Current Concepts

Fever in Immunocompromised Patients

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THE past two decades have witnessed an increase in the number of patients who are immunocompromised as a consequence of a primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system. Broadly defined, an immunocompromised host has an alteration in phagocytic, cellular, or humoral immunity that increases the risk of an infectious complication or an opportunistic process such as a lymphoproliferative disorder or cancer.[1] Patients may also be immunocompromised if they have an alteration or breach of their skin or mucosal defense barriers that permits microorganisms to cause either a local or a systemic infection (e.g., from burns or indwelling catheters). Table 1 reviews several conditions with acquired immunosuppression and the alterations in host defense that increase the risk of infection.

Although the causes of fever in immunocompromised hosts are numerous, some guidance is given by the specific immunologic defect or defects present in the patient. In addition, the length of time that the immune defenses are altered has an extremely important effect on the types of infectious complications that are likely to occur. This review focuses on patients who are immunocompromised because of cancer or its treatment, those undergoing transplantation of bone marrow or solid organs, patients who have had a splenectomy, and patients with human immunodeficiency virus (HIV) infection or the acquired immunodeficiency syndrome (AIDS). Recognizing that this brief review cannot be comprehensive, I will try to highlight some of the specific issues and challenges in the management of fever in immunocompromised patients, focusing on infectious complications. It must, of course, be remembered that fever can also be due to noninfectious causes such as drugs, certain cancers, inflammation, and vasculitis.

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FEVER, IMMUNOSUPPRESSION, AND INFECTION

Fever is the principal and sometimes the only manifestation of serious infection in the immunocompromised patient.[1-3] Although a number of fever patterns have been associated with various infectious or noninfectious illnesses, no pathognomonic pattern or degree of fever has been clearly associated with a specific infection in immunocompromised patients. There is also no pattern of fever that can be used to rule out a noninfectious cause.[4] Furthermore, patients who are profoundly immunocompromised can (albeit rarely) have serious local or systemic infections in the absence of fever. Fever can also be suppressed or muted by immunosuppressive agents that may be part of the therapeutic regimen, especially steroids and nonsteroidal antiinflammatory agents. However, patients with infection usually have fever despite the use of these agents.

Fever is a manifestation of the release of proinflammatory cytokines (interleukin-1α, interleukin-1β, interleukin-4, interleukin-6, and tumor necrosis factor α) from macrophages, lymphocytes, fibroblasts, epithelial cells, and endothelial cells as a consequence of infection or inflammation.[4] Analogues of these cytokines are inherent in the innate immune response throughout phylogeny as well as being part of the acquired immune system that confers antigen-specific immune defense.[5] Although endogenous pyrogens are classically thought to originate from polymorphonuclear leukocytes, patients with profound neutropenia have high fevers when they have infections, so reservoirs of pyrogens other than neutrophils are also important.

NEED FOR URGENT EVALUATION AND INTERVENTION

One of the most important decisions with respect to an immunocompromised patient is whether a fever requires urgent evaluation and prompt empirical antimicrobial therapy.[1-3] Among the clinical conditions associated with a risk of life-threatening infections are profound neutropenia (i.e., an absolute neutrophil count of less than 500 per cubic millimeter) or a history of splenectomy. In patients with these characteristics, rapidly progressive infection may be life-threatening if untreated.[6] Because of the blunted inflammatory response in patients with neutropenia, the signs and symptoms of infection can be minimal, so a heightened index of suspicion for infection is essential.

However, not every patient with neutropenia is equally vulnerable to acute life-threatening infection. Important cofactors include the degree of neutropenia, its duration, and whether there are other perturbations in the host defenses. Patients who have neutropenia after cytotoxic chemotherapy or immediately after preparative therapy for transplantation

TABLE 1. RISK FACTORS FOR FEVER AND CAUSES OF FEVER IN PATIENTS WITH ACQUIRED IMMUNOSUPPRESSION.

CONDITION	MAJOR RISK FACTORS	PREDOMINANT CAUSES OF FEVER
Cancer		
Low risk	Underlying disease, therapy, neutropenia ≤10 days, altered mucosal immunity, indwelling catheter	Fever of unknown cause Gram-positive or gram-negative bacteria, respiratory viruses or herpesviruses, *Pneumocystis carinii* (rarely)
High risk	Underlying disease, therapy, neutropenia >10 days, altered mucosal immunity, defects in humoral or cellular immunity, indwelling catheter	Fever of unknown cause Bacteria: gram-positive or gram-negative aerobes, anaerobes at sites of mixed infection Viruses: respiratory syncytial virus, parainfluenza virus, adenoviruses, herpes simplex virus, cytomegalovirus Fungi: candida, aspergillus, cryptococcus, trichosporon, fusarium, phaeohyphomycosis *Pneu. carinii,* toxoplasma
Transplantation		
Bone marrow	Risk factors for high-risk cancer, plus immunosuppressive regimen, prior infection with cytomegalovirus, graft-versus-host disease	Similar to those with high-risk cancer; pattern of infection is influenced by time since transplantation and type of procedure (i.e., autologous or allogeneic)
Solid organ	Site of transplant, underlying disease (e.g., cystic fibrosis) and prior infection status, status of underlying disease, nutritional status, age, immunosuppressive regimen	Pattern of infection is influenced by time since transplantation and type of transplant Bacteria: varies according to type of transplant and includes gram-negative and gram-positive bacteria Viruses: cytomegalovirus, Epstein–Barr virus, hepatitis B and C viruses, adenovirus Fungi: aspergillus *Pneu. carinii*
Splenectomy	Age, reason for splenectomy (e.g., trauma), underlying disease (e.g., hematologic, immunologic, neoplastic), defects in humoral immunity and complement	Bacteria: primarily encapsulated organisms, especially *Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Capnocytophaga canimorsus* (DF2) Parasites: babesia, malaria
HIV infection or AIDS*	Age, CD4 number and function, humoral status (hypogammaglobulinemia or dysgammaglobulinemia), altered neutrophil number or function, indwelling catheter	Bacteria: more common in children, although incidence of *Strep. pneumoniae* is increased in adults as well; other encapsulated bacteria, salmonella, enteric bacteria, pseudomonas; mycobacteria, especially *Mycobacterium avium* complex and *M. tuberculosis* Viruses: herpes simplex virus, cytomegalovirus, varicella–zoster virus, Epstein–Barr virus, respiratory viruses (especially respiratory syncytial virus, adenovirus, parainfluenza virus, measles virus) Fungi: candida (can be invasive in patients with catheters), cryptococcus (rare in children), aspergillus (uncommon), histoplasma, coccidioides, *Penicillium marneffei* (depending on location) *Pneu. carinii,* toxoplasma, cryptosporidia, microsporidia

*HIV denotes human immunodeficiency virus, and AIDS acquired immunodeficiency syndrome.

nearly always have breaches of physical defense barriers, typically with oral and gastrointestinal mucositis, which permit changes in colonization as well as serving as nidi for local infection and entry points for systemic invasion. Such patients are also likely to have alterations in cellular immunity (including drops in CD4 cell counts and function) as well as hypogammaglobulinemia,[7] which make these patients among the most vulnerable to acute infections.[8]

Patients in whom neutropenia develops after a viral infection do not have the same risk of acute bacterial infection as those who have neutropenia after chemotherapy or preparative therapy for transplantation. Presumably this is because they do not have concurrent breaches of mucosal integrity.[9] Similarly, although patients with aplastic anemia or congenital neutropenia are vulnerable to acute bacterial infections, they are generally at lower risk for the acute life-threatening bacterial infections seen in patients who have neutropenia after cytotoxic chemotherapy, probably because of the absence of concomitant mucositis or other immunologic deficits.

Not infrequently, neutropenia develops in patients with HIV infection as a consequence of retroviral infection of hematopoietic progenitors, secondary infections (e.g., *Mycobacterium avium* complex or cytomegalovirus infection), or bone marrow suppression from antiretroviral therapy (e.g., zidovudine treatment). The development of fever in an HIV-infected patient who also has neutropenia suggests the possibility of an infectious complication, although the relative risk is less than in patients whose neutropenia is consequent to cytotoxic chemotherapy.[10-12]

Patients who are functionally asplenic (e.g., from sickle cell disease) or who have had a splenectomy, especially those in whom a splenectomy was performed because of a malignant disorder (e.g., Hodgkin's disease), have increased vulnerability to life-threatening infections with encapsulated bacteria (e.g., *Streptococcus pneumoniae, Neisseria meningitidis,* and *Hae-*

mophilus influenzae), particularly if they have not been immunized. Such patients require prompt attention when they become febrile, regardless of their neutrophil count, since they are vulnerable to acute hemodynamic deterioration or central nervous system infection if not promptly treated.

In addition to neutropenia, severe alterations in either humoral or cellular immunity can lead to life-threatening infections. Patients with substantial depressions of CD4 cell counts (to less than 1500 per cubic millimeter during the first year of life, 750 per cubic millimeter in children between two and six years of age, and 200 per cubic millimeter in children more than six years of age and adults) are at risk for life-threatening infections with *Pneumocystis carinii* and acute infections with other organisms that might have serious consequences if not promptly evaluated and treated (e.g., *Toxoplasma gondii* encephalitis and cytomegalovirus retinitis).[13] In HIV-infected adults, opportunistic infections are uncommon unless the CD4 count is less than 200 per cubic millimeter, with the exception of tuberculosis, which should be considered whenever patients become febrile. In contrast, *M. avium* complex infection is rarely observed until the CD4 count falls below 50 per cubic millimeter.

The risk of these infections is also heightened by certain immunosuppressive agents (e.g., cyclosporine) that are given after solid-organ transplantation or for the treatment of serious autoimmune diseases.[14-16] Although bacterial infections with gram-negative or gram-positive organisms are the most common infectious complications immediately after transplantation, the profound alterations in cellular immunity also heighten the risk of serious opportunistic infections (such as *Pneu. carinii,* cytomegalovirus, and aspergillus infection).

DOMINANT ORGANISMS ASSOCIATED WITH INFECTION

The spectrum of organisms responsible for infectious complications in immunocompromised hosts is daunting, since virtually any organism can become invasive if host defenses are severely impaired.[1-3] Although no guideline is sacrosanct, the most probable offending organisms can be identified on the basis of the degree and duration of immunosuppression and the type of immune defect (isolated or part of a multifactoral process). The predominant organisms are also influenced by the patient's treatment regimen as well as by where the patient resides and receives care.

Bacteria represent the immediate threat to most immunocompromised hosts. During the past two decades, there have been changes in the dominant organisms responsible for infection in immunocompromised hosts with neutropenia.[3,17-19] Gram-positive organisms, especially the coagulase-negative staphylococci, have emerged as the leading cause of acute bacterial infections associated with fever and neutropenia in patients in the United States and western Europe. The increased prevalence of these organisms may be partly due to the increased use of indwelling intravenous-access devices, although this trend began before the routine use of these devices. In contrast, in developing countries gram-negative organisms, including *Pseudomonas aeruginosa, Escherichia coli,* and klebsiella species, still predominate, with a pattern of infection similar to that in the United States and Europe in the 1960s and 1970s.

In addition to the coagulase-negative staphylococci, *Staphylococcus aureus* as well as streptococci and enterococci (the latter associated, in some centers, with resistance to vancomycin), are the principal gram-positive isolates, accounting for over half of the microbiologically defined infections. Enterococci, including vancomycin-resistant enterococci, are a particular problem for patients receiving liver transplants. Despite their predominance, most of these gram-positive organisms do not cause immediately life-threatening infections. The main reason for the prompt evaluation and empirical treatment of immunocompromised patients with bacterial infection is the risk of an untreated infection with gram-negative bacteria.[3]

In patients who have undergone splenectomy and in both children and adults infected with HIV, *Strep. pneumoniae* is the leading bacterial pathogen, and it can be associated with bacteremia.[20] Gram-negative organisms, including *Pseud. aeruginosa,* can also cause pneumonia and bacteremia in patients with AIDS, especially those with low CD4 counts.[21]

Patients with neutropenia who have received cytotoxic therapy or who are receiving bone marrow transplants are also vulnerable to infections with viruses, including herpesviruses and respiratory viruses, as well as fungi and parasites. Certain viruses can cause acute fever, particularly respiratory syncytial virus, adenovirus, parainfluenza virus, and cytomegalovirus. In contrast, infections with opportunistic and endemic fungi are secondary complications in patients with protracted neutropenia or in organ-transplant recipients with cytomegalovirus infection (Table 1).

For practical purposes, patients with neutropenia can be divided into low- and high-risk groups on the basis of the projected duration of neutropenia. Patients at low risk (generally those with solid tumors and those who have received less intensive chemotherapy regimens) have had neutropenia for no more than 10 days and usually have excellent outcomes, rarely complicated by secondary infectious complications.[3] In contrast, patients at high risk (those who have had neutropenia for more than 10 days) are vulnerable not only to acute bacterial infections but also to second or even multiple infectious complications from bacteria, fungi, viruses, or parasites (Table 2). Clearly, treatment of the latter group is a major challenge.

TABLE 2. ASSOCIATION OF SPECIFIC SITES WITH FEVER IN SELECTED IMMUNOCOMPROMISED STATES.

SITE	HIGH-RISK CANCER*	TRANSPLANTATION					SPLENECTOMY	HIV INFECTION OR AIDS	
		BONE MARROW	KIDNEY	LIVER	LUNG	HEART		CHILDREN	ADULTS
Blood	Bacteremia (10–15% of patients), fungemia	Bacteremia, fungemia	Bacteremia (relatively common)	Rare	Rare	Rare	Encapsulated bacteria	Encapsulated bacteria, *Mycobacterium avium* complex	*Streptococcus pneumoniae*
Respiratory tract	Sinusitis (especially fungal) with prolonged neutropenia Local or diffuse pneumonia (especially fungal) with prolonged neutropenia	Sinusitis (especially fungal) Bacterial or fungal pneumonia with neutropenia Cytomegalovirus about 30 to 60 days after allogeneic transplantation	Not specific	Not specific	Common Local or diffuse pneumonia (especially fungal)	Common Local or diffuse pneumonia	Not specific	Bacterial sinusitis, otitis Pneumonia: pseudomonas, *Pneumocystis carinii, Strep. pneumoniae*	Bacterial sinusitis Pneumonia: *Pneu. carinii,* cryptococcus, pseudomonas, *Strep. pneumoniae*
Gastrointestinal tract	Mucositis or esophagitis (due to candida, herpes simplex virus, bacteria) Rarely, typhlitis, necrotizing fasciitis, perianal cellulitis	Mucositis or esophagitis (herpes simplex virus, cytomegalovirus) Rarely, typhlitis, necrotizing fasciitis, perianal cellulitis	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Mucositis, esophagitis, colitis due to candida, herpes simplex virus, cytomegalovirus, *M. avium* complex, *Clostridium difficile,* cryptosporidia, microsporidia	Same as for children
Liver	Hepatosplenic candidiasis (on recovery from neutropenia)	Hepatosplenic candidiasis (on recovery from neutropenia)	Uncommon	Hepatitis, cholangitis, abscess	Uncommon	Uncommon	Uncommon	Hepatitis	Hepatitis A, B, and C viruses; perianal herpes simplex virus
Nervous system	Uncommon	Uncommon (toxoplasma, nocardia, cryptococcus)	Uncommon (listeria)	Uncommon (listeria)	Uncommon (listeria)	Uncommon (listeria)	Meningitis *(Strep. pneumoniae, Haemophilus influenzae, Neisseria meningitidis)*	Cytomegalovirus	Toxoplasma, cryptococcal meningitis, neurosyphilis, cytomegalovirus
Cutaneous	Ecthyma due to pseudomonas or aeromonas	Same as high risk	Cytomegalovirus	Uncommon	Uncommon	Uncommon	Uncommon	Viruses: chronic varicella–zoster virus, herpes simplex virus, cytomegalovirus	Herpes simplex virus, cytomegalovirus, varicella–zoster virus
Other	Fusarium pyomyositis	Hemorrhagic cystitis (adenovirus, BK virus, cytomegalovirus) Uncommon, fusarium pyomyositis	Pyelonephritis	Uncommon	Uncommon	Mediastinitis	Uncommon	Bacterial osteomyelitis, pyomyositis	Pyomyositis

*Patients with low-risk fever and neutropenia rarely have clinical or microbiologic manifestations of infection.

TABLE 3. EVALUATION OF FEVER IN IMMUNOCOMPROMISED PATIENTS.*

TYPE OF EVALUATION	CANCER		TRANSPLANTATION					SPLENECTOMY	HIV INFECTION OR AIDS	
	LOW RISK	HIGH RISK	BONE MARROW	KIDNEY	LIVER	LUNG	HEART		CHILDREN	ADULTS
History and physical examination	+	+ (repeat daily if fever is present)	+ (repeat daily if fever is present)	+ (repeat daily if fever is present)	+ (repeat daily if fever is present)	+ (repeat daily if fever is present)	+ (repeat daily if fever is present)	+	+	+
Hematologic										
CBC and differential count	+	+	+	+	+	+	+	+/−	+/−	+/−
Platelets	+	+	+/−	+/−	+/−	+/−	+/−	+/−	+/−	+/−
Coagulation studies	−	+/−	+	+/−	+	+/−	+/−	+/−	−	−
Microbiologic										
Nose and throat	Sx	Sx	Sx	Sx	Sx	Sx	Sx	−	−	−
Urine	+	+	+	+	+/−	+/−	+/−	−	Sx	Sx
Stool	−	−	−	−	−	−	−	−	Sx	Sx
Blood	+	+	+	+	+	+	+	+	+	+
Cytomegalovirus antigen	−	−	+	+	+	+	+	−	Sx	Sx
Epstein–Barr virus PCR	−	−	Sx	Sx	Sx	Sx	Sx	−	Sx	Sx
Cerebrospinal fluid	−	−	−	−	−	−	−	+/−	+/−	Sx†
Radiologic										
Chest	Sx	+	+	+	+	+	+	+	+	+
Sinus	−	+/−	+/−	−	−	+/−	+/−	−	Sx	+/−
Special studies§	Sx	Sx‡¶	Sx‡	Sx	Sx	Sx	Sx	Sx	Sx	Sx

*A plus sign denotes indicated; a minus sign, not necessary; a plus sign and a minus sign, may be necessary; Sx, when symptoms are present; CBC, complete blood count; and PCR, polymerase chain reaction.

†An evaluation of cerebrospinal fluid is especially important in patients with persistent fever.

‡Lung computed tomography to detect pulmonary aspergillosis should be performed in patients with persistent fever and neutropenia and more than one week of empirical therapy with antibiotics.

§Special studies include computed tomography and magnetic resonance imaging.

¶Abdominal computed tomography or magnetic resonance imaging to detect hepatosplenic candidiasis should be performed in patients recovering from neutropenia who have new or persistent fever.

Patients who have received bone marrow transplants are initially like high-risk patients with neutropenia. After hematologic reconstitution, particularly during the late post-transplantation period (more than 100 days after transplantation), they are susceptible to infection with encapsulated bacteria, especially *Strep. pneumoniae*. Patients who have received solid-organ transplants also have an increased risk of bacterial infections. For these patients, bacterial infections are the most common type of infection in the first few weeks after transplantation.

The risk of infection is influenced by the type of transplant and the time since it was performed. For example, for kidney-transplant recipients, septicemia and peritonitis caused by gram-negative bacteria, including *Pseud. aeruginosa,* are the most common types of infection.[14] Enteric organisms (including vancomycin-resistant enterococci) account for at least 50 percent of the bacterial infections after liver transplantation. Ascending cholangitis must also be considered in these patients. Bacterial mediastinitis and pneumonia are problems worthy of special consideration in recipients of heart or heart and lung transplants with new onset of fever.

The risk of viral and other infections can also be related to specific perturbations of host defense. For example, the times of onset of specific types of herpesvirus (e.g., herpes simplex virus, cytomegalovirus, or varicella–zoster virus) range over the course of recovery of patients who have received bone marrow or solid-organ transplants. Herpes simplex virus infections occur early (2 to 6 weeks after transplantation), cytomegalovirus infections after 1 to 3 months, and varicella–zoster virus infections after 6 to 12 months. Epstein–Barr virus can contribute to a broad array of clinical symptoms, ranging from fever to lymphoproliferative syndromes.[22,23] Adenovirus can cause fever associated with necrotizing hepatitis, pneumonitis, or hemorrhagic cystitis. When manifestations of central nervous system disease develop in a patient who has received a solid-organ transplant, listeria infection and cryptococcal meningitis should be included in the differential diagnosis.

The likelihood of other infections in an HIV-infected patient can be related to the CD4 count and the age of the patient. For example, *Pneu. carinii* infection occurs only in patients with low age-corrected CD4 counts, except for infants two to eight months old. Similarly, infections with *M. tuberculosis, M. avium* complex, and other opportunistic pathogens (e.g., cryptococcus and toxoplasma) are seen in patients with profound loss of their CD4 repertoire.[24]

TABLE 4. TREATMENT OF IMMUNOCOMPROMISED PATIENTS WITH NEW FEVER.

CATEGORY	INTERVENTIONS
Cancer	
Low risk	Begin broad-spectrum antibiotic therapy with a single parenteral agent (e.g., ceftazidime, cefepime, imipenem, meropenem) or possibly oral therapy (ciprofloxacin and amoxicillin plus clavulanate potassium).
High risk	Begin broad-spectrum parenteral antibiotics with a single agent (see low risk, above) or a combination regimen.
	Additions to or modifications of the initial regimen are likely in patients with persistent fever or prolonged neutropenia.
Transplantation	
Bone marrow	Immediate postpreparative therapy management is similar to that with high-risk cancer.
	After engraftment, patients are at risk for viral (cytomegalovirus, varicella–zoster virus), parasitic, and fungal infections.
	Late infections (>100 days post-transplantation) may be due to encapsulated bacteria; fevers in such patients are managed with antibiotic therapy.
Kidney	Immediately postoperatively, patients should be treated empirically with broad-spectrum antibiotics for possible septicemia, pyelonephritis, or pneumonia.
	Postoperatively, consider viral (especially cytomegalovirus) and parasitic infections.
Liver	Immediately postoperatively, patients should be treated empirically for bacteremia (especially enteric organisms) and ascending cholangitis.
	Postoperatively, consider cytomegalovirus, Epstein–Barr virus, and adenovirus.
Lung	Immediately postoperatively, consider pneumonitis, especially with gram-negative bacteria (in patients with cystic fibrosis, pseudomonas is a risk).
	Late infections with aspergillus are a risk.
Heart	Postoperatively, issues to be addressed include empirical therapy for gram-positive and gram-negative bacteria with particular focus on pneumonia and mediastinitis. Post-transplantation infections include viruses (especially cytomegalovirus and Epstein–Barr virus) and parasites (*Pneumocystis carinii* and toxoplasma).
Splenectomy	Patients should receive an antibiotic regimen with activity against encapsulated organisms.
HIV infection or AIDS	
Children	Therapy is ideally directed against the specific site associated with the fever (e.g., upper or lower respiratory tract).
	Management depends on age-corrected CD4 count for patients with low CD4 counts. Opportunistic infections (e.g., *Pneu. carinii,* cytomegalovirus, and *Mycobacterium avium* complex as well as bacterial infections) must be considered. These are sometimes treated empirically.
Adults	Treatment is similar to that in children.
	Bacterial infections are less common (except for *Streptococcus pneumoniae*), but other opportunistic infections are more common (e.g., *M. tuberculosis, M. avium* complex [especially when the CD4 count is <50/mm^3], toxoplasma, and cryptococcus) and require special attention.

Accordingly, the organism causing a fever can be reasonably predicted from the stage of the patient's underlying disease.

INITIAL EVALUATION OF FEVER

The initial evaluation of a febrile, immunocompromised patient is guided by the underlying disease and the urgency of the need for empirical therapy. It is important to ascertain whether the patient is at risk for a local or systemic infection and whether there are any symptoms or signs that can help pinpoint the site of infection.

For patients with neutropenia, a specific site of infection is generally lacking. In nearly two thirds of cases, the initial evaluation does not identify a focus of infection.[1-3] This may be partly because most of these patients have already been given broad-spectrum antibiotics empirically, which may make it harder to determine the site of infection. Nonetheless, attention should be directed to the most common sites of infection, including the oral cavity, lungs, gastrointestinal tract (including the perineal area), skin, and soft tissues. Careful physical examinations should be repeated at least daily in patients with neutropenia, even after the initiation of empirical antibiotics. Table 3 reviews the most important components of the initial evaluation in patients with neutropenia. The need for additional studies is guided by the patient's symptoms, which may change over time.

Fever in other immunocompromised patients is more often caused by infection at specific sites (e.g., *Pneu. carinii* pneumonia in HIV-infected patients), but a specific site is often not clinically definable. However, when a site is defined, it is generally possible to manage the infection more specifically rather than empirically. In patients receiving allogeneic bone marrow transplants, attention should be directed to the possibility of interstitial pneumonitis, especially with cytomegalovirus, from 30 to 60 days after transplantation. Although cytomegalovirus is also important in patients receiving solid-organ transplants, it is relatively uncommon in patients receiving autologous bone marrow transplants.

Clinicians must remember that profoundly im-

munocompromised patients are vulnerable to more than one infection, and that different organisms may emerge during a single febrile episode, especially when the immunosuppression is profound and prolonged. There are differences, however, in the types of secondary infections that occur, according to whether the patient's immunocompromise is related to defects in phagocyte number or function or to alterations in cellular or humoral immunity.

MANAGEMENT OF INFECTIOUS COMPLICATIONS

Management of fever and infection in immunocompromised patients can be guided by the nature of the host-defense defects (e.g., neutropenia or cellular immunity), their severity, the duration of the specific episode, the type of symptoms, local environmental factors that affect the nosocomial microflora and their resistance patterns, and the economic factors or barriers that affect prescribing practice and the cost of care. The guiding principle has been to treat severely immunocompromised, febrile patients empirically for the major pathogens to which they are vulnerable at the particular period of their immunosuppression (e.g., immediately after chemotherapy as compared with weeks or months after bone marrow or solid-organ transplantation).[25] Broad-spectrum antibiotic therapy is administered to cover gram-positive and gram-negative aerobic organisms. Either combination antibiotic regimens or monotherapy with selected third-generation cephalosporins or carbapenems is used.[26-29] The specific approach varies according to the type of immunocompromise (Table 4). The proportion of immunocompromised patients treated outside the hospital is increasing.[30-32] However, patients with prolonged immunosuppression may have multiple febrile episodes or persistent fever despite empirical therapy. These patients may need frequent modifications of their regimen, which may improve the outcome. Patients with prolonged or unabated immunocompromise require prolonged antimicrobial treatment.

In summary, fever is common in patients who are immunocompromised. The cause is usually an infection, which may be difficult to diagnose. The treatment of these patients benefits from anticipation of the major sites and causes of infection and from appropriate presumptive antimicrobial therapy.

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