose cancer patients to pneumonia are cellular and humoral immune deficiencies, neutropenia, impaired tracheobronchial clearance, use of antibiotics and steroids, and surgery.

Etiologic agents The etiologic agents responsible for pneumonia in the cancer patient run the gamut of most bacterial, fungal, and viral organisms (Figure 3).

Noninfectious processes mimicking pneumonia Numerous noninfectious processes can mimic pneumonia in cancer patients. They include congestive heart failure, aseptic emboli, metastatic disease, adult respiratory distress syndrome, diffuse alveolar hemorrhage, a periengraftment infiltrate, radiation injury, hypersensitivity disorders and reactions, and trauma.

FIGURE 3: Pneumonia in neutropenic/immunocompromised host

RSV = respiratory syncytial virus; hMPV = human metapneumovirus; CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella zoster virus

Pinpointing the pathogen Certain characteristics of each cancer patient may help predict the specific etiologic agent.

Type of immunosuppression One characteristic that is particularly useful is the type of immunosuppression that the patient is experiencing. This depends on the type of neoplastic disease (eg, lymphoma, leukemia) and, more importantly, the type of therapy (eg, chemotherapy, radiation therapy, allogeneic HCT). For example, certain gram-negative and gram-positive bacteria are more prevalent during neutropenia, whereas other bacteria (*S pneumoniae*, *Haemophilus influenzae*) are more common with a humoral immune deficiency, such as occurs after splenectomy.

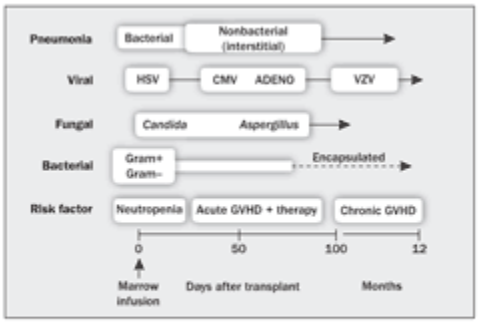


FIGURE 4: Timing of infectious syndromes after bone marrow transplantation

ADENO = adenovirus; CMV = cytomegalovirus; GVHD = graft-vs-host disease; HSV = herpes simplex virus; VZV = varicella zoster virus

Adapted, with permission, from Meyers JD: Infections in marrow recipients, in Mandell GL, Douglas RG, Bennett JE (eds): Principles and Practice of Infectious Diseases, 2nd ed, pp 1674-1676. New York, Wiley, 1985.

Timing of pneumonia Another important characteristic is the timing of the pneumonia; in other words, the phase of the immunosuppression can help predict the etiology. For example, an interstitial pneumonia occurring during the first 30 days after allogeneic HCT would not be expected to be due to CMV (Figure 4).

Other factors Finally, other factors such as the duration of neutropenia, prior antimicrobial therapy, other agents (such as steroids and alemtuzumab [Campath]) used, and the specific local microbiota help in prediction. For example, if an allogeneic HCT patient receiving steroids for GVHD develops nodular infiltrates after weeks of broad-spectrum antibacterial antibiotics, an *Aspergillus* species would be highly suspected.

Signs and symptoms

Although a productive cough is almost always present in a normal host with pneumonia, often neither a cough nor sputum is seen in an immunocompromised cancer patient with such an infection.

Fever, however, is almost invariably present in the cancer patient with pneumonia and, by itself, should prompt a workup for pneumonia.

Other possible symptoms include shortness of breath, pleuritic chest pain, and hemoptysis.

Diagnosis

Because pneumonia can progress rapidly and result in high morbidity and mortality in the compromised host, and because the etiologic agent is often difficult to ascertain, the clinician needs to be aggressive in diagnosing and treating these infections.

The diagnosis of pneumonia is most commonly made by a simple chest radiograph. However, there are occasions when a pulmonary infiltrate or small nodular lesion is seen only on a CT scan.

Etiologic diagnosis
An etiologic diagnosis is made by the following procedures: sputum (expectorated or induced), bronchoscopy with bronchoalveolar lavage and transbronchial biopsy, transthoracic needle biopsy/aspiration, open lung biopsy, and serologies.

Sputum An adequate sputum specimen is difficult to obtain from cancer patients, especially during neutropenia.

Bronchoscopy with bronchoalveolar lavage is a much more sensitive technique than sputum analysis but may miss the organism when the pulmonary disease is peripheral or nodular.

Transthoracic needle biopsy/aspiration under CT guidance may be helpful if the lesion is proximal but may be contraindicated in a severely thrombocytopenic patient. This procedure is indicated when there is a focal/nodular lesion in the periphery.

Open lung biopsy is the most definitive diagnostic procedure but also the most invasive. It is still not clear whether the information obtained by open biopsy improves overall survival. The less invasive thoracoscopic open lung biopsy is becoming more popular than open lung biopsy.

Smears and cultures Both fluid and tissue specimens should be sent for bacterial smears (including acid-fast bacilli and modified acid-fast bacilli) and cultures (including those for anaerobes, acid-fast bacilli, and *Legionella* organisms), fungal smears (potassium hydroxide) and cultures, direct fluorescent antibody test for viruses, cytology (for viral inclusions and silver stains for fungi and *P jirovecii*), and histopathology.

Diagnostic approach to pneumonia is depicted in Figure 5 using risk stratification (low vs high risk). Patients with suspected pneumonia should undergo aggressive etiologic workup along with broad-spectrum empiric antimicrobial treatment. Preemptive antifungal therapy should be based on risk. Treatment is then tailored accordingly.

FIGURE 5: Diagnostic approach to pneumonia

* Sputum cultures are usually not available or useful in most cases and should not be solely relied upon. There should be no delay in proceeding to bronchoscopy.
† Stains such as gram, KOH (potassium hydroxide), and AFB (acid-fast bacilli) and cytology such as GMS (Gomori methenamine silver) and PAS (periodic acid Schiff) should be performed on respiratory samples.
‡ Consider fungal markers and serologies for various organisms based on history: Legionella urine antigen, Aspergillus galactomannan, (1-3)-beta-D-glucan assay; serologies for Histoplasmosis, Coccidioides, Cryptococcus, Q fever.
HCT = hematopoietic cell transplant

Treatment

The therapeutic approach to pneumonia in the cancer patient should take into consideration the category of immunosuppression (neoplastic disease and immunosuppressive therapy), as well as the timing of onset and pattern of the pneumonia.

Empiric antibiotic therapy

In neutropenic patients experiencing their first fever and localized pulmonary infiltrates, one can justify initiating empiric therapy similar to that used for febrile, neutropenic patients (see previous discussion), because the majority of pneumonias in this setting are caused by gram-negative bacteria. However, in other situations, such as pneumonia that has a later onset, develops after empiric antibiotics have been initiated, is more aggressive or severe, occurs in a more severely compromised host (eg, a patient who has had allogeneic HCT), or is characterized by a diffuse or interstitial infiltrate, one should proceed to immediate bronchoscopy with bronchoalveolar lavage (and possibly transbronchial biopsy).

Additions to empiric therapy

If no diagnosis is forthcoming after bronchoscopy and bronchoalveolar lavage, additions to empiric therapy should be made.

Anaerobic, gram-positive, and *Legionella* coverage Certainly, anaerobic coverage should be considered, as well as gram-positive coverage. *Legionella* coverage should be added, especially if warranted by the epidemiologic setting.

Antifungal and antituberculous therapy Finally, antifungal therapy should be initiated if there is no response to antibacterial therapy and especially if there are nodular or cavitary lesions. In addition, if such lesions are present and/or the epidemiologic setting is compatible, antituberculous therapy should be added.

Further diagnostic procedures If bronchoscopy with bronchoalveolar lavage does not reveal an etiology and the pneumonia is progressing despite empiric therapy, consideration should be given to transthoracic needle biopsy/aspiration and open lung biopsy. As mentioned previously, if there is a peripheral, focal lesion, transthoracic needle biopsy/aspiration can be attempted.

The ultimate diagnostic procedure is open biopsy, but because its contribution to increased survival is unknown, the decision to proceed with this most invasive procedure must be undertaken carefully.

Specific antimicrobial therapy

A specific treatment approach is suggested in Figure 6 based on whether treatment is empiric or targeted.

Prevention

Methods to prevent pulmonary infections fall into the following categories: colonization prevention, antimicrobial prophylaxis (and preemptive treatment), vaccination, and immunomodulation.

The simplest method of colonization prevention is hand-washing.

Other colonization prevention methods, such as protective environments, are discussed in the previous section.

With regard to pulmonary pathogens, HEPA-filtered rooms can eliminate Aspergillus spores from the immediate environment. Water supplies can be checked for *Legionella* contamination and/or adequate disinfection maintained (eg, chlorination, copper/silver ionization, temperature [60°C]).

Antimicrobial prophylaxis is discussed in the previous section.

The influenza and pneumococcal (killed) vaccines should be administered to cancer patients.

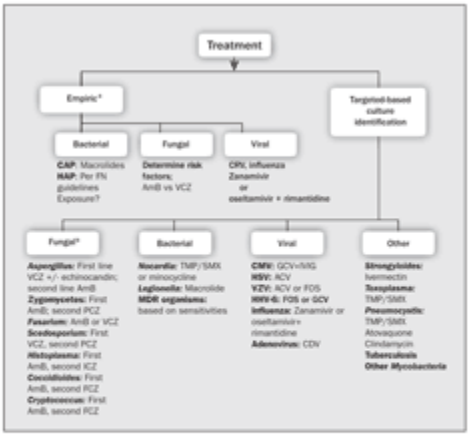


FIGURE 6: Antimicrobial treatment approach

* Empiric treatment should be directed by patient risk factors.

† Surgical intervention with zygomycosis/aspergillosis, and removal of central venous catheter for fusariosis.

Note: ACV = acyclovir; AmB = amphotericin B products; CAP = community acquired pneumonia; CDV = cidofovir; CMV = cytomegalovirus; CRV = community respiratory virus; FN = febrile neutropenia; FOS = foscarnet; FCZ = fluconazole; GCV = ganciclovir; HAP = healthcare-associated pneumonia; HHV6 = human herpes virus 6; ICZ = itraconazole; IVIG = intravenous immune globulin; MDR = multidrug resistant; PCZ = posaconazole; RSV = respiratory syncytial virus; TMP/SMX = trimethoprim/sulfamethoxazole; VCZ = voriconazole; VZV = varicella zoster virus

Immunomodulators, such as granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine]), may help reduce infection by decreasing the duration of neutropenia.

CATHETER–ASSOCIATED INFECTIONS

Chronic indwelling right atrial catheters are commonly placed in cancer patients, as they permit frequent, long-term vascular access for drug and blood product administration, hyperalimentation, and blood drawing.

Hickman and Broviac catheters have an exit site on the skin surface, are anchored with a subcutaneous Dacron felt cuff, and have a subcutaneous tunnel entering the venous system (via the subclavian, external jugular, internal jugular, cephalic, saphenous, or femoral veins), where they lead into the superior or inferior vena cava or right atrium. These catheters can have single, double, or triple lumens. Another type of catheter has a totally implanted port (Port-A-Cath) that is accessed percutaneously.

There are four types of catheter-associated infections: exit-site infections,tunnel infections, catheter-associated bacteremia/fungemia, and septic thrombophlebitis.

There are approximately 0.4 infections per 100 catheter-days and 0.26 bacteremias per 100 catheter-days.

Etiology

It is assumed that catheter-associated infections are caused by tracking of organisms from the skin along the catheter, contamination of the lumen during manipulation, or direct seeding during bacteremia/fungemia.

By far, the most common micro-organisms associated with catheter-associated infections are coagulase-negative staphylococci. The next most common pathogen is coagulase-positive *S aureus*.

Less common pathogens include gram-negative bacilli, gram-positive bacilli (such as *Corynebacterium* JK and *Bacillus* species), fungi (especially *Candida* species), and rapidly growing mycobacteria.

Signs and symptoms

Exit-site infections may be manifested by local erythema, warmth, and tenderness. Purulent drainage may be present.

Tunnel infections are characterized by tenderness along the subcutaneous track.

Catheter-associated bacteremia/fungemia usually displays no local findings. A fever may be the only sign, but other signs and symptoms of sepsis or even full-blown septic shock syndrome may be present.

Likewise, septic thrombophlebitis may have no findings, except those associated with sepsis or venous thrombosis (edema).

Diagnosis

In any cancer patient with a right atrial catheter who becomes febrile or is shown to be bacteremic or fungemic, a catheter-associated infection should be suspected. Without the signs or symptoms of an exit-site or tunnel infection, however, a diagnosis may be difficult.

Cultures Two blood cultures should be drawn: one from the catheter and one from a peripheral vein. There are two methods that may be helpful in making a diagnosis of right atrial catheter infection. Both depend upon drawing both (catheter and peripheral vein) blood cultures simultaneously. In the first method, quantitative colony counts are determined from both cultures. If the catheter colony counts are several-fold (3- to 10-fold) higher than the colony count from the peripheral vein, it suggests a catheter-associated infection. The second method, differential time to positivity (DTP), requires an automated continuously monitored blood culture system, which determines the time at which a blood culture turns positive. If the catheter culture turns positive at least 2 hours before the peripheral vein culture, it suggests a catheter-associated infection. A catheter infection should be assumed when the organism isolated is a coagulase-negative *Staphylococcus*, *Corynebacterium*, *Bacillus*, or *Candida* species or a mycobacterium.

If signs are consistent with an exit-site or tunnel infection, an attempt should be made to culture any exit-site drainage.

Treatment

Catheter removal

Although it was once believed that all catheters had to be removed to eradicate infection, it is now clear that many catheters can be salvaged. An exception to this guideline would be if the organism isolated is *Corynebacterium* JK, a *Bacillus* species, a *Candida* organism, or a rapidly growing mycobacterium. Some physicians would add to this list *S aureus*, vancomycin-resistant enterococci (VRE), *P aeruginosa* , polymicrobial bacteremia, and *Fusarium* species. The catheter also should be removed in patients with septic thrombophlebitis or evidence of septic emboli. A tunnel infection or pocket-space abscess should prompt catheter removal as well. Finally, fever or bacteremia that persists (> 72 hours) after therapy has been initiated necessitates removal of the catheter if there is no other source of infection.

Antibiotic therapy

Empiric therapy If a catheter-associated infection is suspected, vancomycin should be initiated empirically. If the patient is known to be colonized with vancomycin-resistant enterococci, empiric therapy with quinupristin/dalfopristin (Synercid) or linezolid (Zyvox) should be considered.

Two new antimicrobial agents with activity against MRSA and VRE have been approved: daptomycin (Cubicin) and tigecycline (Tygacil). Both drugs have activity against MRSA and VRE, but they are approved only for MRSA infections. Although some of these new agents have shortcomings (eg, activity of daptomycin is neutralized by surfactant in the lungs and emergence of resistance while on this antibiotic), they enlarge our armamentarium for fighting these resistant gram-positive infections.

Specific therapy When a micro-organism has been isolated and tested for sensitivity, specific antimicrobial therapy should be added. If the catheter is left in place, a minimum of 14 days of parenteral (not oral) therapy should be administered through the catheter (rotating through each port), and follow-up cultures should be obtained.

There are treatment concerns with alternative agents for the treatment of C difficile enterocolitis. They include resistance with rifaximin Johnson S, et al: Clin Infect Dis 44:846 848, 2007), and non-inferiority of nitazoxanide (Alinia) to metronidazole (*Musher DM, et al: Clin Infect Dis 43:421-427, 2006*). The

use of probiotics is cautioned due to potential for more invasive disease in the immunocompromised patient.

Search for infectious metastasis
Whether or not the catheter is removed, if the patient remains febrile, a search for sources of metastatic infection (lungs, liver, spleen, brain, heart valves) should be initiated.

Fibrinolytics and anticoagulants
The use of fibrinolytics and anticoagulation is controversial. Anticoagulation is indicated in cases of septic thrombophlebitis when the deep venous system is involved.

C difficile–ASSOCIATED DIARRHEA

Although many infectious complications involve the GI tract and abdomen in cancer patients, *C difficile* –associated diarrhea and typhlitis are the most important clinically.

Diarrhea is common in the cancer patient during chemotherapy. One of the most common causes of diarrhea is antibiotic-associated colitis. By far, the predominant etiology of antibiotic-associated colitis is *C difficile*. *C difficile* may also be contracted in the community.

Etiology and risk factors

Antibiotics The major risk factor for *C difficile*–associated diarrhea is treatment with antibiotics, especially broad-spectrum -lactams with activity against enteric bacteria, quinolones, and clindamycin. Antibiotic therapy causes a disruption in the normal bacterial flora of the colon. Pathogenic strains then produce toxins that cause diarrhea and pseudomembranous colitis.

Other risk factors include surgery (primarily colonic, gastric, and pelvic), colon carcinoma, leukemia, and uremia. Obviously, the hospitalized cancer patient undergoing chemotherapy and/or surgery and receiving broad-spectrum antibiotics is most vulnerable to this infection.

Signs and symptoms

Infection with *C difficile* can be asymptomatic. When signs and symptoms do occur, they may range from mild to moderate diarrhea with lower abdominal pain, to colitis without pseudomembranous formation, to pseudomembranous colitis, to fulminant colitis. Fulminant colitis may be associated with toxic megacolon and even perforation of the viscus and peritonitis. On occasion, a patient may present with just abdominal pain or fever and no diarrhea.

Pseudomembranes may be absent in mild disease but usually are present in severe disease and are easily recognized on sigmoidoscopic or colonoscopic examination as adherent yellow plaques that may coalesce over large areas.

Diagnosis

The development of diarrhea or even abdominal pain or fever in a cancer patient should prompt a work-up for *C difficile*–associated diarrhea.

The laboratory diagnosis of *C difficile* infection depends on the demonstration of *C difficile* toxins in the stool. The gold standard is the stool cytotoxin test, a tissue-culture assay that demonstrates cell rounding by *C difficile* toxin B.

Another test that can demonstrate *C difficile* toxins (A and/or B) in the stool is an enzyme immunoassay. It is less expensive and faster than the cytotoxin test and does not need to be performed by specially trained laboratory personnel.

Although a stool culture for *C difficile* may also be obtained, it has less significance in making the diagnosis.

Treatment

Initial management

The initial step in the management of *C difficile*–associated diarrhea is to discontinue antibiotic therapy. Patients may not require any other therapy. However, stopping antibiotics in a cancer patient may not be possible or the patient may be severely ill from the colitis. In these instances, specific anti–*C difficile* therapy is required.

Specific antibiotic therapy
Metronidazole and vancomycin Metronidazole (500 mg po tid) or vancomycin (125 mg po qid), both given for 10–14 days, are the drugs of choice. Metronidazole is preferred because it is less expensive. However, in the case of suspected severe hypervirulent *C difficile* enterocolitis, vancomycin may be the drug of choice.

For the patient who cannot tolerate oral medications, IV metronidazole (500 mg q8h) can be given. IV vancomycin should not be used, as high intraluminal levels cannot be attained. A vancomycin retention enema may be useful for cases of ileus.

Other agents that might be used for treatment include rifamixin and nitazoxanide (Alinia). Bacitracin (25,000 U po qid) and cholestyramine (4 g po qid) may be used as adjuncts.

Surgical therapy Subtotal colectomy with ileostomy may be required for severe *C difficile* enterocolitis.

Probiotics should be avoided in neutropenic patients.

Treatment of relapse

Relapse occurs in 10% to 20% of patients. Mild cases may not need to be treated. If treatment is indicated, a repeat 7- to 14-day course of either metronidazole or vancomycin may be administered. If the infection persists after repeated therapy, longer courses (4 to 6 weeks) followed by a gradual tapering of the dose may be helpful.

Prevention

Patients with *C difficile*–associated diarrhea and those who are known carriers should be placed in "contact isolation"; ie, the use of gloves, gowns, and careful hand-washing should be instituted.

During outbreaks, the use of sodium hypochlorite to disinfect contaminated surfaces has been recommended.

Antibiotic prophylaxis of high-risk patients or carriers is not recommended.

TYPHLITIS

Typhlitis (necrotizing enterocolitis) occurs in patients who are severely neutropenic, usually in the setting of chemotherapy. Pathologically, the areas of involvement include the cecum and terminal ileum. Typhlitis is a broad-spectrum disease characterized by bowel wall edema, diffuse or patchy necrosis involving the mucosa alone or the full thickness of the bowel wall, mucosal ulcerations, hemorrhage, inflammatory infiltrates, and infiltration of the bowel wall by bacteria or fungi. Mild cases are self-limiting when treated with bowel rest/antibiotics. Death may occur in severe cases.

Signs and symptoms

Signs and symptoms of typhlitis can be nonspecific but usually include fever, abdominal pain (typically in the right lower quadrant), and abdominal distention. The patient may have diarrhea (sometimes bloody), nausea, and vomiting or may demonstrate signs and symptoms consistent with those of acute appendicitis.

There may be abdominal guarding and rebound tenderness, diminished bowel sounds, or even a mass in the right lower quadrant of the abdomen.

Diagnosis

Radiographs or CT scans of the abdomen may demonstrate a thickened cecum, mass, or even gas within the colon wall.

Treatment

Mortality from typhlitis is high (> 50%), and therapy is controversial. However, broad-spectrum antibiotics covering both gut aerobes and anaerobes and resection of necrotic bowel are recommended.

FUNGAL INFECTIONS

Fungal infections are a leading cause of morbidity and mortality in cancer patients. These infections pose a formidable management challenge, in that diagnosis is often difficult to make at an early stage and, therefore, appropriate treatment may be delayed.

Etiology and risk factors

Candida species The most common fungal infections in cancer patients are caused by *Candida* species. Of the candidal pathogens found in these patients, *C albicans* is the most common. However, more recently other *Candida* species, such as *C tropicalis, C glabrata, C parapsilosis, C krusei,* and *C lusitaniae,* have become more prevalent. This finding is significant, as many of these species can be resistant to fluconazole (*C krusei, C glabrata, C lusitaniae*) and echinocandins (*C parapsilosis, C guilliermondii*).

Major risk factors for candidal infections include neutropenia, a breakdown in physical defense barriers (such as mucositis induced by chemotherapy and radiation therapy), broad-spectrum antibiotics, immune dysfunction (caused by chemotherapy and steroids), surgery (especially GI surgery), long-term indwelling vascular catheters, and poor nutritional status/total parenteral nutrition.

Aspergillus species is a less common cause of infection in cancer patients than candidal organisms but is more virulent. The most common of the Aspergillus species is *A fumigatus*, followed by *A flavus*, *A niger*, and *A terreus*.

Risk factors for *Aspergillus* infections include severe immunosuppression (primarily allogeneic HCT), steroid therapy, antitumor necrosis factor therapy, GVHD, and environmental exposure.

Other fungi Other fungal pathogens in the cancer patient include *Fusarium, Trichosporon, Zygomycetes* , and *Scedosporium* species; *Cryptococcus*; and the dematiaceous/pigmented fungi (eg, *Bipolaris spicifera, Cladosporium bantianum*).

Finally, the endemic fungi, *Coccidioides immitis* and *Histoplasma capsulatum*, are often more virulent and aggressive than other fungi in the immunocompromised host.

Signs and symptoms

Candidiasis

Candidiasis can present as a wide spectrum of diseases, from mucosal infection to disseminated and invasive disease.

Oropharyngeal candidiasis can present as classic thrush with beige plaques. It may be painful, as there may be a concurrent mucositis due to the ablative chemotherapy. Oropharyngeal candidiasis may extend into the esophagus as esophagitis, which may manifest as odynophagia. Epiglottitis may present as odynophagia and laryngeal stridor.

Candidemia may present simply as an asymptomatic fever or may result in a full-blown septic shock syndrome (acute disseminated candidiasis). In contrast, chronic disseminated candidiasis, which involves the chronic, indolent infection of different organs, such as the liver, spleen, and kidneys, may be manifested by fever alone.

Aspergillosis

Invasive aspergillosis most commonly involves the lungs and sinuses. However, it can also disseminate to the brain (and may be the most common cause of brain abscesses in HCT patients). Less commonly, aspergillus can disseminate to other organs, including the skin.

Signs and symptoms of invasive pulmonary aspergillosis include pleuritic pain, pulmonary hemorrhage, hemoptysis, and cavitation. The chest radiograph or CT scan may demonstrate pulmonary nodular infiltration and/or cavitary lesions.

Patients with sinusitis may have few signs (swelling) or symptoms (pain), especially if they are neutropenic.

Patients with brain abscesses may have headaches and neurologic signs consistent with the specific site of the lesion.

Skin involvement may present as necrotizing skin nodules or ulcers.

Other infections

The signs and symptoms of *Fusarium* infections are similar to those of aspergillosis; ie, pulmonary infiltrates, sinusitis, and cutaneous lesions are prominent.

Trichosporon infections are similar to *Candida* infections in that they can cause disseminated disease in multiple organs.

Zygomycetes infections cause sinopulmonary disease.

Scedosporium species are similar to *Aspergillus* species in their structure and predilection for the respiratory tract.

C immitis and *H capsulatum* also target the lungs but can disseminate to other organs.

Cryptococcus infections can cause pneumonia or cellulitis.

Diagnosis

Diagnosis of fungal infection in the cancer patient requires documentation by culture or histologic examination.

Candidiasis Although the diagnosis of oropharyngeal candidiasis often is made on clinical grounds, the lesions should be scraped for microscopic examination and culture. Biopsy of esophageal lesions via endoscopy should be performed to confirm *Candida* (as opposed to HSV or CMV) as the etiology of the infection.

A positive blood culture for *Candida* (especially a species other than *C albicans*) should never be considered a "contaminant" and often implies a right atrial catheter infection. Less likely to result in positive blood cultures are chronic, deep-seated infections, such as hepatosplenic candidiasis. Such infections require biopsy for confirmation.

Aspergillus species, like other species, such as *Zygomycetes* and dematiaceous fungi, is rarely found in the bloodstream and requires tissue sampling for diagnosis. Occasionally, bronchoalveolar lavage fluid or sinus drainage will yield *Aspergillus*, but often a lung biopsy is required. Recently, an *Aspergillus galactomannan* enzyme immunoassay test has become available for the diagnosis of invasive aspergillosis. Unfortunately, it is not clear that it is a sufficiently sensitive (especially in patients receiving antifungal agents) or predictive test for the disease. There are also two other diagnostic tests now available: the glucan assay (for [1,3]--d-glucan) and the *Aspergillus* DNA PCR. Unfortunately, there is a paucity of data and lack of experience with these assays to determine their utility in diagnosing and predicting invasive fungal infection in patients at highest risk.

Fusarium, Scedosporium, and Trichosporon species, in contrast to *Aspergillus* species, are often isolated from the bloodstream.

Skin lesions Any skin lesion should be suspected of being of fungal origin and should be biopsied, cultured, and examined histologically.

Search for sites of infection When a fungal infection is suspected or documented, a search for possible sites of infection should ensue. For a blood culture that grows a Candida species, the intravascular catheter should, in most cases, be removed for diagnostic as well as therapeutic reasons, and the catheter tip should be cultured. A CT scan of the abdomen should be obtained. In cases of suspected Aspergillus infection, in addition to a CT scan of the chest, a CT scan of the brain and sinuses should be performed.

Treatment

ANTIFUNGAL AGENTS

There are now three major groups of antifungal agents: 1) the polyenes (amphotericin B deoxycholate and its lipid formulations [amphotericin B lipid complex, liposomal amphotericin B, amphotericin B cholsteryl sulfate]); 2) the azoles (fluconazole, itraconzaole, voriconazole, posaconazole); and 3) the echinocandins (caspofungin, micafungin, anidulafungin [Eraxis]).

Amphotericin B deoxycholate has been the standard therapy for invasive fungal infection for 50 years. It is fungicidal and has a broad spectrum of activity against yeasts and molds, including the *Zygomycetes*. It is thought to be less active against *A terreus, Scedosporium, C guilliermondii*, and *C lusitaniae*. However, it is limited by its nephrotoxicity and infusional toxicity. The lipid formulations are less nephrotoxic but much more expensive than the other formulations.

The azoles are not nephrotoxic. The first-generation azoles (fluconazole and itraconazole) are considered fungistatic, whereas the extended-spectrum azoles (voriconazole and posaconazole) are considered more fungicidal. Fluconazole is well absorbed orally and can be administered orally or intravenously but is not active against molds and certain *Candida* species (*C krusei*). Itraconazole is hepatoxic and is not well absorbed when orally administered. Voriconazole is well absorbed orally and can also be administered intravenously. It is broadly active against most *Candida* species and most molds, with the exception of the *Zygomycetes*. Posaconazole can only be orally administered and is well absorbed. It is broadly active against most *Candida* species and most molds, including the *Zygomycetes*. Drawing azole levels should be considered for itraconazole, voriconazole, and posaconazole.

The echinocandins are the least toxic of the antifungal agents. They can only be administered intravenously. They are said to be fungicidal against yeasts but fungistatic against molds.

Candidiasis

Local mucosal candidiasis In patients with local mucosal candidiasis (including esophagitis), oral fluconazole or itraconazole can be used. If the patient has difficulty in taking oral medication, IV fluconazole should be used. If the patient was receiving prophylactic fluconazole when candidiasis developed, there is a high likelihood that the causative *Candida* species may be azole-resistant, and either an echinocandin or a lipid formulation of amphotericin B should be used.

Candidemia If candidemia is documented, the intravascular catheter should be removed. This step should be followed by the administration of an antifungal for at least 2 weeks after the last positive blood culture is obtained and all signs and symptoms have resolved. Although fluconazole has been shown to be an effective and safe agent in the treatment of candidemia, there are certain circumstances in which an alternative (an echinocandin or a lipid formulation of amphotericin B) might be preferable. These situations would include hemodynamic instability, neutropenia, or high suspicion of azole resistance (eg, a patient who is colonized with a resistant *Candida* species or has been on recent fluconazole prophylaxis or treatment).

Disseminated, deep-seated candidiasis (eg, hepatosplenic infection). Although the standard of therapy for deep-seated candidiasis has been long-term therapy with amphotericin deoxycholate, it has been limited by nephrotoxicity. Thus, the lipid formulations of amphotericin B have allowed higher cumulative doses with a lower nephrotoxic potential. The azoles (fluconazole, voriconazole) have the advantage of convenient (ie, oral) administration and good absorption, with little toxicity. The echinocandins also have been shown to be effective against this infection.

Aspergillosis

Antifungal therapy Amphotericin B deoxycholate (1.0 to 1.5 mg/kg/d) had been the standard therapy

for invasive aspergillosis. However, voriconazole led to better responses, improved survival, and fewer adverse events than did amphotericin B when used as initial therapy in patients with invasive aspergillosis. Thus, voriconazole is the standard therapy for invasive aspergillosis. Amphotericin B lipid complex, amphotericin B cholesteryl sulfate, liposomal amphotericin B, posaconazole, and caspofungin can be used. All of these formulations are less nephrotoxic than amphotericin B deoxycholate.

Surgical removal of infected sites In addition to antifungal therapy, it is important to attempt surgical removal of infected sites, if at all feasible. Sinus surgery should be performed. Resection of pulmonary lesions should be attempted if there are only one or two limited, discrete lesions.

Infections with other fungi

Although amphotericin B is the drug of choice for most invasive fungal infections, there are exceptions. *Scedosporium* and *Fusarium* species are often resistant to amphotericin B, and voriconazole may be the drug of choice for these infections. Voriconazole, however, is not active against *Zygomycetes* species, and if an infection with this organism is suspected or documented, amphotericin B deoxycholate, an amphotericin B lipid formulation, or posaconazole should be used. The dematiaceous/pigmented fungi also may be better treated with itraconazole. For *Trichosporon* infections, voriconazole may be more effective than amphotericin B.

Prevention

Because invasive fungal infection occurs with high frequency in the setting of HCT, most prophylactic studies have been performed in HCT recipients. Thus, the following recommendations apply mainly to this group, although prophylaxis can be justified when the incidence of these infections in any population is high enough.

Fluconazole Two randomized, placebo-controlled studies using prophylactic fluconazole (400 mg/d) have demonstrated a decrease in invasive and superficial *C albicans* infections. One study showed a reduction in mortality. As fluconazole is not active against *C krusei*, *C glabrata*, or *Aspergillus* species, there is concern that its prophylactic use will increase the incidence of these resistant fungi. Some authors have reported such an occurrence.

Obtaining Aspergillus galactomannan from bronchoalveolar lavage may be more sensitive than from serum for detection of pulmonary aspergillosis (*Husain S, et al: Clin Vaccine Immunol 15:1760-1763, 2008*).

Micafungin has been approved for use as an antifungal (candidiasis) prophylactic agent in HCT. There was also a trend toward protection against Aspergillus infection with micafungin, although it was not significant.

Itraconazole has been shown to be an effective antifungal prophylactic agent in HCT, but no survival benefit has been demonstrated, possibly because of the toxic GI effects and hepatotoxicity associated with this agent.

Low-dose amphotericin B was observed, in a retrospective study, to decrease the incidence of *Candida* infection. However, this regimen only delayed the onset of *Aspergillus* infections.

Posaconazole has been shown to be effective antifungal prophylaxis in two settings: (1) neutropenic AML and MDS patients; and (2) allogeneic HCT recipients with GVHD.

Other prophylactic regimens have been used in small numbers of patients, with varying degrees of success. They include aerosolized amphotericin B, intranasal amphotericin B, and amphotericin B lipid complex.

The prophylactic regimen of choice in HCT might be an echinocandin (eg, micafungin) intitially (while the patient is neutropenic and hospitalized) followed by an oral azole (eg, posaconazole) administered to those outpatients who remain at high risk for mold infections.

HEPA filtration Other than using prophylactic antifungals, there is little that can be done to prevent fungal infections in cancer patients. The one possible exception is the use of HEPA filtration, which can eliminate *Aspergillus* spores from the environment. However, most patients emerge from this environment still possessing the same risk factors (steroids, GVHD) for aspergillosis.

VIRAL INFECTIONS

Opportunistic viral infections are a particular problem in cancer patients who undergo HCT and those with hematologic cancers. Accurate diagnosis of viral infections is important, as treatment is available for many of them.

Etiology

As mentioned previously, viral infections in cancer patients are caused predominantly by herpesviruses (HSV, VZV, CMV, and EBV). The herpesvirus infections usually are reactivations of latent infections. Respiratory viruses that infect cancer patients include respiratory syncytial virus, influenza viruses A and B, parainfluenza virus, rhinovirus, and adenovirus.

Signs and symptoms

Although all of the herpesviruses can cause fever and a septic picture, HSV usually presents as mucositis or a vesicular rash, VZV presents as a vesicular rash in a dermatomal distribution, and CMV, in the HCT setting, presents as interstitial pneumonia. When HSV or VZV disseminates, each virus can cause disseminated cutaneous lesions or visceral (liver, lung, brain) involvement. VZV infection can present with GI symptoms, such as epigastric or general abdominal pain.

Diagnosis

To make a specific viral etiologic diagnosis, tissue or fluid must be obtained from the infected site and processed for histologic/cytologic examination and culture.

Vesicular skin lesions When a cancer patient presents with a vesicular rash, it is invariably due to either HSV or VZV. If the distribution of lesions is in a dermatomal pattern, a clinical diagnosis of VZV can be made. However, if there is cutaneous dissemination, the vesicular lesions should be aspirated (and sent for viral culture) or scraped down to the base, smeared on a glass slide, and sent for direct fluorescent antibody staining (for HSV and VZV).

Visceral involvement When there is visceral involvement with HSV, VZV, or CMV, biopsy material is examined for inclusions and is submitted for culture.

Respiratory infection For the respiratory viruses, diagnosis is usually made by examination of bronchoalveolar lavage fluid (obtained by bronchoscopy) or biopsy (obtained by transbronchial, percutaneous thoracic, thoracoscopic, or open lung biopsy). In the special case of CMV interstitial pneumonitis in the HCT setting, diagnosis of infection (prior to disease onset) can be made by detection of antigens or virus in the bloodstream, in addition to evidence of the virus in bronchoalveolar lavage fluid. PCR is available for various CRV (eg, adenovirus, parainfluenza, influenza, RSV, and metapneumovirus).

Voriconazole (Vfend) was compared with fluconazole for prophylaxis in HCT recipients. Voriconazole was found to be as efficacious as fluconazole; however, it did not result in a significant prevention of aspergillosis or demonstrate a survival benefit. There were no increases in zygomycosis in either arm (*Wingard JR, , et al: Blood 110: abstract 163, 2007*).

CNS involvement can be determined by PCR performed on the cerebrospinal fluid for the following agents: HSV, VZV, human herpesvirus 6 (HHV-6), CMV, and adenovirus.

Antibody testing is of little use in the diagnosis of viral infection in the cancer patient.

Evidence of CMV viremia, which is utilized to initiate preemptive therapy, can be determined by PCR, antigen detection, or blood (shell-vial) culture.

Treatment

HSV infection Localized HSV infection is usually treated with acyclovir, 5 mg/kg IV q8h. If there is dissemination, a dose of 10 mg/kg q8h can be used, and if there is CNS involvement, up to 15 mg/kg IV q8h can be utilized. If acyclovir-resistant HSV is suspected, foscarnet can be used (see Table 1 for doses). However, this is a nephrotoxic drug.

VZV infection is usually treated with acyclovir, administered at a dose of 10 mg/kg IV q8h.

CMV infection is treated with ganciclovir or foscarnet. Ganciclovir is the drug of choice but is toxic to bone marrow.

During the 2008-2009 influenza season, 98% of 50 isolates of seasonal H1N1 (influenza A) tested resistant to oseltamivir (Tamiflu), and all were sensitive to zanamivir, amantadine (Symmetrel), and rimantadine. The interim CDC recommendations for the 2008-2009 season were 1) for seasonal H1N1, use zanamivir or oseltamivir + ramantidine; 2) for H3N2 and influenza B, use only zanamivir or oseltamivir. (*Centers for Disease Control, Avaiable at: http://www2a.cdc.gov/HAN/archivesys/ViewMsgV.asp?AlertNum=00279. Accessed April 10, 2009*). More recently, in April of 2009, a novel influenza A (H1N1) emerged from Mexico and progressed to a worldwide pandemic within weeks. But this novel influenza A (H1N1) strain appeared to be less virulent than seasonal influenza A and has remained sensitive to zanamivir with rare cases of oseltamivir resistance reported (eg, in two hematopoietic cell transplantation recipients). (*Center for Disease Control. Available from http://www.cdc.gov/h1n1flu/recommendations.htm#B. Accessed August 17, 2009*). The selection of antiviral therapy should be guided by the circulating strain(s) in the community, and, thus, combination therapy may be appropriate where inhaled zanamivir (to which both influenza A strains are susceptible) cannot be used. In some cases, compassionate use IV zanamivir is available through GlaxoSmithKline.

In the HCT setting, "preemptive" treatment (treatment to prevent disease after evidence of infection is obtained) consists of ganciclovir, 5 mg/kg IV bid for 7 days followed by 5 mg/kg/d IV for another 3 to 5 weeks. Actual treatment of CMV interstitial pneumonia consists of ganciclovir, 5 mg/kg IV q12h, along with immunoglobulin, 500 mg/kg IV every other day for 21 days (induction phase). Maintenance therapy (for as long as immunosuppression is present) consists of ganciclovir, 5 mg/kg/d IV for 5 days each week, and immunoglobulin, 500 mg/kg IV every week.

Foscarnet can be used instead of ganciclovir if there is marrow toxicity but poses a potential risk of nephrotoxicity.

For CMV infection resistant to both ganciclovir and foscarnet, cidofovir (Vistide) can be used.

HHV-6 infection/disease can be treated with ganciclovir, foscarnet, or cidofovir.

Respiratory viral infection Among the respiratory viruses, there is specific antiviral therapy only for respiratory syncytial virus and influenza A. Ribavirin (Virazole), 1.1 g/d by aerosol (20 mg/mL), has been used for respiratory syncytial virus (but has not been shown to be effective) and rimantadine (Flumadine) or amantadine (Symmetrel), both 100 mg po bid, for influenza A. Zanamivir (Relenza) and oseltamivir (Tamiflu, 75 mg po bid) can be used for both influenza A and B. Finally, cidofovir has been used (but not FDA approved) for adenovirus infection.

Prevention

Herpesvirus infections

Acyclovir HSV and VZV reactivate with great frequency in cancer patients undergoing chemotherapy and/or radiation therapy. This finding is especially true in the HCT population, in which 80% of HSV-seropositive patients and up to 40% of VZV-seropositive patients have a reactivation of HSV or VZV. Therefore, in HSV-seropositive HCT patients, prophylactic acyclovir is indicated. Any HSV infection that occurs during acyclovir prophylaxis should be considered resistant to acyclovir. Acyclovir has also been shown to reduce the incidence of CMV infection after HCT. It is now recommended by some to extend HSV prophylaxis for 1 year or longer for patients with allogeneic HCT or GVHD. In patients exposed to VZV, acyclovir should be given at a dose of 800 mg (adults) or 20 mg/kg (pediatrics, maximum 800 mg/dose) four times daily on days 3 to 22 after exposure.

Ganciclovir is generally considered too (marrow) toxic to be used as universal prophylaxis against CMV. Thus, the preemptive approach was developed to focus on only treating those who had evidence of CMV infection (viremia) as determined by PCR, antigen detection, or blood (shell-vial) culture. This approach allows treatment of viremia before it evolved into CMV disease (interstitial pneumonitis).

CMV-seronegative blood support In the small group of HCT recipients who are CMV-seronegative, the use of CMV-seronegative blood support has been shown to reduce CMV infection dramatically.

Varicella and varicella-zoster virus vaccines (Varivax) should not be given to those with hematologic malignancies, malignant neoplasms, or immunodeficiencies. The exception is with varicella vaccine in those with childhood leukemia in remission for 1 year, when selected criteria are met.

Influenza

Influenza vaccine Although the efficacy of the influenza vaccine is unknown in the HCT setting, it should be administered to all cancer patients.

Rimantadine, amantadine, zanamivir, or oseltamivir can be given prophylactically during an outbreak of influenza.

SUGGESTED READING

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Abbreviations in this chapter

CDC = Centers for Disease Control and Prevention; EORTC = European Organization for Research and Treatment of Cancer; NCCN = National Comprehensive Cancer Network; NCIC = National Cancer Institute of Canada