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Fever and Septicemia

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1. Introduction

Fever is the hallmark of infection, but is not specific for it. Infection can begin and progress in the absence of fever. When fever occurs in the immunocompromised host, the single major challenge in clinical decision-making is to ascertain whether the onset of temperature elevation is a reliable indication of the onset of infection rather than a manifestation of the underlying disease, a hypersensitivity reaction, or a factitious development. Another major issue that frequently stirs acrimonious bedside debate involves the clinical wisdom of suppressing fever with or without evidence of documented infection. Despite many decades of controversy, it has not been conclusively established whether fever is "good" for the patient or just adds to patient discomfort without benefiting host defenses against infection or the underlying disease.

Whatever the cause and however great the temperature elevation, the appearance of fever in the immunocompromised host is an urgent signal to initiate a comprehensive search for its etiology. If the clinical situation warrants, a presumptive diagnosis of systemic infection is made, and empiric drug therapy may be initiated in the absence of microbiologic confirmation. "Unstable" patients will require constant observation in a well-staffed setting. Although the decision to initiate therapy may be precipitous, the clinician who cares for immunocompromised patients must be flexible, persistently inquisitive, and willing to change course as more clinical and laboratory information becomes available.

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2. Criteria for Fever, Fever of Undetermined Origin, and Septicemia

A widely read textbook of infectious disease defines fever as an oral temperature above 100.2°F (37.8°C) or a rectal temperature above 101.2°F (38.4°C).[1] These are practical criteria for distinguishing febrile from normal states. Nonetheless, it must be recognized that a single definition of fever is quite arbitrary, and there is a considerable range in temperatures even in normal individuals. For instance, 42% of subjects in one study had temperatures exceeding 98.6°F (37°C) and reaching 100°F (37.8°C) in some instances.[2] A wide variety of factors, including ovulation, smoking, exercise, and psychoneural factors, may affect body temperature.

Fever of undetermined origin (FUO) is a well-known term used by various investigators to describe persistence of fever over a period of several (2–5) weeks during which conventional diagnostic measures are unfruitful.[3] Several "thresholds" for FUO have been proposed, such as temperature elevations above 100.5°F (38°C) or 101°F (38.3°C). Regardless of definitions, we believe that the experience reported in several classic studies of FUO[4,5] has limited applicability to the immunocompromised host for several reasons. First, the classic studies have summarized the clinical experience obtained from evaluating febrile patients who present without a known underlying disease. In the immunocompromised host, the nature of the basic disorder is usually identified, and when fever appears, the challenge is to determine whether something else, i.e., something of infectious etiology, is also present. Second, the classic definitions of FUO require a period of weeks of persistent fever. When fever develops in an immunocompromised subject, an immediate therapeutic decision is often required. The clinician does not enjoy the luxury of a diagnostic evaluation that may span 1 or 2 weeks. Conversely, a diagnosis of FUO after a single initial evaluation by a physician is inappropriate because the results of initial diagnostic studies will not be available

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for 12–72 hr, and the patient could have a readily identifiable bacterial infection.

We believe that a practical working definition of FUO in the immunocompromised subject can be made after initial diagnostic measures to rule out an acute bacterial or fungal infection. Since 90% of positive blood cultures for bacteria are identified within 72 hr of incubation,[6] and candidal growth takes perhaps a day longer, this working definition sets a boundary of perhaps 100 hr. Beyond that point, more aggressive and invasive diagnostic measures may be required. Obviously, if indicated by clinical developments such as progressive diffuse pulmonary infiltrates, such procedures should be undertaken even earlier than that.

In clinical parlance, the terms *septicemia* and *bacteremia* are used interchangeably, usually with little chance for misunderstanding.

During the decade of the nineties, however, variable definitions for infection of a systemic nature have been proposed and modified by authors working in the critical care area.[7,8] Perhaps the major motivating factor behind these changes in definition has been the recognition that patients may have systemic evidence of toxemia related to infection, particularly endotoxemia, and yet have negative blood cultures. Widespread use of antibiotics even before patients reach the hospital setting or the prevalent use of prophylactic antibiotics in the compromised host has led to a number of clinical situations in which patients appear to be infected systemically and yet have negative blood cultures. Table 1 is an attempt to summarize the various definitions proposed by several groups of workers. Insofar as clinicians understand the specific definition for a clinical condition, these categorizations should prove clinically useful.

TABLE 1. Sepsis and Related Disorders

Disorder	Definition
Bacteremia	Bacteria present in blood, as confirmed by culture; may be transient.
Septicemia	Same as bacteremia, but implies greater severity.
Sepsis	Clinical evidence of infection, plus evidence of a systemic response to infection.
Sepsis syndrome	Sepsis plus evidence of altered organ perfusion with at least one of the following: hypoxemia, elevated lactate, oliguria, altered mentation.
Septic shock	Sepsis syndrome plus hypotension (systolic blood pressure lower than 90 mm Hg or decrease in mean arterial blood pressure of more than 40 mm Hg from baseline).
Refractory septic shock	Septic shock that lasts for more than 1 hr and does not respond to intravenous fluid administration or pharmacologic intervention.

Bacteremia can be transient (as following mastication), whereas septicemia implies systemic spread of infection. For reasons that are poorly understood, some bacterial (nocardiosis and tuberculosis) and fungal infections (*Candida* and *Aspergillus*) may spread systemically in the face of negative blood cultures. Therefore, in addition to positive blood cultures or blood smears, we would accept as evidence of septicemia or disseminated infection histologic evidence of the presence of an organism in muscle, soft tissue, bone marrow, organ sections, or skin lesions. In the impaired host, we would accept as evidence of septicemia positive cultures of peripheral venous blood, even though the bacteremia or fungemia might result from contaminated intravascular lines. Positive blood culture samples drawn through a possibly infected vascular catheter should be confirmed with a repeat peripheral venous blood culture. Foreign bodies may serve as an iatrogenic source of infection that nonetheless results in systemic spread.

By contrast, we cannot accept the recovery of an organism from mucosal surfaces, expectorated respiratory secretions, stool, or skin surfaces as prima facie evidence of systemic infection with organ involvement because of the well-known bacterial and fungal overgrowth that can take place when the host has a debilitating illness and is treated with a variety of antimicrobial agents.

3. Pathogenesis of Fever

A scientific understanding of the pathogenesis of fever in animal models dates back to the pioneering discovery of Beeson,[9] who reported in 1948 that a pyrogen distinct from bacterial endotoxin could be recovered from rabbit leukocytes. More recent work has indicated that at least one protein moiety, so-called "endogenous pyrogen," is elaborated by a variety of cell types, including blood monocytes, alveolar and peritoneal macrophages, and the phagocytic cells of the reticuloendothelial system present in liver (Kupffer cells), spleen, and lymph nodes.[10,11] By contrast, lymphocytes are apparently incapable of pyrogen production.

Important work has also demonstrated the identity between endogenous pyrogen and interleukin-1 (IL-1), an important lymphokine elaborated by macrophages.[10,11] IL-1 appears to be responsible for muscle wasting and protein catabolism during severe infection.[10,11] It has also become apparent that in addition to IL-1, a variety of peptide molecules with immunomodulatory properties, called *cytokines, monokines,* or *immunomodulators,* are elaborated by leukocytes and

have pyrogenic properties and, in a sense, may be considered endogenous pyrogens. These include tumor necrosis factor (TNF), IL-6, and the interferons (IFNs). Figure 1 summarizes the broad pathways by which pyrogens like IL-1 cause fever by their "central" or hypothalamic action. However, Fig. 2 now attempts to "fill in" the concept of endogenous pyrogens by more specific understanding of the cytokine network and the relationships between such substances and IL-1, TNF, IL-6, and IFN-γ.[3,10]

The basic mechanism underlying the production of fever in rabbits involves a period during which certain exogenous agents (activators) stimulate protein synthesis, because normal phagocytic cells from rabbits neither contain nor produce endogenous pyrogen when incubated *in vitro*. These activators include both gram-positive and gram-negative cell walls, viruses, phagocytizable particles such as latex, and certain pyrogenic steroids. Incubation of activating agents with phagocytic cells results in phagocytosis within minutes and the elaboration of endogenous pyrogen, which continues for many hours *in vitro*. In the rabbit, endogenous pyrogen appears in the blood at the same time that the fever develops. Following removal of the provocative agent, injection of supernatant fluids from cells activated *in vitro* into blood or brain at sites in or near the anterior hypothalamus results in prompt elevation of animal body temperature. Thus, as shown in Fig. 1, the pathway to temperature elevation includes (1) elaboration of endogenous pyrogen by activated cells after an exposure to the proper stimulus, (2) release of endogenous pyrogen into the circulation,

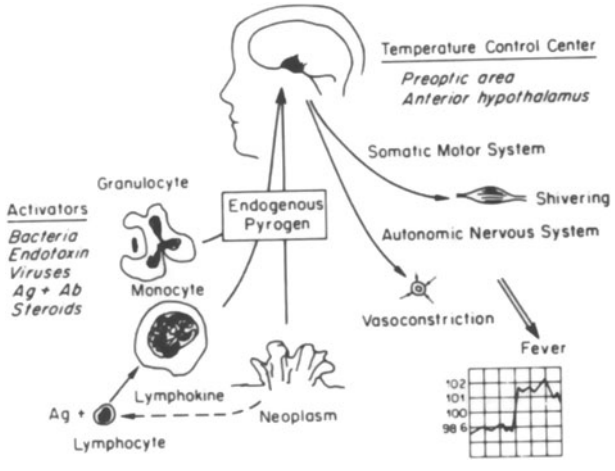

FIGURE 1. Pathogenesis of fever. This schematic diagram summarizes the mechanisms by which fever is induced in man. Activating substances consist of microorganisms or drugs such as steroids. Phagocytosis by granulocytes or antigen (Ag) interaction with lymphocytes followed by lymphocyte–monocyte collaboration can lead to release of endogenous pyrogen. The latter acts directly on the hypothalamic temperature-control center by initiating processes such as shivering and vasoconstriction that lead to temperature elevation. (Ab) Antibody.

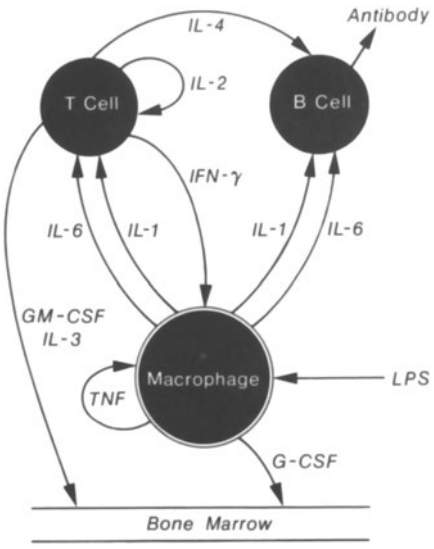

FIGURE 2. Cytokine network and the inflammatory response. Following an infectious stimulus, such as lipopolysaccharide [(LPS) commonly known as endotoxin], an interlinked group of peptide mediators of inflammation are produced within minutes in sufficient quantities that they appear in the circulation. These mediators are also called *cytokines, monokines,* or *immunomodulators*. Cytokines include the interleukins, of which IL-1 (endogenous pyrogen) and IL-6 cause fever and can induce shock, while IL-2 (T-cell growth factor) is produced by T cells and supports T-cell proliferation (autocrine activity). Autocrine activity is also characteristic of tumor necrosis factor (TNF), which is produced primarily by macrophages and can trigger both fever and hypotension. The interferons (IFN-γ) are also pyrogens and are involved in the process of macrophage activation. Colony-stimulating factors (CSFs) are produced by lymphocytes and macrophages. They act directly on the bone marrow to induce terminal differentiation and accelerated production of neutrophils [granulocyte-colony stimulating factor (G-CSF)], or more "broad-spectrum" stem-cell proliferation [granulocyte-macrophage colony stimulating factor (GM-CSF)]. The CSFs may also have mild pyrogenic activity.

(3) interaction of pyrogen with neurons of the temperature-control center of the anterior hypothalamus, and (4) a change in the set point of the body temperature resulting in initiation of processes involving heat conservation (e.g., vasoconstriction through the autonomic nervous system) and increased heat production (e.g., the muscular action of shivering).

Purification of endogenous pyrogen or IL-1 has been accomplished. It has been made immunogenic, and a radioimmunoassay for its detection has been developed.[8] Similarly, simple enzyme-linked immunoassays have been developed for all the mediators shown in Fig. 2. Following the administration of a potent pyrogenic substance (like endotoxin) to human volunteers or to experimental animals, a rather predictable stepwise progression in the elaboration of cytokines can be detected in the peripheral circulation. TNF in humans usually appears first, followed by IL-1 and IL-6. While high levels of mediators such as TNF have presaged poor

prognosis in septicemias, the mere measurement of cytokine levels has limited clinical value. These substances are rapidly metabolized in the circulation and possess half-lives of minutes. Furthermore, they are of little value in distinguishing gram-negative bacterial infections from gram-positive bacterial infection, or even distinguishing a parasitic from a fungal process.

Much interest has been focused on the mechanism of fever production in hypersensitivity reactions and in neoplastic diseases. There appear to be two separate pathways for the development of hypersensitivity fevers in experimental animals. One mechanism, as shown in Fig. 1, involves the reaction of antigen with antibody. Immune complexes can function as activators and are probably phagocytized by monocytes with the subsequent release of endogenous pyrogen. The other mechanism appears to involve cell-mediated immune recognition. When lymphocytes harvested from lymph nodes of rabbits sensitized with an antigen are incubated with the antigen *in vitro,* the lymphocytes fail to produce pyrogen but are able to stimulate normal blood leukocytes to release pyrogen when these two types of cells are incubated together.[12] Thus, it appears that antigen recognition by lymphocytes results in release of a nonpyrogenic intermediate substance, such as a lymphokine, which then activates mononuclear cells, resulting in release of endogenous pyrogen.

Recurrent fever is a common manifestation of many neoplastic disorders such as leukemias, lymphomas (Hodgkin's disease in particular), hypernephromas, sarcomas of bone, and atrial myxomas [see Tables 7 and 8 (Section 13)]. There are many reports of fever associated with a wide variety of tumor types. A common observation is that fever can coincide with tumor growth, disappears with appropriate treatment or extirpation of malignant disease, but reappears on return or recrudescence of the neoplasm. Several major hypotheses have been advanced to explain tumor-associated fever-including elaboration of a toxin by the tumor, tissue necrosis with leukocyte infiltration and release of tissue pyrogen, obstruction of secretory functions (as in the case of solid tumor metastatic to liver), abnormal liver function with altered conjugation of pyrogenic steroids, or excessive heat production by tumor cells. There is a surprising paucity of evidence that really supports these hypotheses. The popular concept of tumor necrosis being associated with fever has been supported by one study but refuted by others.[13]

Since normal human leukocytes neither contain pyrogen nor produce it *in vitro* unless stimulated by some agent, the focus of investigations into tumor-associated fever has been on the possible elaboration of pyrogens by malignant cells. Bodel[13] presented evidence that certain tissues, including hypernephromas and spleens and lymph nodes from patients with Hodgkin's disease, contain cells that spontaneously release pyrogen when incubated *in vitro.* Mononuclear cells and probably malignant cells appear to be the most likely source of pyrogen, and they differ from phagocytes, which require an activating stimulus. Fever characteristic of endogenous pyrogen resulted when spleen cells from 11 of 20 patients with Hodkin's disease were incubated *in vitro* and their supernatant fluids were injected into rabbits. By contrast, febrile responses were observed with only 2 of 70 supernatants following incubations of spleen cells from patients with nonmalignant diseases. Pyrogenic responses were similarly observed with supernatant fluids prepared after incubation of cells from lymph nodes of patients with Hodkin's disease. Because such cell preparations contain few if any granulocytes, mononuclear cells are apparently responsible for pyrogen production.

The work on tumor-associated fever indicates that malignant cells per se can be the source of a pyrogenic material, but it is also possible that tissue inflammatory cells that respond to tumor growth might be activated by products released from the tumor to release endogenous pyrogen. Such products could include tumor antigens, and they may vary with different neoplastic diseases, thus accounting for differences in incidence of tumor-associated fever. Furthermore, tumor-associated fever might well result from a hypersensitivity reaction. As Bodel[13] postulated, it is possible that the early release of pyrogen that is characteristic of spleen cells from patients with Hodgkin's disease is also mediated by lymphocytes in tissue that are reacting with a tumor-associated antigen. These lymphocytes may then activate other tissue cells (i.e., phagocytes) to release pyrogen.

4. Syndrome-Oriented Approach to Fever and Suspected Infection: Differential Diagnosis

The onset of fever should immediately trigger an exhaustive evaluation to determine what clues can be found to its etiology. Tables 2–6 summarize infectious etiologies suggested by certain clinical findings. In adopting this syndrome-oriented approach, we make no claims to completeness and refer the reader to other chapters for more detailed coverage of pneumonia (Chapter 6) and central nervous system (CNS) infection (Chapter 7). What is desirable, however, is to formulate an orderly approach to differential diagnosis whereby the most likely causes of symptoms referable to an organ system or a physical finding are most expeditiously considered and then ruled in or out. Unfortunately, too many reviews of opportunistic infection stress the organism rather than the presenting manifestations, whereas in ac-

TABLE 2. Infectious Disease Syndromes and Etiologic Agents in the Compromised Host: Disseminated Disease with Skin Lesions

Bacteria	Fungi
S. aureus	*Aspergillus*
Gram-negative bacilli	Zygomycetes
P. aeruginosa	*Candida* species
Aeromonas hydrophila	*Cryptococcus neoformans*
Marine vibrios (halophilic)	*Trichosporon* species
Nocardia species	Viruses
	Herpes simplex
	Varicella–zoster

tuality the reverse is what is encountered. The problems posed by specific opportunistic pathogens are highlighted in Chapters 8–13.

Evidence of disseminated disease with skin lesions—abscesses, vesicles, macules, vasculitis, infarcts, ulcers, maculopapular lesions—should suggest certain groups of bacterial, fungal, and viral pathogens (Table 2). *Staphylococcus aureus* has classically been associated with hematogenously spread abscesses that can involve any skin or subcutaneous area.

Of all the gram-negative rods that cause sepsis in the compromised host, *Pseudomonas aeruginosa* has been most associated with vasculitic skin lesions. Ecthyma gangrenosum is the term applied to the classic cutaneous lesions of *P. aeruginosa*.[14] These lesions are striking in appearance. They may begin as small macules enlarging into an oval or round halo of erythema. Within this halo of erythema (which becomes indurated and slightly raised), a vesicular lesion may develop which may enlarge and become frankly bullous. Palpation of the skin and detection of a round or oval area of induration are valuable means of detecting early ecthyma lesions. It is not unusual to see multiple crops of ecthyma gangrenosum lesions evolve over a matter of hours. The centers of these lesions may become frankly necrotic and ulcerate, while the surrounding areas become ecchymotic. One of the major problems in the differential diagnosis of these lesions is that they often tend to occur in thrombocytopenic patients and may be misinterpreted as ecchymoses. Two areas that must be searched assiduously for ecthyma lesions are the perirectal area and groin. A perirectal abscess may be the first of a series of disseminated pseudomonal skin lesions. In a strict sense, a perirectal abscess is not an ecthyma gangrenosum lesion. (For that matter, in a granulocytopenic patient, a perirectal lesion is more likely to be cellulitis rather than an abscess because of the lack of a neutrophil response.) However, *Pseudomonas* vasculitis may spread from a perirectal cellulitis, and ecthyma lesions may be present in the perirectal area. Perirectal lesions (including thrombosed hemorrhoids) in the neutropenic patient should be regarded as caused by *P. aeruginosa* until proved otherwise.

Some observers have believed that ecthyma gangrenosum lesions might represent a hypersensitivity reaction in the skin analogous to a local Shwartzman reaction. However, in most cases in which antimicrobial therapy has not been initiated, either biopsy or culture will reveal the causative organism. Histopathologic studies carried out on ecthyma gangrenosum lesions indicate that the initial mechanism is a venous thrombosis triggered by invasion of small vessels by microorganisms.[15] Furthermore, it is likely that microbial products such as enzymes and exotoxins are responsible for the evolution of the progressive gross and microscopic changes. Nonetheless, the initial event appears to be localized intravascular thrombosis caused by direct invasion of small and medium-sized blood vessels by viable bacilli.

It has become increasingly apparent that other gram-negative organisms besides *P. aeruginosa* have the capacity to produce ecthyma gangrenosum–like lesions. Septicemic infections caused by the gram-negative bacillus *Aeromonas hydrophila* are uncommon compared to those caused by *P. aeruginosa,* but in one series of *Aeromonas* bacteremias, some 40% of neutropenic patients had either cutaneous lesions that were indistinguishable from *P. aeruginosa* lesions or a gangrenous type of cellulitis accompanied by myonecrosis.[16] *Aeromonas* species are taxonomically distinct from pseudomonads and the enteric bacilli. Like *Pseudomonas,* such organisms can be quite antibiotic-resistant. In addition, there are several reports of marine vibrios (*parahemolyticus, alginolyticus,* and *vulnificus*) causing septicemia characterized by necrotizing skin lesions.[17–19]

Over the past 20 years, we have had the opportunity to study a number of neutropenic patients who developed colorful cutaneous lesions in association with gram-negative rod bacteremia. Some lesions have been ecthyma-like, whereas others have been violaceous blisters, orange-yellow vesicles tensely filled with fluid, or a rapidly progressing angry cellulitis. The causative organisms have included *Escherichia coli, Klebsiella, Enterobacter, Proteus,* and *Serratia* species. The appearance of these cutaneous lesions has been an indication for both immediate culturing of the blood and other potentially infected sites and initiating systemic antimicrobial therapy. If possible, these lesions should be biopsied as well as aspirated or cultured. Some organisms may not be grown (particularly if antimicrobial therapy has already been given), but biopsy followed by appropriate stains will reveal the infecting pathogen.

Nocardia species are higher bacteria previously classified among the fungi. *Nocardia* initially infect the lung, but the next most common sites of involvement are subcutaneous tissues and brain. If *P. aeruginosa* and *S.*

aureus have been reasonably excluded in a patient with pulmonary abscesses, subcutaneous abscesses, or brain abscesses, *Nocardia* infection is one of the leading diagnostic possibilities. The species *N. asteroides* is the most commonly encountered organism, but *N. brasiliensis* can cause an indistinguishable clinical syndrome. Nocardial organisms are gram-positive, beaded in appearance, acid-fast, and branch at 90° angles (see Chapter 9). Although a fair number of cases of *Nocardia* infection have been described in immunosuppressed hosts, particularly those receiving corticosteroids or with underlying lymphoma, the isolation of this organism, in our recent experience, has been on the decline. A possible explanation for this trend is the widespread empiric use of broad-spectrum agents that display activity against *N. asteroides,* such as carbenicillin, trimethoprim–sulfamethoxazole, and some cephalosporins. If patients suspected of having nocardiosis are already receiving antimicrobial therapy, diagnostic efforts must concentrate on microscopic identification of the organism in respiratory secretions or metastatic lesions.

As pointed out in Chapters 8 (fungal infections) and 19 (infections complicating leukemia and lymphoma), one area of major concern in the management of the immunocompromised host is the rising incidence of disseminated fungal infection. Deep infections are notoriously difficult to diagnose, but cutaneous involvement is an important clue that may spare the patient an invasive diagnostic procedure. There have been well-described examples of cutaneous involvement by *Candida,*[20] *Cryptococcus,*[21] zygomycetes (*Mucor* and *Rhizopus* species),[22] and *Aspergillus.*[23] The candidal skin lesions may have an indwelling vascular catheter as the source, and patients may have other evidence of metastatic candidal disease in, for example, the eye (although in our experience, we have never seen *Candida* endophthalmitis in a markedly neutropenic patient). Cutaneous lesions with *Candida* are maculopapular in appearance and may be frankly purulent providing the patient has an adequate cellular inflammatory response. The lesions of *Aspergillus* and Phycomycetes can be oval, raised, and easily mistaken for ecthyma gangrenosum as in one interesting case published by Meyer et al.[22] Although most of the lesions reflect blood-borne dissemination, one recent report has associated cutaneous *Rhizopus* infection with contaminated adhesive dressing.[24] Cutaneous lesions of herpes simplex virus (HSV) and varicella–zoster virus (VZV) infection are so familiar that they need not be commented on further. Any doubt about the underlying nature of the viral infection can be resolved by aspiration of these lesions and inoculation into tissue culture (see Chapter 13). A preliminary diagnosis can be made with the Tzank stain, which will reveal multinucleated giant cells in the case of both HSV and VZV infection; usually (but not always), the two infections can be distinguished on clinical grounds alone.

The pneumonitic processes covered in Chapter 6 may logically be assessed by systematically considering bacterial, fungal, viral, and parasitic etiologies. Diffuse pulmonary infiltrates call for vigorous diagnostic efforts to rule out such life-threatening yet treatable complications as *Pneumocystis* pneumonia. As a result of extensive coverage in the current medical literature, the role of organisms such as *P. carinii* and *Legionella pneumophila* has probably been emphasized out of proportion to their true incidence. No physician who cares for the immunocompromised patient can ignore these possibilities in a patient with pneumonitis, but the initial diagnostic emphasis should be placed on detecting infection caused by the more common gram-negative and gram-positive bacteria. As studies using the transtracheal aspiration technique have documented, gram-negative bacilli are the most common cause of nosocomial aspiration pneumonia,[25] and aspiration is the probable mechanism for the development of most pneumonias. Patients who develop fever and have pneumonitis secondary to in-hospital treatment are likely candidates for infection by the more antibiotic-resistant bacilli such as *P. aeruginosa, Proteus* species, *Enterobacter* species, and *Serratia marcescens.*[25]

Many reviews cite the lung as the most common locus for infection in the immunocompromised host.[26,27] This conclusion must be accepted with some caution, however, because a chest radiograph is a readily obtainable noninvasive procedure associated with negligible inconvenience and risk. Thus, pulmonary disease may be documented more frequently than other types of organ involvement. Appearance of pulmonary infiltrates, however, may often reflect a noninfectious pulmonary process. The pitfalls of diagnosing pulmonary infiltrates by examination of expectorated sputum have been emphasized by many investigators, but there are obvious hazards to obtaining samples of intrapulmonary secretions or lung tissue. To compound the problem of defining the nature of infection, it has been claimed that a number of neutropenic patients lack early radiographic evidence of pneumonia, and evidence for pneumonitis has cited such findings as rales in the absence of pulmonary infiltrates.[28] However, reliance on auscultatory or radiologic findings alone may be misleading, since congestive heart failure (CHF) may be difficult to rule out in such subjects. There is little doubt that one of the major current problems in evaluating fever and pulmonary changes in the immunocompromised host is the multitude of noninfectious etiologies of lung infiltrates, including radiation pneumonitis, a number of drug reactions (due to busulfan, bleomycin, and methotrexate), intrapulmonary hemorrhage, neoplasm, or a combination of these factors.

TABLE 3. Infectious Disease Syndromes and Etiologic Agents in the Compromised Host: Central Nervous System Infection[a]

Bacteria	Fungi
Listeria monocytogenes	*Cryptococcus neoformans*
Nocardia species	*Aspergillus fumigatus*
S. aureus	Zygomycetes (*Mucor* and *Rhizopus*)
P. aeruginosa	*Candida* species
M. tuberculosis	Viruses[b]
	Varicella–zoster
	Herpes simplex

[a]Meningoencephalitis, possibly brain abscess.
[b]In patients with AIDS, the possibility of retrovirus encephalopathy or infection with papovavirus should be considered

There are a limited number of tools for determining the etiology of CNS infection. Much of the information published on opportunistic fungal infection involving the nervous system has been based on autopsy studies. The bacteria, fungi, and viruses that should be considered are listed in Table 3. In the initial diagnostic evaluation, emphasis should be placed on those possibilities that are not only common but also treatable. Two CNS pathogens, *Listeria monocytogenes* and *Cryptococcus neoformans*, are so readily treatable even in markedly immunosuppressed patients that it would be most unfortunate to overlook them. In most cases, therapy directed against these two pathogens is curative despite marked impairment of host defenses.

In our experience, *L. monocytogenes* is the most common cause of bacterial meningitis in the immunocompromised host and has a special predilection for patients on corticosteroid therapy or with impaired T-cell function, as in Hodgkin's disease. Interestingly, *Listeria* infections have been rare in patients with acquired immunodeficiency syndrome (AIDS), when everything we know about AIDS would have led to the prediction of fairly frequent *Listeria* infections. *Listeria monocytogenes* involvement in the CNS is primarily a meningoencephalitis, although a few cases of brain abscess have been described.[29] By contrast, involvement of the brain by *Nocardia* species or *Toxoplasma gondii* is usually a more focal infectious process, with the patient presenting with a seizure disorder or a mass lesion with neurologic impairment. *Pseudomonas aeruginosa* can cause meningitis, but this process usually reflects overwhelming septicemia. Thus, the prognosis is particularly poor because spread of *P. aeruginosa* to the brain or meninges clearly reflects an inability to contain bloodstream infection. *Mycobacterium tuberculosis* can cause meningitis, and the well-known difficulty of diagnosing tuberculous meningitis in even a normal host is further compounded in the immunosuppressed subject, in whom cerebrospinal fluid (CSF) pleocytosis may not be as striking because of drug-induced immunosuppression. However, it is our impression that CNS tuberculosis in immunosuppressed hosts has become a relatively rare event because of the tendency to use isoniazid (INH) prophylaxis in patients with exposure history or positive tuberculin tests or both.

Of the fungal pathogens, *C. neoformans* ranks highest on the list of organisms that must be considered if there are signs of CNS infection. The availability of a highly accurate diagnostic test, the cryptococcal antigen test, and improved antimicrobial therapy of proven disease make it imperative to rule out cryptococcal disease in patients having any sign of a meningeal inflammation. However, we have encountered a case in a febrile renal transplant recipient in whom the initial lumbar puncture (performed for fever and headache) showed entirely normal values for CSF protein, cell count, and sugar. After many days' incubation, the CSF from this patient grew out a yeastlike organism. On recognition of the possibility of cryptococcal infection, we performed the latex agglutination antigen detection test and found it to be positive on both CSF and serum. Only in retrospect was it appreciated that the patient had a solitary lung abscess consistent with cryptococcal involvement that predated CNS infection.

The outlook for the therapy of other types of mycotic involvement of the CNS is less sanguine. *Candida* infection of the CNS (like *Aspergillus*, zygomycosis, and cryptococcosis) is on a metastatic basis and is frequently associated with infection of lung, liver, and other deep organs. The prognosis in *Aspergillus* and zygomycotic involvement in the CNS has been extremely poor, but this is probably a reflection of late or terminal recognition of the problem. Some investigators have questioned whether *Aspergillus* or zygomycosis involving the brain is a curable condition.[30] Isolated instances of recovery from zygomycotic infection (*Mucor* or *Rhizopus* species) when the internal carotid artery has been occluded have been reported.[31,32] It appears that the chance of recovery, with or without therapy with agents such as amphotericin B, is critically related to improvement in underlying disease, or amelioration of predisposing factors such as immunosuppressive treatment, or both. Using an antibody detection test,[33] we have followed several leukemic patients who developed focal CNS signs during the nadir of their white blood cell (WBC) counts and then were found to have elevated levels of serum *Aspergillus* antibodies. They fortunately achieved remission, and neurologic findings resolved. However, these examples can be considered only presumed cases of fungal involvement of the brain in the absence of histopathologic documentation.

With the introduction of drugs that can be used to treat herpes virus meningoencephalitis, adenine ar-

abinoside and acylovir, measures to diagnose this infection have become more justified. In varicella–zoster, another DNA virus infection, involvement of the CNS may be observed. Lumbar puncture performed on patients with localized zoster may show a CSF pleocytosis. In most cases, this pleocytosis will resolve as the disease resolves. Unfortunately, we have seen situations in which patients have concurrently had *P. carinii* pneumonia, disseminated herpes zoster infection, and cryptococcal infection of the CNS. Thus, documentation of CNS pleocytosis in the patient with VZV pneumonia should not lead to the assumption that this is a reactive process occurring in the CSF, but an assiduous search should be initiated for another concomitant treatable infection.

A fourth major category of signs and symptoms relates to the head and neck region (Table 4): the oral cavity, the nasal passages, and the esophagus. Although the hemolytic *Streptococcus* is the most commonly occurring bacterial organism causing acute pharyngitis, hemolytic streptococci belonging to many serogroups besides group A can cause pharyngitis and infection around the tonsillar crypts.[34] *Staphylococcus* has not been convincingly shown to cause pharyngitis, but may be the primary pathogen in a number of soft tissue infections of the head and neck. Anaerobic organisms are a major part of the normal flora of the mouth, but can cause serious soft-tissue infections of the floor of the mouth, of the retropharyngeal area, and of the sinuses. Generally speaking, gram-negative rods and *P. aeruginosa* in particular cannot be considered causes of bacterial pharyngitis. However, with the aggressive use of certain antineoplastic agents such as daunorubicin, pharyngeal ulceration can occur followed by colonization and infection by gram-negative bacteria. Indeed, we have observed a number of cases in which *P. aeruginosa* was isolated from the pharynx in association with bacteremia caused by a *Pseudomonas* serotype of identical nature and antimicrobial susceptibility. Furthermore, in such cases, *P. aeruginosa* was not isolated from stool, suggesting that the origin of the bacteremia was actually the oropharynx.

By far the most common type of fungal involvement of the oropharynx is candidal colonization of the mouth, tongue, and mucosal surfaces. Initially, this can be a mild mucositis, but the inflammation may progress to a state wherein the patient virtually becomes unwilling to eat or swallow. Candidal involvement of the esophagus can be a prelude to systemic invasion. A characteristic symptom in candidal esophagitis is pain on swallowing accompanied by postglutition substernal burning. However, caution should be exercised in assuming that all substernal burning pain is the result of *Candida* esophagitis. Herpes simplex can involve the esophagus and be associated with a radiologic picture indistinguishable from the feathery or ulcerative pattern observed when barium is swallowed by a patient with advanced *Candida* esophagitis. Occasionally, cytomegalovirus (CMV) has been recovered from similar esophageal lesions, but the virus may have originated from a higher (pharyngeal) source. Definitive diagnosis of esophageal involvement requires some endoscopic procedure with biopsy rather than reliance solely on the barium-swallow procedure.

Both *Aspergillus* and the zygomycetes can cause infection of the esophagus and nasal tissues, as well as the paranasal sinuses. Histoplasmosis has been associated with oral ulcerations.[35] Although progressive clouding of the sinuses is suggestive of aerobic and anaerobic bacterial infection, fungal invasion of the sinuses can occur in the absence of glucose intolerance. Pain over the sinuses or dysesthesias of the face can also be important early manifestations of fungal involvement. Pain and clouding of the sinuses should not be attributed to bleeding per se, but an exhaustive evaluation should be initiated to determine the etiology of sinus inflammation in the neutropenic, thrombocytopenic patient. Aspiration or biopsy of this sinus involvement is clearly necessary to distinguish a fungal, e.g., *Aspergillus*, from an anaerobic bacterial process (as in chronic sinusitis).

A large proportion of immunosuppressed patients in any hospital have underlying neoplasms, and an important aspect of any diagnostic evaluation is to distinguish spread of tumor from an infectious complication. In addition, it is now well recognized that patients with one neoplasm may develop second primary tumors and that recipients of organ transplants are at increased risk of developing cancers of a variety of cell types. The finding of a space-occupying lesion of the brain or a nodular (coin-type) mass in the lung could obviously represent spread of tumor. In the febrile patient, however, the possibility that such a finding can be caused by an infectious process such as toxoplasmosis or histoplasmosis must be evaluated in a comprehensive manner.

TABLE 4. Infectious Disease Syndromes and Etiologic Agents in the Compromised Host: Pathogens in the Head and Neck

Bacteria	Viruses
Anaerobes	Herpes simplex
Aerobes	Cytomegalovirus
Streptococci and gram-negative rods, particularly *P. aeruginosa*	
Fungi	
Candida	
Aspergillus	
Zygomycetes	
Histoplasma capsulatum	

TABLE 5. Infection Mimicking Neoplasm: Diagnostic Considerations

Finding	Causative organism
Brain metastases	*Nocardia asteroides*
	Toxoplasma gondii
Budd–Chiari syndrome	*Mucor* species, *Aspergillus*
Intestinal obstruction	*Strongyloides*
	Entamoeba histolytica
Nephrotic syndrome	*Mucor* species, *Aspergillus*
Renal vein thrombosis	Gram-negative bacilli, *Aspergillus*
Obstructive nephropathy	*Candida*
Oculomotor palsy	Zygomycosis
Pulmonary nodules	Histoplasmosis, pneumocystosis
Superior vena cava syndrome	Histoplasmosis

Table 5 summarizes some of the infectious agents that might be responsible for a laboratory, radiologic, or physical finding mimicking tumor. Mass lesions in the CNS are particularly suggestive of nocardial brain abscess or toxoplasmosis. The ability of the zygomycoses and *Aspergillus* species to invade blood vessels and precipitate thrombosis can result in a Budd–Chiari syndrome, nephrotic syndrome, and oculomotor palsy.[23,31,35] Fungal involvement need not be direct; however, in the case of histoplasmosis, fibrosing mediastinitis can lead to a superior vena cava syndrome.[36] In some instances, the growth of organisms rather than the reactive inflammation can be so dense as to cause or enhance an obstructive clinical picture. One example is heavy candidal growth in both ureters, which leads to a clinical picture of postrenal obstructive uropathy characterized by oliguria and rising serum creatinine. Intestinal overgrowth of *Strongyloides* may exacerbate a clinical picture of paralytic ileus, although the role of the parasite may not be primary. One form of intestinal amebiasis is a dense localized area of inflammation, the ameboma, containing viable trophozoites, that mimics colon carcinoma clinically, radiologically, and even in gross appearance. Solitary or multiple pulmonary nodules can be caused by a variety of infectious processes. Those caused by histoplasmosis can "grow" like a tumor.[37] Even *P. carinii*, the pattern of pulmonary involvement of which is usually diffuse, can present as a solitary nodule.[38]

Finally, one of the more annoying symptoms in immunosuppressed patients is onset of diarrhea. While typical causes of gastroenteritis (e.g., *Salmonella*, *Campylobacter*, and *Shigella*) need to be considered, a common cause of diarrhea is use of antibiotics. Antibiotic-associated diarrhea is not synonymous with pseudomembraneous colitis, and the clinical evaluation of patients with diarrhea often results in negative cultures for *C. difficile* and negative tests for enterotoxin. Nonetheless, a patient with severe diarrhea may have high fever solely on the basis of colitis; sigmoidoscopy that reveals typical pseudomembranes can be diagnostic. Viral causes of diarrhea include adenoviruses, coxsackie viruses, and rotaviruses. The parasitic causes of diarrhea are being much more commonly recognized, especially cryptosporidia, microsporidia, and isopora. These parasitic entities, as well as *Giardia lamblia*, are reviewed in Chapter 10.

5. Some Emerging Pathogens in the Immunocompromised Host

The major categories of opportunistic pathogens that afflict the immunocompromised host have not changed significantly during the past decade. On the other hand, some specific pathogens within a group—a previously uncommon species or a more antibiotic-resistant organism belonging to a generally susceptible group—may become more common or have attracted attention because of their role in well-defined nosocomial outbreaks. Perhaps the most important trend among hospitalized patients is the increase in bacteremias due to gram-positive organisms—coagulase-positive and coagulase-negative *Staphylococcus* (*S. epidermidis*) and *Corynebacterium* (commonly referred to as diphtheroids).[39,40] Changes in the types of opportunistic pathogens can be a real challenge to the clinician, who should be prepared for unusual microorganisms even though his basic diagnostic thinking is oriented along the lines outlined in the previous sections.

Table 6[41–54] lists some of the more unusual emerging pathogens and their major clinical manifestations. No claim is made that the clinical patterns listed are comprehensive or that these disease-producing agents are really new. Indeed, *Hemophilus influenzae* is a well-known pathogen in young children, but its appearance in adult septicemias has been uncommon. The isolation of these organisms should lead to careful consideration of their disease-causing potential, and they should not be dismissed as nonpathogenic organisms or as saprophytes. Conversely, the findings of vasculitis, myositis, or necrotizing pneumonia in immunosuppressed subjects should raise suspicion that some of these more unusual pathogens might be involved.

6. Clinical Approach to Fever: History and Physical Examination

The initial evaluation of the patient must always begin with a carefully taken history. Recognition that the patient is immunocompromised by virtue of his or her underlying disease (e.g., a neoplasm) or some form of

TABLE 6. Some Emerging Pathogens in the Immunocompromised Host[a]

Organism	Reference	Host	Clinical patterns
Aeromonas hydrophila	Ketover et al.[16]	Neutropenic patients	Necrotizing vasculitis or myositis
Bacillus species	Ihde and Armstrong[41]	Cancer patients	Sepsis and pneumonia
Candida tropicalis	Wingard et al.[42]	Neutropenic patients	Skin lesions, myositis, polyarthralgias
Corynebacterium species	Kressel et al.[43]		Lung abscess and sepsis
equi	Berg et al.[44]	Lymphoma patients	Sepsis and pneumonia linked to hyperalimentation lines; organism sensitive only to vancomycin
Other	Stamm et al.[45]	Marrow transplants	
Eiknella corrodens	Brooks et al.[46]	Cancer and rheumatology patients	Infections of bites around head and neck
Fusarium	June et al.[47]	Neutropenic patients	Disseminated disease
Hemophilus influenzae	Nixon and Aisenberg[48]	Lymphoma patients	Overwhelming septicemia
Pseudallescheria (Petriellidium) boydii	Winston et al.,[49] Yoo et al.[50]	Neutropenic patients	Vascular thrombosis and infarction
Pseudomonas cepacia	Bottone et al.[51]	Chronic granulomatous disease	Sepsis, multiple abscesses
Staphylococcus epidermidis	Winston et al.[49]	Patients with intravascular devices	Catheter-associated sepsis, often highly antibiotic-resistant
Scopulariopsosis	Neglia et al.[52]	Steroid therapy	Disseminated disease
Torulopsis glabrata[b]	Aisner et al.[53]	Cancer patients	Sepsis and pneumonia
Trichosporon species[51]	Haupt et al.[54]	Neutropenic patients	Pneumonia, necrotizing skin lesions
Vibrio (halophilic species)	Blake et al.[17]	Hepatic disease	Wound infection, sepsis with necrotizing vasculitis

[a]See also Chapters 6 and 7 for pulmonary and CNS pathogens.
[b]Taxonomically renamed *Candida glabrata*.

treatment (e.g., cyclophosphamide and steroids for pemphigus) should be followed by a careful review and analysis of the following factors:

1. *Time of initial disease diagnosis or procedure:* The date of organ transplant or date of surgery should be noted.

2. *History of treatment for underlying disorder:* Factors such as radiation, drug treatment, or transfusion of blood products will be extremely important in interpreting new findings such as a pulmonary infiltrate or an allergic reaction. The nature of drug therapy, corticosteroids in particular, can be important in considering or excluding such important infectious etiologies as listeriosis, nocardiosis, and pneumocystosis. The time of administration and dose of medication may be crucial in diagnosing drug-induced fevers. Perhaps more important, such information is useful in assessing the magnitude of risk to the patient from drug-induced neutropenia following use of cytotoxic or myelosuppressive agents. Patients whose circulating neutrophil counts are rapidly plummeting are those in maximum danger from gram-negative bacillary and opportunistic fungal diseases.

Records of transfusions of all blood products should be carefully scrutinized. Prior use of analgesic/antipyretic medications and their effect on masking previous symptomatology may alert the clinician to the fact that illness has actually been of longer duration than suspected or that important manifestations such as fever had been masked. Often, as with use of steroids, an apparent flare-up of symptoms and fever is related to reduction in dosage [see Chapter 10, (Section 2)]. Recent (e.g., abdominal) exploration or antecedent surgery (splenectomy in a patient with Hodgkin's disease) is obviously crucial in pointing to possible infectious complications. Even "minor" surgical procedures should be noted, such as the date of insertion of an intravenous cutdown or the date of a tracheostomy.

3. *Stage of the underlying disease:* This information is sometimes helpful in predicting some opportunistic infections. Freshly diagnosed leukemics and patients with plasma cell dyscrasias are more likely to have pyogenic infections (streptococcal and staphylococcal) than disseminated mycotic infections and pneumocystosis. Similarly, the more drug-resistant systemic or pulmonary gram-negative bacillary infections are more likely to follow repeated courses of chemotherapy or long-term immunosuppression and thus are complications of advanced stages of disease (or, in the case of transplants, multiple episodes of rejection). The clinician should be alerted to possible exceptions to the latter rule, however, if there has been a delay in diagnosis of the underlying disease and the patient has received courses of broad-spectrum antibiotics for fever. Thus, we have seen patients with marrow aplasia, lymphoma, or leukemia who were treated with ampicillin or oral cephalosporins prior to accurate diagnosis of the underlying

disease and who, in the interim, became heavily colonized by antibiotic-resistant gram-negative rods. Septicemia caused by organisms such as *P. aeruginosa* occurred early during attempts to treat the underlying disease.

4. *History of previous infections and antibiotic treatment:* This information can be both helpful and misleading to the clinician. Infections can certainly recur in immunosuppressed individuals even after appropriate therapy and often in the setting of an underlying disease that fails to improve. Persistently positive cultures of a local site (e.g., wound drainage, deep cough sputum) can be a helpful but not infallible clue to the possibility of recurrence. On the other hand, if the patient has experienced a microbiologic and clinical cure of a documented infection, our experience has been that the reappearance of fever and signs of infection, more often than not, signals the onset of a new process rather than a recrudescence of an old one. Thus, our working rule has always been, "The cause of the first successfully treated infection is not the same as that of a new infection," and a vigorous search for the etiology of fever is renewed without any preconceptions. The clinician should also be aware of the possibility of the presence of multiple infections, each involving the same area, such as lung. Knowledge of previous antibiotic treatment can also be applied with the same principle, since the more antibiotic-susceptible infections tend to occur earlier. *Pseudomonas aeruginosa* infections usually follow staphylococcal disease, but we have almost never seen staphylococcal superinfection after treatment of *P. aeruginosa*.

5. *Presence of symptoms other than fever:* This factor is often crucial to localizing the source of infection and extent of involvement. Particular attention should be focused on the symptom of pain as one of the major clues to the presence of infection. In one review of infection in neutropenic patients, only local pain or tenderness and erythema were present in all patients irrespective of site of infection and level of granulocyte count.[55] Headache has always been an important finding pointing to the possibility of CNS infection.

6. *Travel history, dietary history, and exposure history:* Often components of a routine history, these factors should be broadened to include whether fever and evidence of infection developed in the community or in the hospital setting. A history of illness in the patient's family or community may occasionally be a helpful clue. By contrast, the development of infection in a nosocomial setting alerts the clinician to the severity of infection (tending to be more antibiotic-resistant) and of suggested underlying disease–pathogen associations: the intensive care unit (ICU) with gram-negative pneumonia, the burn unit with *Pseudomonas* infections, and so forth. Salmonellosis may be a nosocomial problem related to specific dietary exposure. An avocational or pet history is like a travel history in usually being of little value. Rarely will knowledge that a patient is a pigeon fancier, raises cats, or has a pet turtle lead to the diagnosis of cryptococcosis, toxoplasmosis, or salmonellosis, but the vast majority of owners of such pets suffer no ill consequences even if they become immunocompromised.

7. *Complications of previous therapy:* Knowledge of side effects, including drug reactions, may be helpful in evaluating the possibility of hypersensitivity reactions mimicking infection.

8. *History of recurrent temperature elevations and their pattern:* This is usually of very limited value in diagnosis. Rare instances of morning fever pointing to tuberculosis or periodic fever suggesting malaria are often cited, but it is unusual for classic fever patterns to occur and actually be of major importance in establishing a specific diagnosis. The evidence for this conclusion is well presented in a study by Musher et al.[56]

A complete physical examination should be carried out as expeditiously as possible in a period of no more than 45 min. It must always be borne in mind that patients who are immunosuppressed or granulocytopenic or both suffer the consequences of an impaired inflammatory response. Many typical physical signs of infection such as induration, fluctuance, local heat, reactive regional lymphadenopathy, and exudation of pus tend to be less frequent than in normal subjects who are infected. In pneumonia, there may be decreased cough and little sputum production; in pharyngitis, there may be an absence of a prominent exudate; with urinary tract infection, patients may not have significant symptoms and may not develop pyuria. The classic sign of nuchal rigidity may be absent in meningitis; thus, two very important clues are headache and poor performance on the mental status component of the neurologic examination. Of the physical findings in neutropenic subjects, erythema is the most reliable clue to the presence of infection irrespective of the absolute level of the WBC count.[55]

Within the context of a complete physical examination, emphasis should be placed on the following:

1. Neurologic examination covering both mental status and cranial nerves, including examination of optic fundi
2. Skin: major flat and intertriginous surfaces, perirectal area in particular
3. Oropharynx
4. Chest: careful auscultation of lungs and heart
5. Abdomen: liver and spleen enlargement
6. Lymph nodes: careful examination of all node-bearing areas
7. Pelvic examination in female if any symptoms are referable to this area

8. Site of insertion of any catheter site or drain
9. Site of a diagnostic procedure (e.g., thoracentesis, lumbar puncture)

The following special examinations have some risk, but should be done if symptoms are present:

1. *Rectal examination in patient with perirectal pain:* Perirectal pain may be the major clue to a perirectal (and often pseudomonal) abscess in a neutropenic patient. If the patient has neither obvious induration from external examination nor infected, thrombosed hemorrhoids, gentle rectal examination is indicated despite the danger of triggering bacteremia.

2. *Lumbar puncture:* This subject is covered with CNS infections in Chapter 7. The examination of spinal fluid should be an initial diagnostic study for anyone with suspected CNS infection. On the other hand, caution must be observed in two specific situations: (a) if there is any suggestion of increased intracranial pressure, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain should be performed to rule out a mass lesion that might result in brain herniation if lumbar puncture is performed; (b) if the patient is markedly thrombocytopenic, platelet transfusions should be given as soon as possible. Lumbar puncture in the presence of a low platelet count has a small but definite hazard, and there should be clear-cut indication for the procedure if the patient is thrombocytopenic ($<40{,}000$ platelets/mm^3). We do not routinely recommend a lumbar puncture as part of the fever workup in the patient who does not have neurological signs or a change in mental status.

We do not hesitate to treat possible bacterial meningitis in a patient with evidence of increased intracranial pressure using a penicillin plus a third-generation cephalosporin before spinal fluid is obtained (but after blood cultures are drawn).

7. Interaction between the Clinician and the Microbiology Laboratory

If a group of clinicians and the hospital where they practice are to become involved in the care of immunocompromised patients, the clinical microbiology laboratory must assume a major role in the total effort. Such a laboratory must provide work of high quality and accuracy and, in important situations, be willing to perform special studies irrespective of when specimens become available. By the same token, microbiologists cannot be expected to be mind readers in anticipating what the clinician wants or considers desirable. Improved communication between the wards and the laboratory will help microbiologists select the most appropriate isolation techniques for any special problem that a clinician may have in mind. On our clinical service, we expect house officers and fellows to spend some time in the microbiology laboratory each day, not only collating laboratory results but also discussing challenging problems of clinical and laboratory diagnosis.

8. Specific Laboratory Studies

A fundamental approach involves cultures taken of blood and any site or body fluid suspected of being infected. For the more rapid and accurate detection of bacteremia, one major advance in recent years has been the so-called "blind subculture" technique for processing blood cultures. The conventional procedure for detecting positive growth in blood cultures involves daily (or twice-daily) observation of broth cultures for visible turbidity. However, it has been well documented that as many as 10^6 organisms can be present in broth without rendering these suspensions turbid. The blind subculture or blind passage technique involves subculturing apparently clear-broth culture bottles to both aerobic and anaerobic plate media. Pseudomonads are obligate aerobes, and the blind subculture technique is a useful method for decreasing the time to isolation of these important organisms from blood cultures. Not surprisingly, anaerobic organisms may be detected by blind subculture even from the aerobe bottle, particularly if the specimen is removed from the bottom of the culture bottle with a long pipette and immediately incubated in an anaerobic atmosphere.

In addition to the relatively simple technique of blind subculture, a whole variety of laboratory equipment has become available for the more rapid identification of disease-causing bacteria. Some offer real improvements, whereas others have major technologic drawbacks. This emphasizes the need for the clinician to become familiar with the basic methods (and potential pitfalls) employed where one practices.

With the trend toward greater laboratory automation, an obviously desirable goal is the development of approaches that might either speed recovery of fastidious pathogens or increase test sensitivity. Two such approaches have been widely introduced into laboratory medicine. The first consists of devices containing resins or materials that remove antibiotics, thus improving detection rates if patients have been inadvertently treated. Some studies support the latter claim, but many of the isolates are gram-positive saprophytic organisms of dubious clinical importance.[57] Our own clinical experience with such devices suggests that they help diagnose bacterial endocarditis occurring in nonimmunosuppressed hosts, a situation in which a patient may have received

oral antimicrobial agents prior to hospitalization and definitive diagnostic studies. On the other hand, in immunosuppressed patients who are persistently febrile and neutropenic while on broad-spectrum antimicrobial agents, the routine use of such antibiotic-removing devices has infrequently yielded reliable information, over and above what could be obtained with carefully collected specimens (of adequate blood volume) for routine aerobic and anaerobic blood cultures.

The other relatively new development is the introduction into blood culture systems of devices that lyse phagocytic cells (usually a compound such as saponin is incorporated into the test system) after differential centrifugation of blood has concentrated the leukocyte-rich fraction.[58] The rationale for such approaches is that some organisms such as fungi and microbes may remain viable within phagocytes. Centrifugation concentrates white cells and lysis releases viable organisms that may then be detected by a variety of routine or radiometric methods. The earliest studies have been highly encouraging in selected situations, particularly those in which an underlying fungal (candidal) or gram-negative infection is a good possibility.[59] In addition, the use of lysis centrifugation methods has now made it possible to routinely detect bloodstream infections caused by mycobacteria, particularly isolates of *M. avium* complex from patients with AIDS.[59] These techniques are costly and should probably be used in selected situations rather than routinely. Furthermore, the use of the lysis centrifugation methods for detection of fungi or acid-fast organisms should probably be incorporated with a method for rapid detection of microbial growth, such as commercially available devices, that measures the respiration or metabolism of slow-growing bacteria or fungi.

Several studies of blood cultures have indicated that for patients not previously receiving antimicrobial therapy, most pyogenic organisms show detectable growth after 3 days of incubation.[60] If, however, the patient has received antimicrobial therapy, the growth of organisms may be suppressed for longer periods (although modern blood culture media contain antibiotic inhibitors and "dilute out" the blood sample by virtue of a large volume of broth so the suppressive effects of antimicrobials are often obviated). Another important observation is that three sets of blood cultures are adequate to diagnose bacteremia, and any more than this number is likely to be a waste of effort and expense.[60] Thus, we have evolved the rule of three: If three sets of blood cultures (three separate venipunctures) have been drawn, and 3 days of incubation have elapsed, the probability of documenting aerobic bacteremia is less than 10% if none has appeared by that time. We advise that the interval between obtaining such blood cultures be determined by clinical circumstances: Certainly no more than a total of 30 min should elapse in the critically ill patient, during which blood cultures are obtained from several sites.

Any skin lesion that develops in a patient should be promptly aspirated, cultured, and biopsied. Occasionally, bacterial, fungal, and viral pathogens may not grow even when obviously present in histological sections, but morphology alone can establish the diagnosis. If antimicrobial therapy has already been initiated, ecthyma gangrenosum lesions may still reveal bacterial growth. In addition, immunofluorescence may be a way to identify pathogens in skin lesions, CSF, or other body fluids (e.g., tubercle bacilli in pleural biopsies, *L. pneumophila* in respiratory secretions after antimicrobial therapy has been initiated).

Fungal cultures may require long periods of incubation, so the aforestated guidelines for judging the likelihood of bacterial blood cultures becoming positive are not applicable. Well-documented cases of *Cryptococcus neoformans* have taken several months' incubation of spinal fluid before growth became detectable. Although the problem of diagnosing cryptococcosis has been significantly reduced by methods for detection of capsular polysaccharide antigen, other fungal organisms such as *Rhizopus* and more unusual fungi may grow very slowly. No mycology laboratory should discard culture plates before at least a minimum of 1 month of incubation.

One of the most frustrating areas in laboratory medicine is the failure to detect fungal growth in blood cultures taken from patients who are eventually found to have widespread disseminated mycotic disease. The reasons for this failure are not clear, but some fungi, such as *Candida* species, may spread through the lymphatics rather than through the bloodstream. On the other hand, hematogenous spread of organisms such as the zygomycetes and *Aspergillus* has been documented on a few occasions, but this occurrence is still rare. Fungal endocarditis, such as caused by *Aspergillus* species, may occasionally present with embolic phenomena, and removal of the blood clot may reveal fungal elements contained therein.

Anaerobic cultures of blood, of transtracheal aspirates, and of any abscess are clearly indicated. Anaerobes can cause CNS and urinary tract infection, but routine anaerobic cultures of CSF and urine are probably not indicated. Viral cultures of blood are probably not indicated except for CMV infection, and these may require a long duration of incubation to become positive.

Occasionally, the clinician encounters a situation in which an isolate from blood, sputum, or wound may be a contaminant. The therapeutic decision must be based on the gravity of the underlying disease and the relationship of an isolate to an objective clinical finding. We have occasionally observed isolation of cryptococci and

Nocardia from sputum in the absence of pulmonary lesions. Such patients can probably be followed carefully without treatment, but we would unhesitatingly initiate therapy if the patient were to develop fever or any pneumonic process.

Interpreting the significance of blood cultures drawn through a catheter is often difficult. Multiple positive cultures may reflect infection in and around the catheter rather than a true sustained bacteremia or fungemia. We do not recommend that cultures be obtained in this manner, but simple expediency is the best explanation for the survival of this practice. A positive culture obtained on blood drawn through a catheter should be validated by samples drawn by conventional venipuncture, but unfortunately, the patient may have been started on antibiotics in the interim, and not all bacteremias are constant. Therefore, it seems prudent to eschew catheter-drawn blood cultures whenever possible.

9. Diagnosis of Infection: Antibody Measurements and Skin Tests

A variety of serologic tests for diagnosis of infection are available in most clinical laboratories, but some are probably overused and others significantly underused. In our experience, obtaining febrile agglutinins has rarely been helpful in establishing the diagnosis of an opportunistic infection in the immunocompromised host. Serologic tests for diagnosis of infection are most helpful when positive, and a negative test in an immunosuppressed subject cannot serve as the basis for excluding a diagnostic possibility. Measuring complement-fixing antibodies against *Coccidioides immitis,* Sabin–Feldman dye titers against *Toxoplasma gondii,* and detection of cryptococcal antigen are usually quite reliable tests with few false-positive or false-negative results. Similarly, serologic tests for hepatitis A–D may be considered very reliable.

On the other hand, fewer than half of all cases of opportunistic histoplasmosis are associated with elevated complement-fixing antibody titer,[35] and the status of diagnostic tests for systemic candidiasis and aspergillosis remain in dispute (see Chapter 8). Reliance on antibody measurements to diagnose infection in immunosuppressed subjects is obviously perilous, and the information obtained must be carefully integrated with other clinical and laboratory findings. Similarly, skin tests for diagnosis of infection are of very limited usefulness but are helpful, if positive, in validating prior exposure to a potential pathogen. A negative skin test is of no value in excluding a diagnostic possibility.

10. Noninvasive Diagnostic Procedures

Radioactive scans of liver and spleen have been available for some years and are very helpful in delineating both organ enlargement and filling defects that could be caused by infectious or neoplastic processes.

Considerable experience has evolved in the use of ^{67}Ga scintography for the detection of abscesses. This radionuclide is taken up by some tumors and by inflammatory masses as well, probably because it is concentrated by phagocytes. Late uptake of gallium (>24 hr) is more suggestive of tumor, whereas early uptake (4–8 hr) is suggestive of an abscess. Gallium scans have been most useful in detecting intra-abdominal and subphrenic abscesses, but significant problems remain because of (1) confusion of areas of uptake with tumor, (2) uptake of radionuclide by reticuloendothelial cells and large bowel, and (3) inability to distinguish pus from an inflammatory reaction. Thus, a high incidence of false-positive results should lead clinicians to be wary about relying on this procedure alone to detect a localized or deep-seated abscess. Improved accuracy of diagnosis may be achieved by combining gallium scanning with diagnostic ultrasound or using it in conjunction with CT or MRI scans.

An alternative to gallium scans is the use of radiolabeled leukocyte scans, which can target an area of inflammation. These scans may take several days to yield positive results, however.

The use of radiolabeled immunoglobulin, either of a human polyclonal nature or of an animal monoclonal source, has also been found useful in pinpointing the presence of abscess collection.[61] While there may be some danger of sensitization when a foreign protein is being used, studies show that this type of diagnostic approach may be increasingly useful, not only in identifying the presence of an occult focus of infection but also in identifying the nature of that infecting organism. In other words, the use of a specific antibody such as directed against *Pseudomonas* species may not only reveal the presence of an occult focus of infection but also provide insights into the microbial composition of the abscess.

Bone scans employing ^{99}Tc-labeled phosphate compounds have been used to establish an early diagnosis of osteomyelitis before significant bone destruction occurs. It has long been recognized that approximately 30–50% of mineral content of bone must be lost before a lytic lesion is detectable by radiography, and this process may take several weeks. Bone scans are particularly valuable in detecting multiple areas of involvement and identifying sites for biopsy, although it has been argued that documented bacteremia occurring concomitantly

with scintiscan evidence of osteomyelitis obviates the need for biopsy. It should be remembered, however, that scintiscan cannot be used as a method for following treatment or assessing cure, because bone remodeling continues after eradication of infection.

CT was initially applied to diagnosis of CNS lesions and has been extended along with MRI approaches to evaluation of intrathoracic and intra-abdominal disease. These approaches are rapidly replacing ultrasound and radionuclide scanning.

11. Invasive Diagnostic Procedures

Invasive procedures may be divided into two categories: (1) those of brief duration, limited risk, and not requiring general anesthesia (e.g., arteriography, lymphangiography, and liver biopsy) and (2) those carried out in an operating suite with all the hazards associated with a major surgical undertaking.

Bone marrow biopsy probably carries little more risk than venipuncture and is a routine approach to the diagnosis of neoplasm. It has been helpful in evaluating granulomatous involvement of marrow. In two series of disseminated histoplasmosis in immunocompromised subjects, the diagnosis was established in approximately one half of the patients by careful histologic examination and culture[62]; the diagnostic yield increased to 61% if liver biopsy was also performed.[35] In our recent experience, culture of marrow for acid-fast organisms has been relatively unfruitful except in patients with AIDS. Any patient with the latter condition who is severely debilitated and who has persistent unexplained fever should have several blood and bone marrow aspirates cultured for mycobacteria, preferably by the lysis centrifugation technique.

Lymphangiography (now performed infrequently because of CT and MRI methods) has been available for almost two decades and has been valuable for delineating the extent of involvement of retroperitoneal lymphomas. Patterns suggesting tumor have also been observed in some infectious granulomatous processes. It is clear, therefore, that lymphangiography is not a means for making an etiologic diagnosis but rather for determining if an abnormal lymph node architecture is present.

Angiography has been particularly useful in detecting anatomic structures with abnormal vasculature, particularly neoplastic processes. An abscess or occult purulent collection is suggested in filling defects or localized areas of hypoperfusion. Angiography should follow ultrasound, CT, or MRI imaging and radioactive scintiscanning to delineate the nature of any abnormalities detected.

Ultimately, if conventional approaches to the diagnosis of infection are unrewarding, and noninvasive techniques also yield negative results, consideration should be given to a more invasive approach such as any one or any combination of percutaneous biopsy of liver bronchoscopy, lung biopsy, and exploratory laparotomy. The closed-needle approach to liver biopsy is widely employed. Unfortunately, the specimens obtained are often inadequate for comprehensive microbiologic studies, but the histopathologic examination is often quite useful. Even though a relatively small core of tissue is removed by needle biopsy, washing of the needle with broth media and incubating the washings may improve the yield from culture. When liver biopsy in a patient with AIDS or suspected AIDS shows the presence of granulomas, blood and bone marrow aspirates should be cultured for fungi and mycobacteria.

Exploratory laparotomy has been considered the definitive diagnostic approach to prolonged FUO.[4] With the introduction of newer noninvasive diagnostic techniques, abdominal exploration is performed far less often, and two conditions should be met before deciding to undertake this approach: (1) clinical signs, symptoms, and laboratory findings that suggest intra-abdominal pathology; (2) ultrasound, radionuclide, and CT or MRI scans, and liver biopsy that are uninformative, equivocal, or give conflicting interpretations. Although laparotomy has been considered a last resort in the diagnostic approach, we do not hesitate to recommend this procedure if the indications are present. The choice is often between laparotomy and a long course of empiric and potentially toxic antimicrobial treatment, following which laparotomy may still be required.

12. Diagnostic Tests of Limited Usefulness

The limited value of standard laboratory tests such as WBC count, urinalysis, and the erythrocyte sedimentation rate (ESR) in immunosuppressed patients must be recognized. Neutropenic patients may register no neutrophilic response in the presence of overwhelming sepsis and may become even more neutropenic through a "consumption" type of mechanism. The ESR is occasionally useful as a marker for inflammation. However, the ESR is a crude reflection of serum fibrinogen, and in hepatic disease states or during consumption coagulopathy triggered by sepsis, the ESR may actually drop secondary to a decline in serum fibrinogen. We believe that the ESR has some value if there is reason to doubt the presence of an inflammatory or infectious process such as in suspected factitious fever. On the other hand, if the patient is both febrile and immunocompromised, there

appears to be little value in measuring the ESR because it should be elevated. If it were not elevated, we would suspect that a depressed level of fibrinogen is the cause.

There have been many efforts aimed at developing rapid, simple "bedside tests" that could aid in the diagnosis of infection and thereby serve as a guide to initiation of antimicrobial therapy. The goal is laudable, but the proposed approaches have not been validated in a number of prospective studies. Two such tests are the nitroblue tetrazolium (NBT) dye test[63] and the limulus lysate gelation test.[64] NBT in its unreduced form is an orange material that can be taken up by phagocytizing leukocytes and converted to blue/black formazan. Neutrophils stimulated by whole bacteria, bacterial products, or endotoxins will demonstrate enhanced uptake and reduction of NBT corresponding to their intraleukocytic microbicidal mechanism. On the other hand, it has been shown that reduction of NBT is no more useful than detecting other morphologic indices of leukocyte reactivity in the presence of infection, and the claims that a certain percentage of NBT-positive cells in peripheral blood correlates with bacterial infection have not been borne out in other studies.[65] Thus, although the NBT dye-reduction test is very useful in ruling out intrinsic defects of granulocyte killing (see Chapter 20), it is not a reliable procedure for making a presumptive diagnosis of bacterial infection or for excluding that possibility.

The limulus lysate test is based on the observation that minute quantities of bacterial lipopolysaccharide (endotoxin) can trigger coagulation of extract prepared from the amebocyte cell of *Limulus polyphemus*. The Eastern horseshoe crab, like man, has a complex clotting system that can be activated by endotoxin or endotoxin-like products. This is a very sensitive *in vitro* technique for quantitating lipopolysaccharides, but in the study of human gram-negative bacterial infection, particularly bacteremia, only one half to two thirds of patients have had positive tests, and there have been studies reporting a significant number of false-positive tests.[66,67] Perhaps one of the major reasons for false negativity is the presence in serum of inhibitors or antibodies that block the effects of endotoxin in triggering the coagulation sequence.[67] In examining CSF, the limulus assay appears to be a very reliable method for ruling out gram-negative meningitis,[68] but the test is not reliable for detecting hematogenously circulating gram-negative bacterial endotoxin. A modification of the limulus test, using spectrophotometry for precisely measuring gelation, is now available but still yields a significant number of false-negative results in specimens from patients with gram-negative bacteremia.

TABLE 7. Causes of Recurrent or Persistent Fever in Immunocompromised Patients with Negative Bacterial and Fungal Cultures

Adrenal insufficiency
Anicteric viral hepatitis
Hepatitis A, B, C
Catheter-associated infection (including candidiasis)
Congestive heart failure
Cryptic abscess
Cytomegalovirus infection (with or without hepatitis)
Drug fever
Epstein–Barr virus infection
Graft-vs.-host disease (bone marrow transplants, recipients of non-irradiated leukocytes)
Hematomas, infected or uninfected
Other viral infections
Pulmonary emboli
Splenic infarct
Tuberculous or other granulomatous infection
Underlying diesease even though all other evidence is negative

13. Persistent or Recurrent Fever in the Patient with Negative Cultures: Diagnostic Considerations

One of the most frustrating clinical situations to deal with in the management of immunocompromised patients is persistent or recurrent fever despite negative bacterial and fungal cultures. The major clinical choices are to pursue the search for a cryptic infectious process or to attribute fever to underlying disease (or, in the case of organ transplants, graft rejection). We would strongly argue that the latter should be a diagnosis of exclusion, and the failure to detect an infectious cause of fever after an initial evaluation mandates a comprehensive reappraisal of diagnostic strategies with emphasis still being placed on finding an infectious cause.

Table 7 summarizes the major causes of fever that should be considered after an initial "negative" evaluation. Some, such as congestive heart failure (CHF) or pulmonary emboli, call for diagnostic and therapeutic approaches outside the infectious disease sphere. The possibility of drug fever calls for careful review of all medications (including topical ones). If a medication is suspected of triggering fever, it should be discontinued, but one must bear in mind that convincing proof of drug fever will depend on provoking fever on rechallenge. An indwelling vascular catheter may have a cutaneous site of insertion that looks benign, but removal of this foreign body may reveal distal infection. Adrenal insufficiency must always be borne in mind for patients who have received long-term steroids and have then had their dose reduced. Fever of adrenal insufficiency tends to be low-grade and may be accompanied by feelings of marked general weakness.

If initial cultures for bacterial and fungal pathogens are negative, the thrust of further diagnostic efforts aimed at uncovering an infectious cause should be directed toward granulomatous and chronic viral infections or a cryptic abscess. Extrapulmonary tuberculosis should always be considered in the febrile immunocompromised patient irrespective of what initial studies show, i.e., in the face of negative tuberculin tests, negative chest radiographs, and absence of cough. It is well known that miliary or disseminated tuberculosis can progress without radiologic involvement of the chest.[3] One helpful clue is the tendency for the alkaline phosphatase of the hepatic type or other liver enzymes that are elevated in "obstructive" liver disease to be mildly to moderately elevated in disseminated tuberculosis. Tuberculous involvement of the fundi, bone marrow, and urine is another helpful clue to this diagnosis, but the yield is quite low in culturing bone marrow or in culturing urine in every patient with suspected tuberculosis. Anicteric viral hepatitis, of which there are several causes, is another possibility. Hepatitis of the A, B, or C type, as well as that caused by the CMV, can produce fever and liver function test abnormalities in the absence of clinical jaundice. Hepatitis serology and measurement of complement-fixing or other types of antibodies against CMV may be important in establishing this diagnosis.

Unfortunately, the category of other viral infection must now include the retrovirus that is identified as the cause of AIDS [human immunodeficiency virus (HIV) or lymphadenopathy-associated virus]. The possibility of transfusion-acquired AIDS must be considered in any immunocompromised patient who has received fresh blood products since the late 1970s. While it is hoped that routine screening for antibodies in blood donors, begun in 1985, will reduce this infection risk, the long incubation period for AIDS should remind clinicians of the potential hazard of AIDS superimposed on another disorder (like cancer) or following organ transplantation. Furthermore, one cannot be totally confident that antibody screening in a previously immunosuppressed patient (non-AIDS) will reveal prior exposure to the virus. The advent of a leukocyte culture technique for HIV-1 or the polymerase chain reaction to detect viral nucleic acid should improve diagnosis in questionable cases of HIV-1 infection.

A cryptic abscess has classically been one of the major entities to consider in any patient with an unexplained fever. Traditionally, the search for cryptic abscesses has focused on the abdomen.

The syndrome of hepatosplenic candidiasis is one that has received increased attention.[69,70] This complication of dissemination may plague the patient with unremitting leukemia and lymphoma as well as the patient who has successfully achieved hematologic remission (probably because of organ "seeding" during a period of antecedent neutropenia). The diagnosis is usually strongly suggested by CT or MRI scanning of the abdomen, and the microbiologic etiology is established by needle aspiration of liver (but splenic aspiration is best avoided). However, consideration should also be given to soft tissue lesions in the extremities, flanks, and perirectal areas.

In many reviews, CHF has been listed as one of the causes of FUO. It would be unusual, however, for CHF to cause high temperature, in excess of 102.1°F (39°C), accompanied by rigors and chills. The evidence for CHF may be subtle and may consist of only mild pulmonary congestion. Fever associated with cardiac failure may quickly respond to a diuretic such as intravenous furosemide.

Pulmonary emboli have long been recognized as causes of high recurrent fever, and they may be accompanied by chills and rigors. It is also well known that many patients with pulmonary emboli and fever may not have clear-cut clinical signs or the classic radiologic findings. Further, patients with pulmonary emboli may not have readily identifiable sources of these emboli. We have observed pulmonary emboli in patients who were markedly thrombocytopenic or who had prolonged prothrombin times secondary to far-advanced hepatic disease. Most patients with angiographically documented pulmonary emboli have fever, and in some 80% of febrile patients with pulmonary emboli, it has been attributed solely to pulmonary thromboembolism and not to a concomitant process.[71] In these studies, high fever, i.e., temperature greater than 102.2°F (39°C), caused by pulmonary embolism may occur early, and low-grade fever may continue for a week or more, but fever persisting beyond 6 days, especially with temperatures in excess of 101.3°F (38.5°C), should not be ascribed to pulmonary thromboembolism unless other causes have been carefully excluded. An interesting report details superinfection of pulmonary emboli in neutropenic patients or patients receiving steroids.[72] This possibility should be considered in patients who have fever more than a week after the acute episode.

Hemotomas located in a wide variety of body sites, and particularly in the CNS, can be the cause of recurrent fever. An assiduous search for hematomas, particularly in the CNS if there is any evidence of altered mentation, is an important part of the diagnostic reevaluation of the patient with persistent fever. Hematomas outside the nervous system may become easily infected, but even bland hematomas are associated with fever.

Infarcts of the spleen are usually observed in conditions where there is splenomegaly, such as chronic myelocytic leukemia or lymphoma. These infarcts may be bland or secondary to a bacteremia, and the mortality

TABLE 8. Fever and Neoplasia

Neoplasia	Often	Occasional	Rare
Hematologic malignancies			
Acute myelogenous leukemia	+		
Acute monocytic leukemia		+	
Chronic myelocytic leukemia (blast crises)		+	
Acute lymphatic leukemia	+		
Chronic lymphatic leukemia			+
Hodgkin's disease	+		
Multiple myeloma		+	
Non-Hodgkin's lymphoma		+	
Solid tumors (without obstruction or metastatic tumor)			
Adrenal carcinoma and pheochromocytoma	+		
Hepatoma	+		
Hypernephroma	+		
Hypothalamic tumor		+	
Ovary		+	
Pancreas		+	
Testicles		+	
Thyroid		+	
Bowel		+	
Breast			+
Colon			+
Lung			+

associated with splenic abscess that follows septic infarcts may be quite high. Patients who have septic infarcts usually have easily documented bacteremia, but bland infarcts may still be accompanied by high hectic fevers and prominent symptoms of pain in the left upper abdominal quadrant.

In receipients of bone marrow transplants, one of the major causes of fever, particularly fever occurring more than 2 weeks after engraftment of new marrow, is onset of graft-versus-host (GVH) disease. The manifestations of GVH disease include pruritis, arthralgias, liver function abnormalities, hepatomegaly, and a diarrhea of varying severity that may not respond to conventional antidiarrheal medications. GVH disease may require a histopathologic diagnosis. Our experience with allogeneic bone marrow transplantation indicates that in the face of a rising white count (representing engraftment), the onset of fever suggests early GVH disease. On the other hand, a demonstration of abnormal liver function studies, diarrhea, and other typical findings of GVH should not exclude a persistent search for infectious causes or coexistent infection caused by an organism such as CMV.

The two major categories of underlying diseases that have been recognized as causes of fever per se are connective tissue disorders and neoplasms. Prior to the availability of effective antinflammatory agents for systemic lupus erythematosus, fever was a prominent disease manifestation that could not be attributed to infection.[73,74] In neoplastic diseases, fever unassociated with infection may be a presenting symptom of leukemia or lymphoma. In patients who achieve a hematologic remission, the subsequent reappearance of fever may be an ominous sign heralding an intramedullary relapse or a deep-seated focus of infection in the liver or spleen. In patients with hematologic malignancies who have a bone marrow that still shows remission, the recurrence of fever may signal a relapse in an extramedullary site such as meninges or testicles.

The problem of fever in lymphoma and leukemia is considered in more detail in Chapter 21. Table 8 is an attempted summary of the association between neoplastic processes and fever. Fever is most common with unremitting hematologic malignancies and is relatively uncommon in the chronic leukemias and common solid tumors of breast, lung, and gastrointestinal (GI) origin. Classically, hypernephroma, hepatoma, adrenal carcinoma, pheochromocytoma, and malignant tumors of the pancreas, thyroid, and hypothalamic areas have been associated with fever. However, it seems clear that all tumors can be associated with fever if they are the cause of obstruction, and metastatic tumor in the liver is an accepted cause of fever even without gross obstruction or infection.

TABLE 9. Findings Suggestive of Microbial Infection Rather Than Fever Secondary to Underlying Disease

Appearance of skin lesions
Change in mental status
Consumption coagulopathy, particularly thrombocytopenia
Hemolysis
Hyperventilation or respiratory alkalosis or both
Hypotension
Increased fluid volume requirements
Localized pain
Metabolic acidosis
Oliguria

14. Findings Suggestive of Microbial Infection Rather Than Fever Secondary to Underlying Disease

There are no hard and fast rules for distinguishing between fever of infection and underlying disease, but Table 9 is an attempt to summarize some of the important findings that would point toward an infectious etiology in the seriously ill patient. None of these findings is specific for infection. For instance, neoplastic processes such as acute promyelocytic leukemia can trigger consumption coagulopathy, and hemolysis may be a prominent feature of a connective tissue disorder complicated by an autoimmune anemia. Nonetheless, the factors listed in Table 9 have been extremely helpful in certain situations. Change in mental status is often seen during the onset of septicemia, as is hyperventilation with ensuing respiratory alkalosis. Hypotension may be a terminal event in patients with far advanced malignancy, but an acute hypotensive episode (although it may possibly also have a noninfectious cause such as pulmonary emboli) should be strongly considered an indication for initiation of empiric antimicrobial therapy. Similarly, oliguria is a frequent sequel of systemic hypotension, and a sudden fall in urine output may be a clue to an underlying gram-positive or gram-negative septicemia. Both hypotension and oliguria may be associated with impaired tissue perfusion and metabolic acidosis.

15. Initial or Empiric Antimicrobial Therapy: Indications for Treatment

For any immunocompromised patient, the sudden appearance of fever should trigger both an intensive diagnostic evaluation and consideration of presumptive or empiric antimicrobial therapy. The concept of giving antimicrobial agents without definite microbiologic proof of infection is disturbing to some physicians who are schooled with the principle of knowing what they treat. However, information obtained from cultures may take days (and sometimes weeks) to become available, and a delay in treating a rapidly progressing infection may be disastrous. A more pragmatic approach is to give treatment based on the best available information and subsequently make adjustments in therapy or discontinue it altogether as the results of specific laboratory tests return. Previously available microbiologic studies, however recent in relation to a febrile episode, should be interpreted with some caution, as new events (e.g., superinfection) can be fast-developing.

Any finding on physical or laboratory examination that establishes the presence of infection in lungs, soft tissues, GI tract, or urine should prompt a decision to treat. In the absence of pain, inflammation, and exudate, any of the findings listed in Table 9 may tip the balance toward giving antimicrobial therapy. If neither objective findings of infection nor any of the changes cited in Table 9 are present, we would still treat the febrile patient if underlying disease is worsening or the neutrophil count is falling or both are occurring. It is hard to cite a definite cutoff point for the neutrophil count, but infection risk is definitely increased at levels below 500/mm.[75] We would still give empiric broad-spectrum antibacterial therapy if the neutrophil count is rapidly plummeting, even if the absolute value of the WBC count is above the 1000/mm^3 mark. For instance, in acute leukemia, it is not unusual for the white count to successively halve each day as the result of intensive cytotoxic treatment. Even though the number of normal neutrophils exceeds 1000/mm^3, the precipitous fall in the WBC count will virtually ensure that the patient will become functionally aplastic within a matter of days. Additionally, the sudden appearance of fever and findings suggestive of septicemia such as hyperventilation, hypoxemia, acidosis, and hypovolemia would be decisive factors in opting for antimicrobial treatment. On the other hand, if the patient's peripheral WBC count is quite low, but a marrow examination reveals repopulation of the marrow with normal morphologic elements, and the peripheral WBC is slowly rising, we would be less inclined to be aggressive about antibacterial treatment with onset of low-grade fever (<101°F).

If patients suddenly become febrile despite treatment with very high doses of anti-inflammatory agents such as corticosteroids, we would be extremely concerned about the possibility of a bacterial or fungal septicemia. We are not proposing that corticosteroids can be used as a diagnostic test for an infectious etiology of fever, but feel that the fever in the face of antipyretic medications is a stronger indication for considering therapy.

Among the principles that must be observed in the

clinical management of the immunocompromised host who has fever and suspected septicemia is the speed with which the diagnostic evaluation should be undertaken and empiric therapy initiated. Any significant delay could be dangerous, particularly in the presence of hemodynamic instability. Our clinical rule is to make a decision about giving treatment within an hour of being notified that the patient has signs of fever or infection or both. The necessary diagnostic steps for culturing of blood, secretions, and other infected sites can usually be performed within 60 min. During this interval, the clinician should assure himself or herself of at least one reliable route for giving intravenous therapy. This may require the insertion of an intravenous plastic cannula or intravenous cutdown. Appropriate monitoring devices should be set in place, and if necessary, the patient should be moved to an area where vital signs can be carefully monitored.

16. Relationship of Antimicrobial Therapy and Underlying Disease to Outcome of Infection

The importance of effective antimicrobial therapy in the management of the immunocompromised host cannot be overemphasized, but it would be difficult to establish unequivocally that antibacterial agents alone have improved survival in certain disease states. More than two decades ago, several major reviews of gram-negative bacillary septicemias pointed out the extremely poor prognosis for patients with so-called "rapidly fatal" diseases.[76–78] Such diseases were defined as bone marrow failure (aplastic anemia) or hematologic malignancies in which the outlook for survival was a matter of months. In a combined series of gram-negative rod bacteremias reviewed in 1971 (which reflected the clinical experience prior to the introduction of antipseudomonal penicillins and modern aminoglycosides), the mortality was 84% among patients with rapidly fatal diseases irrespective of whether appropriate or inappropriate antimicrobial treatment was given (appropriate therapy was defined as use of at least one antibiotic that inhibited the infecting organism). In other underlying disease categories, i.e., so-called "nonfatal" or "ultimately fatal" diseases, the use of appropriate antimicrobial agents could be correlated with lower mortality.[78]

Since the early 1970s, there has been a definite improvement in survival rates, particularly in those patients who would be classified as having rapidly fatal diseases; this improvement has coincided with the introduction of antipseudomonal penicillins and aminoglycosides beginning with gentamicin.[79] Our recent experience is that as many as 80% of patients with leukemias, lymphomas, and bone marrow transplants have survived gram-negative bacillary infections, although the mortality is still higher from bacteremic infections caused by *P. aeruginosa*.[80] A widely accepted concept is that recovery from a septic episode is directly related to the status of host defenses and that ultimate survival is closely linked to improvement in underlying disease. Although we have always subscribed to this view, it must be acknowledged that it represents a circular pattern of reasoning that leaves the relationship between cause and effect unresolved. In the management of the cancer patient, it has been argued that antibiotics keep patients alive while allowing antineoplastic drugs to work. On the other hand, the belief that ultimate recovery from infection is not possible without improvement in the basic disorder implies that effective treatment of the basic disease is crucial to the success of antimicrobial therapy. In the final analysis, these concepts need not be mutually exclusive. In many instances, it is possible to sterilize the blood of patients in the absence of marrow recovery with aggressive use of modern antimicrobial agents even though the basic disease has not improved.[81] This gain is usually temporary, however, because patients whose underlying condition fails to improve often develop new episodes of gram-negative bacillary, fungal, and viral infections within a short time. Nonetheless, antimicrobial therapy "buys time"—an interval during which additional attempts can be undertaken to control the underlying disease. If these attempts are successful, the improved treatment of underlying disease (leading to remission or control of cancer, collagen vascular disorder, or other disease) leads to better control or cure of infectious complications.

17. Factors That Underlie Recommendation of Initial or Empiric Antimicrobial Therapy Regimens

The major factors that influence selection of antimicrobial agents for use in serious bacterial infections include spectrum, potency, pharmacokinetics, ability to penetrate site(s) of infection, stability, and resistance to inactivation by enzymes of bacteria or inactivation secondary to use of other pharmacologic agents. We consider safety a highly desirable feature as well, but in the acute stages of a life-threatening infection, we are more concerned with efficacy rather than avoiding complications of treatment. In order to enhance the potency of therapy, we believe substantial evidence exists for the use of multiple antimicrobial agents as initial therapy. In addition, there is need to ensure that these agents are given in dosage sufficient to achieve adequate therapeutic levels.

Despite the extremely large number of clinical trials of antimicrobial agents reported in the medical, surgical, and pediatric literature, relatively few have included a comparison or control group, and there is a paucity of studies demonstrating the superiority of one regimen over another. Clearly, it is not ethical to have untreated control groups when sepsis is the clinical diagnosis, but comparison of different regimens in large numbers of treated patients is vastly preferable to anecdotal reports or "open," i.e., noncomparative, evaluations. Studies that use historic controls cannot easily be condoned because of the multiplicity of factors that have changed in the management of different underlying disease conditions.

In an effort to adopt more uniform criteria in the conduct of clinical trials, a committee of the Immunocompromised Host Society has published guidelines for the design, analysis, and reporting of clinical trials on the empiric antibiotic management of the neutropenic patient.[82] Clearly, not all immunocompromised patients are neutropenic, but the great majority of clinical studies of newer antimicrobials have focused on this patient population. While caution must be exercised in extrapolating from results in this population to the application of antimicrobial therapy in most seriously ill hospitalized patients, the broad conclusions are usually germane.

A corollary to the guidelines for future clinical trials is a statement drawn up by a specially appointed committee of the Infectious Disease Society of America establishing recommendations for the use of antimicrobial agents in neutropenic patients with unexplained fever.[83] This group considered the many therapeutic options available to physicians and ranked these regimens according to the support for such initial empiric approaches in the available literature. A particularly valuable aspect of this published statement is the comprehensive list of published studies cited. Use of at least two antibacterial agents, such as aminoglycoside plus a β-lactam agent with or without vancomycin, was considered the leading therapeutic choice, but a double β-lactam combination (i.e., a penicillin-like piperacillin combined with a cephalosporin-like ceftazidime) as well as single-agent approaches (e.g., ceftazidime or imipenem) were also viewed as "satisfactory" and supported by some published experience. Circumstances that affect individual choices, such as the presence of catheter-associated infection, renal failure, or desire to avoid interaction with potentially nephrotoxic agents, were all considered justifiable bases for varying the initial therapeutic choices. For example, the presence of clinical evidence of a vascular catheter-related infection would be a rational basis for "front loading" with vancomycin. In the presence of renal failure or use of agents with considerable nephrotoxic potential, such as amphotericin B or cyclosporine, either single β-lactam or double β-lactam therapies might be chosen. Still, use of aminoglycosides in combination with a β-lactam agent can be unhesitatingly recommended for life-threatening gram-negative bacillary infections such as caused by *P. aeruginosa*, and support for this approach has been published.[80,84]

It has been our policy for more than two decades to initiate antimicrobial therapy in the immunocompromised host with at least two agents and to consider adding a third, depending on the history, laboratory findings, and clinical findings. For the neutropenic patient with an absolute granulocyte count of less than 500 cells/mm^3 (and particularly the markedly neutropenic patient with less than 100 neutrophils/mm^3), we still believe that an essential component of empiric therapy should be an aminoglycoside paired with a β-lactam agent. There is persistent debate about (1) the relative merits of agents within the aminoglycoside class and (2) whether the β-lactam agent should be either a cephalosporin, an antipseudomonal penicillin, or one of the newer compounds, such as a monobactam (e.g., aztreonam), carbapenem (e.g., imipenem), or β-lactamase inhibitor paired with a penicillin (clavulanate plus ticarcillin). Many new compounds belonging to the β-lactam class have been introduced into clinical use during the past ten years; many of these agents are considerably augmented in their gram-negative coverage. Nonetheless, a consistent finding has been a relative decrease in antistaphylococcal activity, against both coagulase-positive and coagulase-negative organisms (*S. epidermidis*). Some classes of new compounds, such as the monobactams (e.g., aztreonam), completely lack gram-positive activity and cannot be used alone in empiric therapy.

By employing two agents, we not only achieve a broadening of antibacterial spectrum but also take advantage of possibly synergistic interactions between agents. Antimicrobial synergism between aminoglycosides and β-lactam agents has been documented in *in vitro* experiments and experimental infections.[85,86] Although laboratory criteria have differed, synergism implies an antibacterial effect greater than the sum of the individual activities of the components of a regimen. In the treatment of human infection—whether the infection is enterococcal endocarditis or gram-negative bacillemia—it has not been possible to conduct a rigorous clinical trial that proves the superiority of synergistic combinations of antimicrobial agents. Such a definitive study would have to involve randomization of patients to receive synergistic vs. nonsynergistic combinations of agents. On the other hand, Klastersky et al.[87,88] and our group[84,89] have shown that the use of synergistic combinations in human gram-negative infections is associated with significantly better results than nonsynergistic combinations. In actuality, whether two agents interact additively or syner-

gistically is probably moot. The net result is greater activity than with the use of a single agent, and antagonism is rarely seen. (In fact, we have not documented antagonism in the study of more than 200 episodes of gram-negative rod bacteremia treated with aminoglycoside–β-lactam agent combinations.)

The greater *in vitro* antibacterial activity against gram-negative rods obtained with combinations seems to translate into better clinical results. Table 10 pools results from two studies in which fairly similar treatment protocols were used empirically in febrile neutropenic patients suspected of having systemic gram-negative bacillary infections.[81,90] The aminoglycoside was either amikacin, gentamicin, or netilmicin, while the antipseudomonal penicillin was either carbenicillin or ticarcillin. Each study shows the same trend, and the combined results demonstrate that responses, as measured by defervescence and clearing of bacteremia, were signifcantly better in patients treated with two agents active against the infecting strain than when only one of the assigned agents in a combination inhibited the bacteremic pathogen *in vitro*. Such results argue for the use of the most broadly active agents in an initial empiric regimen. The 82% response rate for combination therapy of gram-negative bacteremia when both agents inhibit the infecting strain is a standard against which other studies may be compared. Indeed, variations on the themes expressed above showed similar response rates when piperacillin–amikacin,[91,92] moxalactam–amikacin,[93] and ceftazidime–tobramycin[94] were used as empiric therapy in cancer patients.

With regard to specific recommendations, our initial choices would therefore involve selection of the most broadly active compounds of the aminoglycoside and β-lactam classes. Admittedly, there will be a number of alternative choices and no clear-cut regimen that most investigators and clinicians would consider ideal. As implied in subsequent chapters and as summarized in Table 11, the following combinations would appear to be the reasonable therapeutic equivalents: either amikacin, netilmicin, or tobramycin plus either piperacillin, azlocillin, ceftazidime, or cefoperazone.

TABLE 10. Combination Therapy of Gram-Negative Bacteremia in Neutropenic Patients[a]

	UCLA		BCRC		
	+	−	+	−	Response (%)
Pathogen susceptibility					
Both antibiotics	31	8	28	5	82%
One agent	2	5	18	9	59%
Neither agent	0	3	2	5	20%
Total	33	16	48	19	70%

[a]Pooled results of University of California at Los Angeles (UCLA)[81] and Baltimore Cancer Research Center (BCRC)[89] experience.
(+) survived, improved, or temporarily improved; (−) died or failed therapy.

TABLE 11. Summary of Recommendations for Empiric Therapy

I. Neutropenia (neutrophils <500 mm³) or rapidly falling WBC:
Aminoglycoside (tobramycin or amikacin + β-lactam (piperacillin, azlocillin, ceftazidime, or cefoperazone)
(Cephalosporin can be used in penicillin allergy manifested by rash; otherwise use aztreonam + vancomycin.)

II. Neutropenia plus (one or more):
Creatinine 1.2 mg% or greater
Age ≥60 years
Eighth-nerve damage
Potential nephrotoxic medication
Ceftazidime + piperacillin

III. Neutrophil count greater than 500 (stable):
Aminoglycoside + first generation cephalosporin (oxacillin or nafcillin)
or
Third-generation cephalosporin (alone)
or
Imipenem (alone)

IV. Add therapy in specific situations:
Diffuse lung infiltrates: trimethoprim–sulfamethoxazole
Multiple areas of lung consolidation: erythromycin or clarithromycin
Catheter site inflammation/pain: vancomycin
Severe diarrhea or abdominal symptoms: metronidazole

In a major study, the so-called Fourth Trial of the European Organization for Research and Treatment of Cancer randomized more than 1200 patients and studied over 120 examples of single-agent gram-negative bacillary bacteremia in neutropenic subjects.[95] The most efficacious regimen in this study—with an 82% response rate—was the combination of ceftazidime plus amikacin, the latter agent being given for a minimum of 9 days. While there are proponents of monotherapy with ceftazidime,[96] this approach is dependent on virtually uniform susceptibility of gram-negative and gram-positive bacteria within an institution where single-agent treatment is selected. Agents such as ceftazidime and imipenem have been used alone to treat febrile neutropenic patients. However, varying clinical criteria have been proposed for these studies, and the likely success of such monotherapeutic regimens is likely to be based on the following: (1) the prevalence of resistant organisms within a hospital environment and (2) the ability to provide close clinical monitoring of the patient such that it will be possible to modify therapy if the patient appears to be failing single-agent treatment. With ceftazidime, the Achilles heel appears to be its gram-positive, particularly antistaphylococcal, coverage. Use of ceftazidime plus vancomycin is a reasonable initial choice, but careful clinical monitoring is required.

Cefotaxime, the first of the third-generation cephalosporins, has markedly augmented activity against many important gram-negative rods such as *E. coli* and *Klebsiella* species. There are some well-conducted studies, such as that reported by Smith et al.,[97] indicating that cefotaxime used alone as a monotherapeutic agent was superior to and less toxic than the combination of nafcillin plus tobramycin. It must be noted, however, that this study did not include immunocompromised neutropenic patients, nor were there large numbers of patients who had bacteremic infections due to organisms like *P. aeruginosa, Enterobacter* species, and *Klebsiella* species. Klastersky and colleagues[98] demonstrated that cefoperazone plus amikacin is a highly effective combination in a small study of gram-negative bacteremic infections. Cefoperazone would appear to be superior to cefotaxime in antipseudomonal coverage, but is probably not as active as ceftazidime, which has been successfully used in immunosuppressed neutropenic patients as monotherapy for *P. aeruginosa* bacteremia with a better than 80% clinical response rate.[94] Either one of these antipseudomonal cephalosporins (cefoperazone, ceftazidime) can usually be used safely in patients with history of penicillin allergy. Further comments on the newer cephalosporin and related β-lactam agents are presented in Section 18.3. It should be noted that even use of ceftazidime alone as empiric therapy may still offer problems, as it is relatively less active (compared with first-generation cephalosporins) against staphylococcal species. Both gram-positive and anaerobic superinfections have been observed secondary to ceftazidime usage.[99] Experiences of this nature still argue for the prudent use of combinations as initial therapy in patients who are severely neutropenic.

An alternative to conventional aminoglycoside plus β-lactam agents has been a resurrection of a therapeutic strategy employed earlier in the 1970s, in which two so-called "double β-lactam" trials in neutropenic hosts were disappointing, particularly with regard to the response in the treatment of *Klebsiella* infection.[100,101] Admittedly, compounds used in earlier studies, such as carbenicillin as the penicillin and cefazolin as the cephalosporin, were relatively less active than newer agents belonging to the same respective drug classes. More recently, double β-lactam therapy has been reeavaluated with the pairing of third-generation cephalosporins with more potent antipseudomonal penicillins. Several large studies of moxalactam–piperacillin[102] and moxalactam–ticarcillin[103] indicate that overall response rates are quite similar to those obtained using comparison regimens of broad-spectrum penicillin with an aminoglycoside. In one of these studies,[103] there was less nephrotoxicity in the double β-lactam regimen as contrasted with the aminoglycoside-containing regimen, but in the other study,[102] no difference in ototoxicity or nephrotoxicity was observed. Interestingly, one of these reports shows poorer responses in patients with *P. aeruginosa* infections given a double β-lactam combination of piperacillin and moxalactam[102] compared with the aminoglycoside-containing arm. Furthermore, in that study, several patients treated with two β-lactam agents experienced relapse of *P. aeruginosa* bacteremia with emergence of multiple β-lactam-resistant organisms, suggesting a selection for strains elaborating inducible β-lactamases by one of the mechanisms suggested by Sanders and Sanders.[104] A review of these recent studies[105] has suggested that these types of double β-lactam regimens may be associated with significantly more fungal superinfection[103] and significantly prolonged neutropenia.[102] It is well known (perhaps related to prolonged duration of therapy) that some patients may develop neutropenia secondary to β-lactam antibiotic therapy. Use of two such agents in large doses for prolonged periods of time may impede marrow recovery, creating a paradoxical situation in which an attempt is made to treat infection in neutropenic patients, but the net result is actually prolongation of neutropenia (and therefore infection risk).

Nonetheless, despite the problems encountered thus far, modern double β-lactam therapy has some attractive features. An increasing proportion of patients being treated with cytotoxic and immunosuppressive therapy have either borderline or impaired eighth nerve and renal function. Many immunocompromised patients are receiving nephrotoxic agents such as *cis*-platinum or amphotericin B, and organ transplant recipients may be receiving cyclosporine. For these reasons, the initiation of double β-lactam therapy in patients above the age of 60 or in patients with impaired or borderline renal and eighth nerve function appears prudent, particularly when it seems less likely that infection is due to the more problematic gram-negative rods (*P. aeruginosa, Enterobacter* sp. and *Serratia* sp.). Probably the most active double β-lactam regimen widely available is the combination of piperacillin and ceftazidime, as suggested in Table 11. With known or likely *Pseudomonas* infection of the lungs or the bloodstream, it would still seem prudent to use an aminoglycoside coupled with either a potent antipseudomonal penicillin or cephalosporin.

There are still gaps in empiric therapy coverage if one focuses on combining a traditional aminoglycoside with a β-lactam agent. The choice of one of the newer cephalosporins risks enterococcal superinfection, particularly when moxalactam is used.[102] With widespread use of indwelling vascular catheters, coagulase-negative staphylococcal bacteremia is one of the leading causes of bloodstream infection; many physicians have added vancomycin as an initial component of the early treatment regimen. Such a decision should probably be related to

physical findings. If physical examination reveals an obviously infected indwelling catheter, such a finding would favor empiric vancomycin.[83] It is interesting to note, however, that there has never been a convincing therapeutic trial in which three initial antimicrobial agents given as empiric therapy have proved superior to a two-drug regimen in terms of overall recovery rates.[106] The second major multicenter EORTC study found that amikacin plus carbenicillin was no less effective than amikacin–carbenicillin–cefazolin.[83] However, the addition of vancomycin to an aminoglycoside and β-lactam agent combination would be justifiable when staphylococcal or enterococcal infections are frequently encountered or appear likely on clinical grounds.

Finally, an alternative nonnephrotoxic empiric therapy regimen that might be used with considerable success would include vancomycin plus ceftazidime, or ceftazidime plus trimethoprim–sulfamethoxazole given parenterally.

Table 11 summarizes currently recommended regimens for empiric antibacterial therapy of immunocompromised patients. These recommendations must be interpreted only as general guidelines that need to be modified if more specific clinical and laboratory information (e.g., history of recent documented infection, results of surveillance cultures) is available.

18. Antimicrobial Agents

18.1. Aminoglycosides

The primary indication for aminoglycoside agents is in the therapy of documented or presumed gram-negative infections, since these antibiotics inhibit most clinically significant bacilli.

The greatest clinical experience has been with gentamicin, which has been available for more than a decade. Tobramycin is identical to gentamicin in pharmacokinetics and is resistant to one enzyme that can inactivate gentamicin. Amikacin is a semi-synthetic derivative of kanamycin, and both these agents achieve blood levels about 4 times higher than gentamicin. Kanamycin, like streptomycin, lacks anti-*Pseudomonas* activity and has no real indications in the immunocompromised patient. Amikacin is susceptible to inactivation by only one of the plasmid-mediated enzymes that can modify gentamicin and tobramycin. Netilmicin is also a semisynthetic aminoglycoside. It is more stable to enzymatic inactivation than tobramycin, but less stable than amikacin.

If infecting agents are equally susceptible to any of these aminoglycoside agents, and therapeutic levels of each are achieved, there is no evidence that one compound is clinically superior to the other. There are differences in *in vitro* susceptibility (taking into account potency by weight and achievable blood levels), including: (1) increased activity of tobramycin against *P. aeruginosa* and (2) increased activity of amikacin against *Klebsiella, Enterobacter, Serratia,* and *Providencia.* It has not been demonstrated, however, in randomized, prospective human studies that such *in vitro* superiority results in enhanced clinical efficacy if patients are carefully monitored and have drug doses adjusted so that peak blood levels fall within therapeutic ranges.[89,107] Table 12 summarizes current dosage recommendations for these aminoglycosides and emphasizes the desired therapeutic ranges. We recommend pulsed infusions of approximately 30-min duration and prefer intravenous to intramuscular treatment in seriously ill patients.

TABLE 12. Calculation of Aminoglycoside Therapy for Systemic Therapy

Agent	Dose mg/kg	Dose mg/body surface area (m^2)	Interval (hr)	Anticipated blood level Peak	Anticipated blood level Valley
Gentamicin	1.5[a]	60	8	> 4	< 2
Tobramycin	1.5[a]	60	8	> 4	< 2
Amikacin	7.5[b]	280	12	>20	<10
	5[b]	200	8	>14	<10

[a]For seriously ill patients, an initial loading dose of 2 mg/kg or 105 mg/m^2 is recommended.
[b]The total daily dose of amikacin should be 15 mg/kg or less. In seriously ill patients, dosage every 8 hr (5 mg/kg) is preferred.

Many authorities have emphasized the need to monitor blood levels to ensure adequate dosage.[107,108] There is a wide range of dose–blood level relationships for gentamicin (the best-studied agent), and this observation is probably true for the other aminoglycosides as well. Adequate blood levels are crucial for the successful treatment of septicemia and pulmonary infections in the impaired host, and many treatment failures and breakthroughs on gentamicin therapy have occurred in association with subtherapeutic levels.[109] Monitoring of blood levels may also alert clinicians to the potentially toxic accumulation of these agents so that dosage can be adjusted.[110] We recommend twice- or thrice-weekly measurements in septicemic patients. In urinary tract infection, urine levels of drug correlate best with outcome, and all aminoglycosides achieve very high concentrations in urine, so that blood level monitoring is not critical. Some authors have recommended continuous infusions of aminoglycosides, but have not demonstrated convincingly superior results.[111] In addition, infusions given in this manner usually require special equipment and additional intravenous lines.

An approach quite the opposite of continuous infusion is that of using a single large daily dose of aminoglycoside. Instead of twice- or thrice-daily infusions, a total 24-hr calculated dose is given in a 30- to 60-min infusion. While this regime is supported by some experimental and human evidence that the results are as good and toxicity less, more experience is needed in neutropenic patients who are also receiving medications that are toxic to hearing and renal function.

Information on the clinical prevalence of resistance to gentamicin and tobramycin shows considerable interinstitutional differences. Clearly, knowledge of local patterns of antimicrobial susceptibility as well as the bacterial species most prevalent in immunocompromised hosts should have the most important bearing on initial antimicrobial selection. While we prefer to use amikacin for empiric therapy before the results of cultures are known, a justifiable concern is the emergence of broad aminoglycoside resistance. Fortunately, this appears to have occurred rather infrequently in the face of widespread usage.[112,113] Organisms that are resistant to all aminoglycosides are not rare, however, and such multiresistant strains have developed permeability barriers to drug penetration. The selection of such resistant strains may occur secondary to the use of any aminoglycoside.

Although aminoglycosides are routinely given with penicillins, clinicians should be aware that under certain circumstances, agents such as gentamicin and tobramycin can be inactivated by carbenicillin. The basis for the inactivation is the formation of a biologically inactive amide between penicillin and aminoglycoside.[114] This phenomenon is dose-, time-, and temperature-related, and inactivation is probably most significant in patients with renal failure in whom both agents circulate and have adequate time for the inactivation to occur. Closed-space infections or urinary tract infection may be other situations in which inactivation occurs.[115] A report indicates that even in patients without renal failure, some inactivation of gentamicin will occur when a penicillin (ticarcillin) is given.[116] We believe that documented renal failure is an indication for amikacin because it is least subject to inactivation, perhaps 10% in 24 hr.[117] If gentamicin or tobramycin is used with a penicillin in renal failure, even more care should be paid to following blood levels because it will probably be necessary to augment the dosage.

18.2. Antipseudomonal Penicillins

Following the introduction of ticarcillin, three other agents in this category have become clinically available: mezlocillin, pipercillin, and azlocillin. It is important to remember that all antipseudomonal penicillins are not reliably effective against staphylococcal infection, with all these agents being readily hydrolyzed by staphylococcal β-lactamase.

Mezlocillin and pipercillin exhibit modest but variable activity against *Klebsiella* species. In both cases, this activity is not predictably reliable against *Klebsiella* organisms. Mezlocillin is relatively less potent than azlocillin and pipercillin against *P. aeruginosa*. The primary advantage of ticarcillin, mezlocillin, azlocillin, and piperacillin compared with carbenicillin is greater potency by weight, permitting lower dosages. The net result tends to be less hypokalemia and less sodium overloading. These differences may be clinically significant.[92] When used in appropriate dosage, all the antipseudomonal penicillins combined with appropriate aminoglycosides appear to give comparable results. Pipercillin and azlocillin are most potent against *Pseudomonas* and for this reason are to be favored in severe infection caused by this pathogen.

18.3. Cephalosporins

During the past decade, the most rapidly changing area in systemic antimicrobial therapy has been the field of parenteral cephalosporins. Traditionally, the activity of the cephalosporins, as exemplified by cephalothin and cefazolin (so-called first-generation compounds), included reliable activity against coagulase-positive staphylococci compared with penicillins such as ampicillin or carbenicillin. In addition, they were usually active against *E. coli* and *Klebsiella*. First- and second-generation (e.g., cefoxitin) cephalosporins lacked activity against the more resistant gram-negative rods, such as *Pseudomonas* and *Serratia*. First-generation cephalosporins have been traditionally favored in surgical prophylaxis. The major development in the cephalosporin field, as commonly acknowledged by many investigators, has been the rapid introduction of compounds belonging to the so-called third generation. Some of these compounds and recommended dosage regimens are summarized in Table 13. For completeness, related compounds such as aztreonam and imipenem are included as well, with recommended dosing intervals.

The third-generation cephalosporins are exceedingly potent against pathogens such as *E. coli* and *Klebsiella* species, pathogens traditionally susceptible to cephalosporins. They are some 100 times more active than predecessor compounds of their class if one considers gravimetric potency. Furthermore, the coverage against enteric organisms is comprehensive, with very low minimum inhibitory concentrations (MICs) for *Proteus* species and related organisms. The activity against *P. aeruginosa* has been variable. Agents such as ceftazidime exhibit considerably more activity than cefotaxime, ceftizoxime, and ceftriaxone. Caution must

TABLE 13. Recommended Dosage and Selected Pharmacokinetic Properties of Third-Generation Cephalosporins and Other New β-Lactam Agents

Agent	Peak serum level (μg/ml)[a]	Half-life (hr)	Protein binding (%)	Daily IV dose[b] (g) and interval
Aztreonam	50	1.7	60	2 q8h
Cefotaxime[c]	40	1.1	40	1–2 q6–8h
Ceftizoxime	75	1.4	30	2 q8–12h
Ceftriaxone	150	8.0	90	1–2 q24h
Ceftazidime	80	1.8	20	2 q8h
Cefoperazone	125	2.0	90	2 q8–12h
Imipenem	50	1.0	50	0.5–1 q6h
Moxalactam	75	2.3	50	1.5 q8h

[a]After administration of 1 g intravenously.
[b]Doses recommended are for an average-size adult with moderately severe infection who has normal renal function.
[c]Cefotaxime is metabolized to an active derivative with a longer half-life (1.6 hr).

still be expressed about the activity of these agents against *Pseudomonas* species, *Enterobacter* species, *Serratia*, and *Citobacter* species, in which there is potential for inducible β-lactamase resistance.[104] It seems prudent, therefore, to employ these potent agents in combinations, at least until the nature of infecting bloodstream pathogens is known. Furthermore, it should be pointed out that many of these compounds may have adverse effects, which undermine the traditional concept that cephalosporins are extremely safe compounds for antimicrobial therapy. Coagulopathy and disulfiramlike reactions are associated with cefoperazone and moxalactam.[93] The potential bleeding complications are a genuine concern for the clinician who must manage thrombocytopenic patients. Minor disulfiramlike reactions may, in fact, occur in patients receiving medications that contain small amounts of alcohol (e.g., cough medications).

Aztreonam is very much like ceftazidime in its antigram-negative spectrum, and the two compounds do exhibit major structural similarities. The major deficiency of aztreonam, however, is lack of activity against all gram-positive pathogens, thereby mandating its use in combination when empiric therapy is given.

Imipenem, a compound marketed with an inhibitor of its metabolism, cilastatin, is a very potent, novel β-lactam agent with broad gram-positive and gram-negative activity. There may still be problems, however, with the emergence of resistance among problematic organisms such as *Pseudomonas*, and its effect against *Enterococcus* is not bactericidal. Nevertheless, its use has occasionally been life-saving in pseudomonal and other gram-negative infections that have been resistant to other forms of antimicrobial chemotherapy.

18.4. Antistaphylococcal Semisynthetic Penicillins

Methicillin, oxacillin, and nafcillin are equally effective antistaphylococcal agents when used in appropriate dosage. Methicillin is preferred for CNS infections because of superior penetration into spinal fluid; however, there may be more hypersensitivity nephritis and neutropenia associated with its use.

19. Is Specific Antistaphylococcal Therapy Necessary?

One of the most frequently asked questions regards the advisability of including an antistaphylococcal agent such as oxacillin, a cephalosoporin, or vancomycin with the initial combination of an antipseudomonal penicillin and an aminoglycoside. The experience of several centers including our own a decade ago is that empiric use of an aminoglycoside and an antipseudomonal penicillin will prevent serious progression of staphylococcal infection (including bacteremia) and that no ground is lost by not giving specific antistaphylococcal coverage.[89] In some countries where methicillin-resistant organisms are prevalent, the use of an aminoglycoside for staphylococcal infections has been associated with satisfactory clinical response rates. Nevertheless, we do not advocate continued use of aminoglycosides when it is known that the patients have methicillin- and cephalosporin-susceptible staphylococcal infections (based on *in vitro* susceptibility tests). Specifically, we will add an antistaphylococcal agent and probably alter the initial antibiotic coverage (by stopping the aminoglycoside).

One potential detraction from our assumption that aminoglycosides constitute adequate initial coverage for staphylococci is the recognition that some hospitals, particularly those that treat patients with thermal injury, have observed infections caused by both gentamicin- and amikacin-resistant staphylococci.[118] These organisms appear to be resistant by virtue of their elaboration of enzymes that inactivate gentamicin and amikacin, respectively. If infections caused by such organisms are documented, alternative therapy must include van-

comycin, inasmuch as such strains can also be methicillin-resistant. The problem of dealing with catheter-associated *S. epidermidis* infection is covered in Section 23.

20. Alteration of Empiric Therapy after Documentation of Bacterial Infection

After documentation of bacterial infection, therapy can justifiably be altered according to the results of *in vitro* susceptibility tests. Such instances include the following:

1. There is resistance to one or more components of the empiric regimen. If azlocillin or ticarcillin was initially used, and infection proves to be caused by *Klebsiella* species, substitution of a cephalosporin or trimethoprim–sulfamethoxazole (if supported by *in vitro* tests) is indicated.
2. A less expensive, better-tolerated alternative is available. If the infection proves to be *E. coli*, ampicillin can be substituted for carbenicillin or a cephalosporin (providing the patient is not penicillin–allergic). Trimethoprim–sulfamethoxazole or a quinolone appears to be a reasonable alternative to β-lactam agents for enterobacterial infection (but not gram-positive infection, for which we would recommend vancomycin).
3. Quantitative *in vitro* susceptibility tests (MIC or equivalent) show that one agent is at least fourfold more potent than another. For instance, it is generally recognized that aminoglycosides have a narrow ratio of therapeutic/toxic levels. If the MIC of gentamicin is 4 μg/ml and that of tobramycin is 1 μg/ml against an infecting strain, we would switch to the latter agent.

Although we believe there is evidence that synergistic interactions have a favorable impact on clinical outcome, routinely performing synergism tests is time-consuming and expensive. Results are usually available after 2–3 days, which is often a week or so after the initial culture was taken. The delayed availability of these results is likely to have little impact on therapeutic decision-making.

Should the infecting pathogen be susceptible *in vitro* to both agents that were initially used, an important question is whether to continue both agents or discontinue the more potentially toxic component, i.e., the aminoglycoside. Our studies[90] suggest the benefit of continuing multiple agents in the more severe underlying diseases (rapidly fatal) and certainly in patients whose neutrophil counts are less than 500/mm^3. For the remainder, we would wait until defervescence occurs and the patient has been afebrile for 72 hr. Even with patients who present less severe underlying disease, we tend to continue double-agent therapy if the infection proves to be *P. aeruginosa, Serratia, Enterobacter,* or indole-positive *Proteus* species.

21. Role of Other Antibacterial Agents in Therapy

The quinolones, chloramphenicol, the polymyxins (colistin and polymyxin B), clindamycin, trimethoprim–sulfamethoxazole (TMP-SMZ), rifampin, and tetracycline have certain indications, but we would not use them as initial compounds of empiric therapy. The polymyxins have impressive *in vitro* activity against *P. aeruginosa, E. coli,* and *Klebsiella,* but are inactive against *Serratia* and *Proteus* species. A principal virtue is that R-factor (plasmid)-mediated resistance to these compounds has not been documented. However, there are persistent doubts about their efficacy, and their role is primarily in the treatment of aminoglycoside-resistant organisms.[79] Occasionally, it can be demonstrated that sulfonamides will potentiate the action of a polymyxin against the highly resistant strains of *Serratia* or *Proteus,* and in such situations, such combination therapy may be considered.[119]

Clindamycin and chloramphenicol have occasionally been added to empiric therapy regimens, particularly for patients with possible anaerobic infection. Although their activity against anaerobes is unquestioned, our experience has been that anaerobic organisms are infrequently a major component of infections in immunocompromised patients unless pelvic inflammation is present or there has been some violation of the integrity of the mucosal surfaces of the GI tract. Furthermore, our experience has been that antipseudomonal penicillins are probably satisfactory antianaerobic agents. Occasionally, we have observed a patient to defervesce following addition of carbenicillin even though bacteremic infection remains undocumented. An unanswered question is whether the effect of carbenicillin against anaerobic microorganisms is responsible for this improvement. No substantial data have been presented to support this hypothesis. By the same token, clindamycin or chloramphenicol added to an initial combination of carbenicillin or ticarcillin and aminoglycoside adds little in terms of antibacterial coverage, poses some risk of toxicity, and has not been shown in any comparative or randomized study to significantly improve the clinical response rate.

TMP-SMZ, on the other hand, is an agent with interesting pharmacologic properties and antimicrobial activity. The excellent tissue penetration of the trimethoprim and sulfonamide components is an advantage over aminoglycosides. There are some strains of Entero-

bacteriaceae, particularly *Serratia*, that are resistant to all other agents including the aminoglycosides, and it is in the treatment of infections caused by these organisms that TMP-SMZ may be distinctly beneficial. *In vitro*, this agent inhibits most clinically significant gram-positive and gram-negative organisms except for *Enterococcus*, anaerobes, and *P. aeruginosa*. We do not believe that the problem of pneumocystosis or toxoplasmosis is sufficiently great to justify empiric use of this compound or its therapeutic trial in persistently febrile patients. On the other hand, this agent might make an effective partner in combination with an aminoglycoside or an antipseudomonal penicillin; such therapeutic approaches require further clinical study.

The dose of TMP-SMZ for certain infections will vary depending on severity of infection, presence of bacteremia, and source of infection. We have extensive experience with the intravenous preparation. Although there are some technical problems with this preparation (including the necessity for administration of large volumes of fluid to maintain solubility of the product), it would clearly be advantageous to use a parenteral preparation in seriously ill patients. We recommend the intravenous TMP-SMZ in a dosage of 240 mg, or 3 mg/kg, every 8 hr intravenously with the intravenous infusion proceeding over approximately 1-hr duration. In more serious infections (and including *P. carinii* pneumonia), that dose may be doubled with little risk of major acute toxicity.

Tetracyclines are bacteriostatic agents that are infrequently used to treat bacterial infection in immunocompromised subjects. Infections caused by non-*aeruginosa* pseudomonads, some anaerobic pathogens, and mycoplasmas are some indications. Some tetracyclines, such as minocycline, are effective components of multidrug therapy of *Nocardia* infection.

Rifampin is a highly effective antituberculous agent and one of the drugs of choice (along with isoniazide) for the treatment of tuberculosis. It will inhibit a number of other bacteria as well, but clinical experience with this agent when used alone was that emergence of resistance developed fairly rapidly. Rifampin is a highly effective antistaphylococcal agent, possibly because of its penetration into leukocytes. Consequently, its use has been in combination with agents such as vancomycin against staphylococci resistant to semisynthetic penicillins or against which the effect of vancomycin is bacteriostatic and not bactericidal. There are a number of strains of coagulase-negative staphylococci that are inhibited by vancomycin but are not killed until fairly high concentrations are used. Against these strains, the addition of rifampin results in bactericidal activity at clinically achievable levels. Coagulase-negative staphylococcal infections are occasionally encountered in infected shunts and catheters, and there could be major problems associated with removal of the infected prosthetic device.

The category of the fluoroquinolones represents one of the fastest-growing group of agents in the therapeutic armamentarium. Depending on the specific compound, *in vitro* activity is demonstrable against staphylococci, enteric bacteria, and often *P. aeruginosa*. Ciprofloxacin must be considered the most active agent in general viewed in the light of its anti-*Pseudomonas* activity. Agents such as ciprofloxacin and its alternative, ofloxacin, are now available for parenteral treatment, and the experience in treating immunocompromised neutropenic patients must be considered limited.[120] More information exists on prophylactic use of quinolones in neutropenia (see Chapter 21). Novel therapeutic applications of quinolones include their use for the treatment of some mycobacterial diseases such as tuberculosis and leprosy. One might consider the quinolones to be an alternative to an aminoglycoside in a treatment of gram-negative bacillary infections, but usually their effect is additive rather than synergistic when added to a β-lactam agent. Enhanced killing of organisms such as enterococci is not observed when fluoroquinolones are combined with penicillin or ampicillin. Still, their nonnephrotoxic nature makes them appealing alternatives for the systemic treatment of patients for whom we might otherwise consider an aminoglycoside. Additionally, one of the areas of widespread application of fluoroquinolones has been in what is known as consolidation or "step-down" therapy following the initial use of systemic broad-spectrum agents (i.e., initial therapy with a third-generation cephalosporin with or without an aminoglycoside). Such a transition from parenteral to oral therapy may be contemplated after the patient has defervesced, definite corollary evidence of clinical improvement is apparent, and the infecting agent has proven susceptible to the quinolone being considered for consolidation therapy.

22. Therapeutic Drug Monitoring

It is clearly desirable to monitor aminoglycoside blood levels during severe infections. The problem of breakthrough bacteremias[109] and the demonstration of better clinical results when targeted levels are achieved[121] support this policy. Other tests have been proposed, such as the monitoring of serum bactericidal activity in a manner akin to measurements obtained during the treatment of endocarditis.[122,123] Some impressive correlations have been demonstrated between high bactericidal levels and clinical success in treating cancer patients[124,15] and patients with endocarditis.[125] The test, however, is cumbersome and poorly standardized and takes days to execute. Equally useful information (in terms of identifying

patients whose dosing regimen requires modification) may be derived by using some of the rapid antibiotic assays that yield results within minutes.

23. Management of Catheter-Associated Infection

The tendency to use large indwelling vascular catheters for delivery of parenteral fluids, blood transfusions, hyperalimentation, and drugs continues to increase. The advantages of this approach are obvious because such indwelling catheters facilitate infusion of large quantities of medications and nutritional support.[126] In addition, it may be possible with a multilumen catheter to also draw blood from a central site, thereby reducing the number of venipunctures that a patient may require. The almost universal acceptance of indwelling central catheters in patients undergoing organ transplantation or intensive chemotherapy underscores their current popularity.

Much of the risk of long-term indwelling catheters is related to infection hazards. Clearly, the technique and experience of physicians inserting such catheters and those who manage such catheters (nursing personnel or the patient him or herself should the individual choose or want to elect to manage the catheter) will affect the subsequent incidence of infectious complications. When highly experienced personnel are involved in surgical insertion of these catheters and their daily maintenance, cleaning, and care, the infection rate may decline to almost negligible levels. With less experienced cathether care, more than half of such catheters can be infected despite the use of parenteral antimicrobial agents.

Major clinical dilemmas arise when neutropenic patients have fever and no readily identified source. The catheter becomes suspect as the source of sepsis by a "process of elimination." Nonetheless, because of the impaired inflammatory response of immunosuppressed patients, there may be slight or even no evidence of inflammation of the cutaneous entry site of even an infected catheter. Thus, the catheter is always a suspected candidate for the source of the fever in a patient with FUO, yet clinicians are reluctant to remove such catheters because they are so convenient to use and the removal of one catheter in a patient who has a venous access problem may merely mean that another one will have to be reinserted within a fairly short interval.

Another area of controversy relates to the fact that patients who have indwelling catheters will clearly have bacteremias from multiple sources, and the source obviously may not be the catheter. If there is clinical evidence of localized infection around the catheter, such a finding is fairly incriminating. If the organism cultured from blood has the same morphologic and antimicrobial susceptibility pattern as an organism in urine or wound, the catheter is far less suspect. However, the possibility exists that the catheter may become secondarily infected (seeded) if the bacteremia was sustained. What seems clear is that routine removal of a catheter in any patient with fever is to be discouraged. When a patient has documented bacteremia due to a gram-negative organism, one should not automatically incriminate the vascular catheter as the predisposing factor. By contrast, bloodstream recovery of *S. epidermidis, Corynebacterium,* and *Candida* species should lead to the other more readily identifiable focus of infection.

Once a catheter is identified as the source of infection (by multiple positive peripheral blood cultures and culture of blood drawn through the catheter), controversy exists about the alternatives of treating the infection *in situ* or removing the catheter. Infectious-disease dogma maintains that foreign bodies that are the focus of infection should be removed, and this remains a generally sound principle. Nonetheless, Pizzo et al.[122] have reported that more than half of such catheters can be maintained in place with appropriate antibiotic therapy. Doing so allows a patient to complete a course of cancer chemotherapy or to be supported during the immediate posttransplantation period (if the patient has undergone such a transplant) and obviates the need for yet another catheter insertion procedure in a very sick patient. From the careful studies of catheters infected by coagulase-negative staphylococci, antibiotic therapy such as with vancomycin either alone or in combination with rifampin or gentamicin can lead to eradication or suppression of staphylococcal infection. Often, defervescence of the patient is but a reflection of the suppression of infection caused by a relatively less virulent organism. Still, suppression may be an acceptable goal providing that only a few additional weeks of treatment of the underlying disease is necessary.

We believe that there are rational guidelines to catheter management. Our own experience is that it is possible to suppress coagulase-negative staphylococcal corynebacterial bacteremia that is associated with a catheter in more than half of cases, using vancomycin with or without rifampin or gentamicin (but sometimes requiring all three agents). On the other hand, we have never been able to sterilize the blood of patients who have had bloodstream infections due to *Candida* species, more resistant gram-negative organisms such as *P. aeruginosa, Serratia,* or *Enterobacter.* With the latter bacteria, the catheter should be removed at the earliest possible opportunity and specific antimicrobial therapy given for 7–10 days (or longer, if there are metastatic foci of infection). Most *S. aureus* and *E. coli* bacteremias that are clearly linked to catheters are not easily suppressed even with very potent antibacterial chemotherapy, and catheter removal is usually necessary. For the more sensitive organisms (coagulase-negative

staphylococci, *Corynebacterium*), a trial of 3–5 days of therapy may be justified if the overall clinical condition is stable. If the patient has not defervesced and improved by the end of such a trial period, then the catheter must be removed. If the patient does respond to suppressive therapy, such treatment should be continued for a total of 10–14 days, with the recognition that the infection may well recrudesce (the value of longer treatment is unclear). Virtually all cases of catheter-related fungemia should be managed with catheter removal and administration of amphotericin for 10–14 days.[128]

24. Should Fever Be Suppressed?

Despite much controversy, there has been no satisfactory resolution to this much-debated issue. There is substantial evidence that fever is beneficial to the host in experimental infections.[3] On the other hand, there is no convincing evidence that, providing adequate antimicrobial therapy is given for a documented infection, the concomitant suppression of fever is detrimental to the clinical outcome. Proponents of suppressing fever argue that patients are more comfortable and have less metabolic demand and that elderly patients in particular benefit from reduced stress on cardiovascular function.

A prudent clinical approach argues that it would be misleading to routinely administer antipyretics while searching for a cause of fever or while assessing the response to treatment. On the other hand, if patients become markedly febrile (temperature 102.2°F, or >39°C), the use of antipyretics can be justified particularly in the elderly or anemic patient. We would recommend initiating a 24- to 48-hr trial of acetaminophen, 600 mg every 4–6 hr, or naproxen, 250 mg every 12 hr, and then stopping the antipyretic and observing for a "rebound" in temperature. This seems preferable to intermittent use of antipyretics for single temperature elevations, a practice that leads to "seesaw" temperature changes, drenching sweats, and much patient discomfort. Younger patients tolerate fever much better, and suppression of temperature is not strongly advocated in this group.

25. Therapy of Underlying Disease during Documented Infection

Whenever an immunosuppressed patient develops documented infection, it is entirely appropriate to consider the possibility of decreasing, perhaps temporarily, the intensity of treatment of the basic disease to aid in combating the infection. However, in some diseases such as acute leukemia where there is rapid cell proliferation, this concept is unrealistic because the malignancy is likely to progress during the hiatus. In bone marrow transplantation, the nature of the conditioning is such that once it is begun, a point of no return is quickly reached. Similarly, in collagen vascular disease or acute graft rejection, the principal aim of therapy is control of the inflammatory or rejection process, and reducing immunosuppression jeopardizes the basic therapeutic approach. In selected situations, decreasing immunosuppression is feasible, such as with an infection that occurs during remission consolidation of leukemia. Although every attempt is usually made to save a renal graft, the ultimate consideration in a life-threatening infection is whether to allow the patient to reject it. The renal transplant recipient enjoys one advantage over the recipient of cardiac or bone marrow transplant: The patient can be supported by dialysis while the complicating infection is being treated.

26. Duration of Antimicrobial Therapy in Documented Infection

The immunocompromised patient who develops infection should be treated for no shorter duration than for the same type of infection in the normal host, but some patients may require a longer course of therapy. There is no substitute for clinical judgment in this decision-making process, with the critical variable being the status of the underlying disease. For neutropenic patients who develop bacteremia, pneumonia, or extensive cellulitis, we would treat for at least 14 days total until the patient becomes afebrile. If the patient remains febrile and still has signs of infection, we would continue until the neutrophil count exceeds 500/mm^3. This plateau might require many more weeks of treatment. We have given one leukemic patient with extensive necrotizing cellulitis of an extremity because of *P. aeruginosa* 4 months of aminoglycosides and carbenicillin until satisfactory healing was achieved. If there is persistent evidence of a localized or systemic infection, it would be foolish to terminate effective therapy "by the calendar."

On the other hand, there are situations in which shorter courses of treatment may be as beneficial as longer courses. In uncomplicated lower urinary tract infection, a day of treatment may be adequate.[129] In vascular and catheter-associated infections, a week of therapy following their removal is usually satisfactory if a rapid defervescence and clinical response are observed.

27. Undocumented Infection and the Decision to Continue or Withhold Antimicrobial Agents

Perhaps one of the greatest clinical dilemmas facing the physician who treats immunocompromised subjects

is how long to wait to assess the clinical effect after empiric therapy is started and what to do if no infection has been documented. Thus, the crucial question is: Should therapy be stopped, modified, or intensified? It is clear that many patients given empiric treatment may take more than 4 days to become afebrile; Rodriguez et al.[130] isolated bacteria after an initial 4 days of fever in 21% of treated patients. Thus, empiric coverage should likely extend beyond 4 days and probably up to a week. In another study,[131] the incidence of superinfection increased after 7 days of empiric therapy, and if infection was not documented by 4–7 days of fever, no patient deteriorated when antibiotics were stopped. Pennington[131] goes on to advocate that a reasonable approach would be that for patients who deferversce within 3–4 days, a total of 5 afebrile days of therapy should be given if cultures are negative, and at least 7 if positive. If patients fail to respond to empiric treatment, alteration in therapy is indicated. The clinically stable but continuously febrile patient who turns out to have negative cultures should receive empiric antibiotics for more than 4 but not more than 7 days. If these patients continue to deteriorate for more than a week, consideration of empiric antifungal therapy is indicated, especially if a fungus is isolated from other body sites.

Unfortunately, there is no uniformity of opinion as to each step in the decision-making process. Although there have been many trials of empiric therapy, particularly in the neutropenic patient, relatively few details have been provided about the factors that influence decisions to continue or discontinue antimicrobial agents. Unquestionably, a large number of patients have fever with undocumented infection (see Chapter 21). In our recent experience with neutropenic patients, more than 70% of patients fall into this category. On the other hand, the clinical response rate to initiation of empiric antimicrobial therapy now exceeds 70% and is no different from the patient population with documented bacterial infection.[89] This raises the tantalizing question about what processes may be responsible for febrility that are yet responsive to empiric antimicrobials.

An interesting study was described by Pizzo et al.[132] at the National Cancer Institute (NCI). It acknowledges that the complications of broad-spectrum antibacterial therapy argue for brief treatment, whereas the risk of inadequately treated infection in the granulocytopenic patient favors longer therapy. Of more than 300 patients at the NCI initially treated with cephalothin, gentamicin, and carbenicillin, an infectious etiology of fever was not identified in 142 (46%) of 306 episodes. Of those patients with persistent granulocytopenia, 33 defervesced, and their granulocytes remained at less than 500/mm^3. These patients were randomized after 7 days of the empiric regimen to continue or to discontinue treatment. There was no problem with patients whose WBC counts exceeded 500/mm^3 because they had no infectious sequelae. However, 7 (41%) of the 17 patients randomly selected to discontinue agents experienced infectious sequelae a median of 2 days after antibiotics were discontinued. This result was statistically significant. No patient continuing on therapy had a resistant superinfection or developed resistant microbial flora. Analysis of the 7 patients who had their therapy discontinued and then experienced a rebound fever or infection showed that 2 had fever alone, but 5 experienced documented infections, of which 2 were ultimately fatal. If the two groups are compared by numbers of documented infections, the significance of the difference is marginal. Nonetheless, this study argues for continued therapy during the duration of granulocytopenia.

The conclusions of Pennington[131] and Pizzo et al.[127,132] are essentially contradictory. The former sees no problem discontinuing antimicrobials in febrile patients (and danger in continuing them without proven infection), whereas the latter group suggests that empiric therapy be continued even if the patient is afebrile. Certainly, the risk of a rebound fever or infection should, if anything, be greater in febrile patients with undocumented infection. The lack of a consensus is even more apparent in the clinically more challenging situation of persistent fever, granulocytopenia, and undocumented infection. Some investigators cite examples of catastrophic developments if antimicrobial agents are stopped.[132,133] Another alternative is suggested by Rodriguez et al.,[130] who recommend, on the basis of a relatively small number of cases studied, adding a third antibacterial agent. If an aminoglycoside and a cephalosporin formed the initial combination, addition of an antipseudomonal (and better antianaerobic) penicillin may occasionally lead to defervescence, but we have rarely seen improvement if the third agent is chloramphenicol or clindamycin. Usually, little is to be gained by adding a cephalosporin to the initial regimen of an aminoglycoside and penicillin unless the patient has a *Klebsiella* or *S. aureus* infection. It does appear justified to add vancomycin to the persistently febrile patient with an indwelling vascular catheter in place.[83]

A more recent follow-up to the initial study by Pizzo and collaborators has been published and offers substantial guidelines for the management of the febrile neutropenic patient who fails to respond to an empiric antibacterial regimen.[134] The initial treatment regimen employed at the NCI has been the combination of cephalothin, gentamicin, and carbenicillin. Satisfactory response rates at that institution have been observed with relatively few problems with drug resistance. Patients who had persistent fever and neutropenia for 1 week were randomized as follows: Group I was randomized to stop all three antibacterial agents. Three of these patients developed rebound bacterial infections and six experi-

enced shock. Group II was randomized to continue the empiric three-drug antimicrobial regimen in the absence of documented infection. Subsequently, five patients were found to have a systemic fungal infection, an incidence of almost one third (consistent with some projections and estimates by other investigators). Group III was randomized to continue parenteral antibacterial therapy with the addition of empiric amphotericin B. In this group, only one opportunistic fungal infection was documented, due to *Pseudallescheria boydii,* an organism resistant to amphotericin B. An important observation was that patients randomized to receive empiric antifungal therapy defervesced more rapidly than patients in the other two groups.

This study clearly gives support to empiric addition of amphotericin B to empiric antibacterial therapy, but it would be dangerous, and certainly wasteful of a valuable drug, if every patient who did not respond within a finite number of days to antibacterial treatment were blindly started on amphotericin B. A number of factors might enter into clinical decision-making; these are reviewed in the next section.

TABLE 14. Factors That Affect the Decision to Stop or Continue Antibiotics in the Face of Fever and Negative Blood Cultures

Factor	Suggested course
Magnitude of WBC	Stop if $\geq 500/mm^3$ for 2 days.
Condition of bone marrow	Stop if normocellular and rising by 50% daily increase in peripheral white count even if total $<500/mm^3$
Continuation of treatment for underlying disease	Continue antibiotics
Surveillance cultures	Continue antibiotics if *P. aeruginosa* or *K. pneumoniae* recovered until white count reaches $500/mm^3$
Recovery of *Candida* or other fungus from blood or urine	Start amphotericin B
Radiography	
Diffuse infiltration consolidation, cavity	Invasive procedure; consider trimethoprim–sulfa or amphotericin B
Severe esophagitis	Start amphotericin B or fluconazole

28. Recommendations for Continuing or Discontinuing Antimicrobial Therapy and Initiating Empiric Antifungal Therapy

We believe that a rational decision can be made on the basis of the clinical and laboratory factors summarized in Table 14. We agree with many investigators that the magnitude of the circulating white count is of crucial importance in determining susceptibility to infection. Thus, if patients have persistent fever, we recommend discontinuing antibiotics after a 7-day trial providing that the granulocyte count exceeds $500/mm^3$ for 2 or more days and all cultures are negative. Perhaps as important as circulating neutrophil count, however, is the condition of the bone marrow. If afebrile patients have evidence of normocellularity of the marrow after a course of cytotoxic treatment, and the peripheral white count is rising by 50% per day, we recommend discontinuing antibacterial therapy even if the peripheral WBC count is low. An even more important factor in decision-making is the anticipated effect of further treatment. In the face of plans to augment the dose of adrenocorticosteroids, give a cytotoxic agent to prevent graft rejection, or resume another cycle of antileukemic treatment, we believe it would be perilous to discontinue antibiotic therapy if the patient has persistent fever. We place considerable reliance on the results of the surveillance cultures in adult patients being treated for acute leukemia and in patients of all ages who are subject to the bone marrow transplant procedure. The rationale for surveillance cultures is that colonization precedes infection in a vast majority of immunosuppressed hosts and that there is a substantial interval between acquisition of colonization and the development of infection (see Chapter 2). Thus, we can have an early warning system about potential infecting organisms. It is an expensive procedure that should not take the place of clinical acumen and careful examination. Of the sites that are sampled, the three most important areas for surveillance cultures are the oropharynx, stool, and nares. The first two sites are important for detecting gram-negative bacterial colonization and the nose culture for staphylococcal carriage.

The manner in which surveillance culture results influence our management of antibiotic therapy is as follows: For the neutropenic patient who has responded to empiric antibacterial treatment, we would treat for the interval to defervescence plus 3 afebrile days or a total of 7 days, whichever is greater, unless surveillance cultures reveal *P. aeruginosa, K. pneumoniae, Enterobacter* species, or *Aeromonas* species. In both afebrile, colonized (by the latter organisms) neutropenic patients and febrile neutropenic patients irrespective of colonization status, we treat with systemic agents until the white count reaches $500/mm^3$. The only exception to this working principle is the patient with severe aplastic anemia or myelofibrosis in whom it is unlikely that a circulating level of neutrophils approximating $500/mm^3$ will ever be reached. In these patients, we continue treatment until

they are clinically stable and afebrile and discontinue antibiotics under close observation.

One of the most dramatic findings in an immunocompromised patient is the rapid development of new pulmonary infiltrates accompanied by hypoxia and hemoptysis. This development may be the first evidence of a fungal or parasitic superinfection because of the difficulty of making the diagnosis of systemic or pulmonary disease on the basis of cultures of blood or expectorated sputum. Of those patients who have received more than a week of broad-spectrum antibiotic therapy directed against gram-negative pathogens such as *P. aeruginosa* and *K. pneumoniae* and then develop pulmonary infiltrates, the etiology—if proven to be infectious—will be fungal in perhaps 90% of instances. The remainder of infectious etiologies include *Pneumocystis,* tuberculosis, CMV, and toxoplasmosis, but fungal superinfection is by far the most likely infectious possibility.

Clearly, we are in favor at this point of obtaining a histologic diagnosis of intrapulmonary pathology, but would favor use of empiric amphotericin B if the chest radiograph shows consolidation mimicking a pulmonary infarct, a cavity, or lobar consolidation.[135] If pneumonitis is more diffuse, *P. carinii* infection is a major possibility, but we cannot exclude many other etiologies, including fungal infection. In the diffuse pneumonias occurring in neutropenic patients in whom no invasive diagnostic procedure can be undertaken, we feel fungal infection is more likely than pneumocystosis. Thus, we would also use amphotericin B empirically in this setting.

In view of the mounting evidence for fungal superinfections following a prolonged course of antibacterial treatment, several realistic guidelines have evolved that form the basis for a rational approach to empirical therapy if histopathologic evidence or blood culture confirmation is not available. Such evidence would be as follows:

1. The development of new pulmonary infiltrates while the patient is receiving broad-spectrum antibacterial therapy.
2. Refractory oropharyngeal *Candida* lesions with symptoms of esophagitis.
3. Onset of candiduria with hyphal forms detected in the urine in the absence of a Foley catheter or an anatomical urinary tract abnormality.
4. Evidence of peripheral embolic phenomena such as large arterial or vein occlusion in the extremities and occasionally the CNS. In the young person who develops sudden cerebral infarction unaccompanied by CNS hemorrhage, a supratentorial fungal process should be strongly suspected. Additionally, the arterial vasculature should not be the only site suspected of involvement by disseminated opportunistic fungal organisms. Some fungi, like *Mucor* species and *Aspergillus,* can invade the vena cava and cause thrombosis of the hepatic vein and a resultant Budd–Chiari syndrome or can cause thrombosis of the renal veins with development of nephrotic syndrome.[135]

If a persistently neutropenic patient remains febrile on broad-spectrum antibacterial agents after a period of 7 days but has no objective findings as suggested in points 1–4, empiric amphotericin B should still be strongly considered if bone marrow examination shows a hypoplastic marrow or a marrow filled with malignant cells. In this circumstance, marrow recovery will take a week and usually longer. The dose should be escalated to a goal of 0.7 mg/kg per day and duration of empiric amphotericin B keyed to the clinical response.

Most of the relatively few studies of empiric antifungal therapy have used amphotericin B, and it remains an obvious choice: Amphotericin B still has the broadest spectrum of any available antifungal agent. Fluconazole appears to be a more limited alternative inasmuch as it lacks reliable activity vs. the filamentous fungi, *Aspergillus,* and zygomycetes. It is possible that in the future, newer azole antifungal agents such as itraconazole will narrow the gap in spectrum vis-à-vis amphotericin B, but comparative studies are clearly necessary before such recommendations for empiric treatment can be given.

If no fungal pathogen is subsequently documented but the patient defervesces, treatment should be given for at least a week after temperature normalizes.

For recommended doses of antifungal agents and techniques for administration, see Chapter 8.

29. Adjunctive Use of Corticosteroids, Antibodies, and Other Therapeutic Modalities in the Sepsis Syndrome

The mortality from systemic infections, particularly those due to gram-negative bacteria, remains high.[19] Several decades ago, therapeutic corticosteroids in large doses (e.g., 2 g prednisolone IV "push") for septic shock were considered the standard of therapy.[136] Recent randomized placebo-controlled studies show, however, no survival benefit from such adjunctive therapies.[137,138] A more recent approach has been to produce antibodies against gram-negative bacteria and to use them adjunctively in combination with antibiotics. Beginning with studies of the cross-protective activity of antibodies against the core regions of endotoxin (lipopolysaccharide), both experimental murine and canine and human studies have suggested a therapeutic benefit.[19,139–143] The advent of monoclonal antibody technology has made available im-

munoglubulin M (IgM) monoclonals that can bind to the toxic lipid A region of gram-negative lipopolysaccharide (endotoxin). Two large clinical trials have been reported thus far, one using a mouse–human hybridoma for production of an IgM antibody (HA-1A)[144] and a purely murine antibody IgM (E-5).[145] Both studies suggest a benefit when such antibodies are used to treat gram-negative infections, but they have had no impact on the outcome of gram-positive infections. However, analysis of these two large trials indicate that, on an "intent-to-treat" basis, no overall benefit could be derived from the use of these antibodies given in addition to appropriate antimicrobial therapy.[146] Indeed, closer analysis of the HA-1A therapeutic study[147] suggests that the quality of antibody treatment in the control group was sufficiently inappropriate to influence the overall outcome of the therapeutic results (a potential bias that made the patient survival in the monoclonal-treated group look better). As a result of these studies, one can envision considerable difficulties in the assessment of complex therapeutic studies assessing interventions such as an antiserum given in addition to standard clinical management.[148] While the HA-1A and E-5 studies clearly targeted an important group of critically ill patients (comprised of individuals with major medical and surgical complications usually hospitalized in an intensive care unit), the great majority of patients entered into the reported therapeutic trials would not be considered to be immunocompromised. Thus, applicability of these monoclonal antibody trials published before 1993 must obviously be qualified with respect to their relevance to compromised hosts. Even if it were to be shown that adjunctive monoclonal antibody therapy is beneficial as suggested by large studies that have been undertaken, clinicians caring for immunocompromised hosts would still want efficacy data on patients with leukemias and lymphomas, organ transplant recipients, and neonates who develop gram-negative infections. Until large controlled studies support the routine use of monoclonal antibodies in populations of compromised patients, the application of monoclonal antibodies directed against endotoxin must still be considered promising but experimental.

In addition to these potential therapies, a wide variety of other therapeutic strategies have been conceptualized and developed in an attempt to block the inflammatory cascade that accompanies the onset of sepsis.[149] Monoclonal antibodies directed against endotoxin have specificity for the gram-negative bacterial outer cell membrane that contains endotoxin.[138] During the process of host response to infection, important cytokines such as IL-1 and TNF are released, and these cytokines, in excess, have the potential alone or in combination to trigger septic shock [see Fig. 2 (Section 3)]. Monoclonal antibodies have been produced that bind to TNF. Recombinant DNA techniques have yielded soluble receptor antagonists of IL-1, immunoadhesins that abrogate TNF activity, and soluble TNF receptors.[149] In animal test systems (the artificiality of which must be acknowledged), antibodies against TNF and IL-6 have proved protective, as have TNF immunoadhesins and soluble receptors.

Viewing all these new therapeutic modalities in the appropriate context may be difficult. In addition to the difficulties in interpreting clinical trial data and of randomizing patients, much of the benefit from such interventions could well be related to the timing of intervention. In other words, the application of such blocking strategies might be therapeutically useful early in the stages of clinical infection, but after the development of full-blown shock (which is clearly a heterogeneous syndrome), such approaches may well be ineffective. It must be acknowledged that no data from human trials with these interventions are yet available on the large population of immunocompromised hosts that are likely to be hospitalized during the first half of the decade of the 1990s. Usually, new therapeutic interventions are first tested clinically in "shock/trauma units," where patients may have relatively intact host defense prior to major surgery, trauma, accident, or other event. The high cost of such interventions and the difficulties of interpreting the clinical data should emphasize caution in the routine adoption of such forms of therapeutic intervention even if they were to become widely available and licensed for clinical use.

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