

Infectious Complications of Cancer

Cancer Treatment and Research

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Infectious Complications of Cancer

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Preface

In spite of major developments in our therapeutic armementarium for the treatment of infections, the morbidity and mortality of these complications remains very high in patients with compromised defenses. Cancer and its treatment represent a major predisposing condition to various infections. These adverse events are still with us, in spite of much progress in the therapy of infectious diseases, because cancer therapy is becoming more aggressive, further lowering the capacity of the host to cope with infections. Moreover, pathogens adapt quite effectively to our drugs at a pace that might overcome the ability of the industry to provide new active agents. Finally, new pathogens appear as a consequence of both selection and severe immunosuppression.

Because infection is so common in cancer patients, its diagnosis and management represent a daily challenge to all oncologists. To help the practicing physician master this broad and changing area of medicine, a continuing educational effort is mandatory. It is the goal of this book to provide a comprehensive review of the most crucial and challenging aspects of infectious complications in cancer patients.

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1 Factors predisposing cancer patients to infection

Claudio Viscoli and Elio Castagnola

Introduction

As a consequence of major advances in medicine in the last few decades, patients with illnesses previously considered untreatable may now receive appropriate treatment and survive. Unfortunately, this progress has not been obtained without a price. The increased aggressiveness and invasiveness of the various medical procedures characteristic of modern medicine creates numerous disruptions of immunological protection systems, with a consequent increased patient susceptibility to developing opportunistic infections. The net result is that patients with a controlled underlying condition may succumb to bacterial, fungal, viral, or protozoal infections. Preventing and treating these infections represent an exciting challenge for the infectious disease physician, because in some instances an appropriate antimicrobial intervention may signify the difference between death and life for the patient. This is particularly true in the field of cancer, in which managing infectious complications has become one of the major goals of treatment. Until the advent of the acquired immunodeficiency syndrome (AIDS), much of what had been written about infections in immunocompromised hosts actually stemmed from studies and experience obtained with cancer patients. These studies represented the mainstay for our understanding of the natural history of infectious complications in patients affected with AIDS. It has not been by chance that infectious disease physicians operating in cancer centers were among the first to report opportunistic infections in AIDS [1–3].

Magnitude of the infection problem in oncology

Ever since early trials of intensive chemotherapy of neoplastic diseases, physicians realized that cytotoxicity and immunosuppression resulted in an increased risk of infectious complications and deaths [4–9]. However, it is not easy to give a reliable estimation of the magnitude of the phenomenon. This is probably due to four main reasons. First, the assessment of the cause of death is particularly difficult and uncertain in this patient population, even when autopsy is performed, since infectious and noninfectious causes often coexist and their relative roles frequently

overlap. Second, very little information is available about the proportion of patients who die from infection as the primary cause of death (i.e., with an underlying disease in remission), making it impossible to quantify the actual impact of infection. Third, many antineoplastic research protocols, whatever the underlying disease, do not give enough attention to precise quantification of the risk of infection focusing only on antineoplastic efficacy. If such an evaluation is planned, it is frequently superficial and is not performed according to internationally accepted rules and definitions. For example, the use of febrile neutropenia as a major endpoint in trials testing prophylactic measures (e.g., antibiotics or colony-stimulating factors) in cancer patients should be criticized. The presence of febrile neutropenia is just an indicator for starting empirical antibiotic therapy, but it is a spurious clinical parameter of efficacy, since it is completely dependent on the neutrophil count. The suspicion that such a soft clinical parameter is introduced only when harder parameters (rate of documented infections, duration of fever) are not significant is intriguing [10,11]. Finally, many oncologists and hematologists rely too much on empirical treatments and do not recognize the crucial importance, both for already diagnosed patients and for future patients, of performing all the necessary, but sometimes invasive, procedures indispensable for achieving a diagnosis. Therefore, many infectious complications remain poorly understood, and many borderline situations between infectious and noninfectious etiologies have not been clarified.

Infectious mortality

Infection, with or without hemorrhage, is thought to represent the final cause of death in about 50–80 percent of patients dying with an acute leukemia and in about 50 percent of those with malignant lymphoma [4–9]. Much less is known about patients with solid tumors. In these patients an infection, as the primary or associated cause of death, is reported to be present in about 50 percent of the cases. In patients with small cell lung cancer, ‘toxic’ deaths, that is, deaths from chemotherapy-related toxicity, including infection during neutropenia, may account for up to 20 percent of the cases in poor risk groups [12]. In recent years, infection has emerged as the leading cause of death in other populations of cancer patients, such as those undergoing allogeneic bone marrow transplantation, probably due to the synergistic effect of the initial conditioning regimen and of subsequent therapies aimed at controlling graft-versus-host disease (GvHD). In this patient population, infectious mortality remains high [13]. For example, among 124 patients who received a bone marrow graft from an unrelated donor at the Fred Hutchinson Cancer Research Center in Seattle, Washington from 1991 to 1992, 18 (19 percent) died from a documented infection within 100 days of the transplant [14], in the absence of a relapse of the underlying disease.

A valuable source of data about infectious mortality can also be retrieved from the results of clinical trials on empirical antibiotic therapy in febrile and granulocytopenic cancer patients. For example, in a recent trial performed by the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC), the overall mortality

rate from any cause at 30 days from the onset of fever among more than 800 episodes was 11 percent. By focusing on the subgroup of patients with bacteremia observed in therapeutic trials I, IV, V, and VIII performed by the same group in the last 20 years, it is seen that among 701 single-agent bacteremias, the infectious mortality rate decreased from 21 percent to 6 percent of the episodes (EORTC-IATCG, unpublished data).

Infectious morbidity

The clinical impact of infectious morbidity is also relevant. For example, it has been shown that about 80 percent of the episodes of neutropenia lasting more than a week will be complicated by fever and that in about 60 percent of these episodes an infection can be documented either on cultural or clinical grounds [15]. The incidence of fever in patients with less prolonged neutropenia, such as, for example, those with solid tumors, is considered to be somewhat lower, although percentages as high as 70 percent have been reported in some studies in patients with small cell lung cancer [10,11]. In these patients the incidence of documented infections approaches 5 percent, with a 2 percent infectious mortality.

Factors predisposing cancer patients to infection

Reviewing and analyzing factors predisposing cancer patients to infection with the aim of giving of them a comprehensive image is a complicated issue because the population of cancer patients is not homogeneous and the degree and type of immunosuppression, with its related risk of infection, varies tremendously according to patient-, disease- and therapy-related factors. As shown in figure 1, the immunodeficiency that characterizes the natural history of cancer is actually an ever-changing and multifaceted phenomenon, which depends on many factors acting independently or concurrently in various phases of the treatment course. These factors are summarized in Table 1 [16]. In the following paragraphs we will try to delineate how the underlying disease, its treatment, and the diagnostic and supportive measures indispensable for optimal management of cancer patients can impair phagocytosis, humoral immunity, cell-mediated immunity, and mechanical defenses. In addition, the role played by the environment and the patient's history, including lifestyle, in predisposing to infection or reinfection will be examined. Finally, recent studies aimed at individualizing treatment and the level of care in subgroups of febrile and granulocytopenic cancer patients will be discussed.

Underlying disease and antitumor treatment

Immune defects caused by cancer and its treatment are summarized in Table 2. All immunological mechanisms can be altered in cancer patients, including phagocytosis, humoral and cellular immunities, and mechanical defenses, as a result of the underlying disease and its treatment, and various mechanisms can be altered simultaneously or subsequently during the treatment course in the individual patient [9, 16–18]. In

From Cancer to Infection

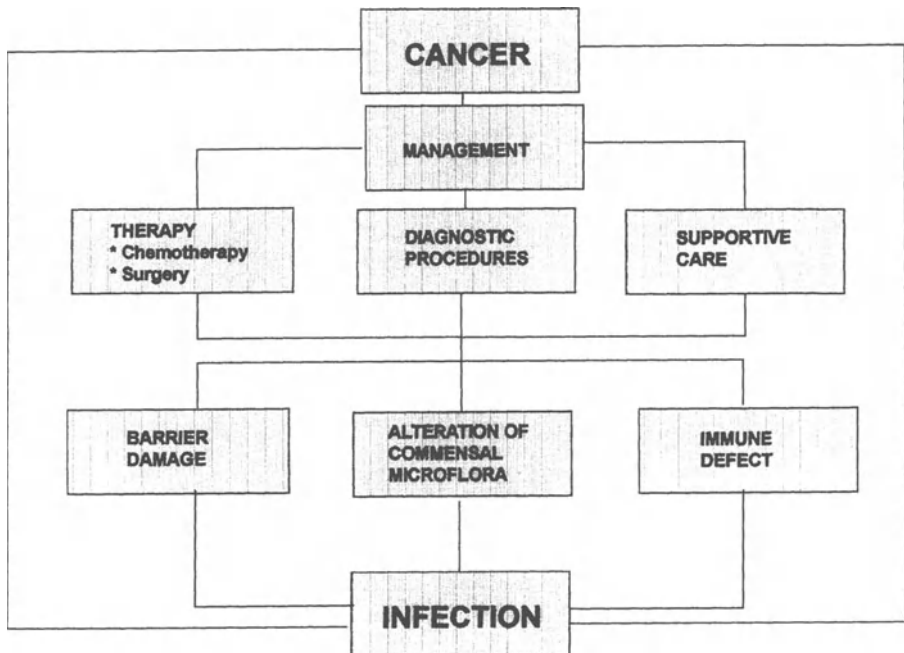


Figure 1. The relationship between cancer and infection can either be direct or be mediated through therapeutic, diagnostic, and supportive procedures. All these procedures ultimately impair antiinfective defense mechanisms, leading to infections.

Table 1. Factors predisposing cancer patients to infection

Underlying disease
Cytotoxic treatments
Other treatments
Surgery
Bacille Calmette-Guérin
Interleukin-2
Desferoxamine
Malnutrition
Supportive care
Central venous catheter
Parenteral alimentation
Blood product transfusions
Antibiotic therapies
Diagnostic procedures
Other factors
Environment
Patient history and lifestyle

Table 2. Immunological alterations related to the underlying neoplasm and treatment

Underlying disease	Defective immune mechanism	
	Disease related	Chemotherapy related
Acute lymphoblastic leukemia	Granulocytopenia Deficit of cell-mediated immunity (children) Hypogammaglobulinemia	Granulocytopenia and abnormal neutrophil function Deficit of cell-mediated immunity Hypogammaglobulinemia Mucositis
Acute myelogenous leukemia	Granulocytopenia Tissue leukemic infiltration	Granulocytopenia and abnormal neutrophil function Mucositis Deficit of cell-mediated immunity
Chronic lymphocytic leukemia	Hypogammaglobulinemia	Hypogammaglobulinemia Deficit of cell-mediated immunity
Chronic myelogenous leukemia	Abnormal neutrophil function	Granulocytopenia and abnormal neutrophil function
Multiple myeloma	Hypogammaglobulinemia Deficit of complement activity	Granulocytopenia and abnormal neutrophil function
Hodgkin disease	Deficit of cell-mediated immunity	Granulocytopenia and abnormal neutrophil function Deficit of opsonization (splenectomy or functional asplenia)
Non-Hodgkin's lymphoma	Deficit of cell-mediated immunity Skin infiltration Mechanical obstructions (gut, biliary tract)	Granulocytopenia and abnormal neutrophil function Mucositis Deficit of cell-mediated immunity
Solid tumor	Skin and mucosal infiltration Mechanical obstructions (gut, biliary, urinary tracts, lungs) Central nervous system abnormalities (loss of gag reflex, impaired motility, changes in micturition)	Granulocytopenia and abnormal neutrophil function Mucositis (children) Deficit of cell-mediated immunity
Autologous bone marrow transplantation (including reinfusion of peripheral blood stem cells)	Factors associated with past history	Granulocytopenia and abnormal neutrophil function Mucositis Deficit of cell-mediated immunity
Allogeneic bone marrow transplantation	Factors associated with past history	Granulocytopenia and abnormal neutrophil function Mucositis Acute or chronic graft-versus-host disease (hypogammaglobulinemia, functional asplenia, deficit of cell-mediated immunity)

general, an association between the underlying immunodeficiency and a particular etiology can be identified (Table 3). Quantitative and qualitative defects of phagocytic mechanisms usually predispose to bacterial and, secondarily, fungal infections. Humoral immunity defects facilitate specific types of bacterial infections. Defects of cell-mediated immunity are associated with infections due to pathogens sharing the characteristic of sustaining intracellular life. Finally, mechanical defects of the integuments typically induce infections from bacteria and fungi that are common inhabitants of the skin and mucosal surfaces [19]. These associations have important teaching implications, but their clinical relevance is much lower than expected, mainly because more than one defense mechanism at the same time is usually impaired in the individual patient.

Among anticancer therapeutic methods, allogeneic bone marrow transplantation really presents peculiar problems and deserves a specific approach. As shown in Table 4, bone marrow transplant patients are at risk of various infectious complications, and both the risk of infection and the pathogen most commonly involved is thought to vary during time. Before engraftment, bacterial and fungal infections predominate, while from engraftment to approximately day 100, viral and fungal infections are common. Thereafter, patients remain at risk of reactivation of viral infections (*Varicella-zoster* virus) and of bacteremias due to encapsulated bacteria [20]. Unfortunately, this traditional distribution is largely schematic, since exceptions exist and are especially correlated with the severity of graft-versus-host disease (GvHD) and the intensity of the immunosuppressive treatment.

Defects of phagocytosis. Granulocytopenia, defined as an absolute granulocyte count lower than 1,000 or 500 cells/mm³, is common among cancer patients, both because of the underlying disease (e.g., acute leukemia) and because of chemotherapy and radiotherapy. As shown by Bodey and coworkers [21] several years ago and as confirmed by many other investigators, granulocytopenia is the most important risk factor for bacterial infection, and strong relationships have been shown to exist between total neutrophil count, the rate of decline of neutrophil count, the duration of neutropenia, and the risk of developing a severe bacterial infection, with a maximum risk correlated with a nadir of less than 100 cells. Once the patient is rendered granulocytopenic and becomes febrile, the total neutrophil count is not as relevant as the duration of neutropenia in predicting a diagnosis of bacterial infection. This information was clearly derived from a recent analysis of factors predictive of a diagnosis of bacteremia in febrile and granulocytopenic cancer patients [22]. This study, which is reported in detail later, showed that both the granulocyte count at the onset of fever and the duration of previous granulocytopenia were significantly associated with a diagnosis of bacteremia in febrile patients in a univariate analysis. However, by multivariate analysis only the latter factor remained significantly associated with bacteremia, while the total neutrophil count at the time of fever was removed from the final mathematical model.

Granulocytopenia is usually considered to be a post-treatment condition, not recognizing that most acute leukemia presents with a variable low granulocyte count and this condition causes a 10–15 percent incidence of bacteremia before any

Table 3. Traditional association between type of immune defect and pathogen most commonly involved

Immunological defect	Bacteria	Fungi	Protozoa	Viruses	Helminths
Granulocytopenia and abnormal granulocyte function	Gram-positive cocci	<i>Candida</i> spp.	—	—	<i>Strongyloides stercoralis</i>
	Gram-negative rods diphtheroids <i>Actinomyces</i> spp.	<i>Aspergillus</i> spp. <i>Fusarium</i> spp. <i>Trichosporon</i> spp. Zygomycetes	—	—	
Hypo- γ -globulinemia and splenectomy or functional asplenia	Encapsulated bacteria (<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i>)	—	<i>Giardia lamblia</i> <i>Cryptosporidium</i> <i>Pneumocystis carinii</i> ^a	Enterovirus	—
	Impaired cell-mediated immunity	Intracellular pathogens (<i>Mycobacterium</i> spp., <i>Listeria monocytogenes</i> , <i>Legionella pneumophila</i> , <i>Salmonella</i> spp., <i>Nocardia</i> spp., <i>Rochalimaea</i>)	<i>Candida</i> spp. (mucocutaneous) <i>Cryptococcus neoformans</i> <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i>	<i>Pneumocystis carinii</i> ^a <i>Toxoplasma gondii</i> <i>Leishmania</i> spp. <i>Cryptosporidium</i> Microsporidia	Enterovirus Herpesviridae Paramyxoviridae Papovaviridae
Disruption of mechanical barriers	Gram-positive cocci	<i>Candida</i> spp.	—	—	—
	Gram-negative rods <i>Corynebacterium</i> spp.	<i>Aspergillus</i> spp. <i>Malassezia furfur</i>	—	—	—

^a New classification proposed among fungi.

Table 4. Relationship between day of transplant (from day 0), cause and type of immune defect, and pathogen most commonly involved in recipients of bone marrow transplants

Time from day of transplantation	Immune defect			Pathogen most commonly involved
	Type of transplant	Type	Cause	
Pretransplant	Autologous and allogeneic	Neutropenia, abnormalities of anatomical barriers	Underlying disease and its management	None (related to previous history of the patient)
Pre-engraftment (day 0-30)	Autologous and allogeneic	Neutropenia, abnormalities of anatomical barriers	Chemotherapy, radiation therapy	Gram-positive and gram-negative bacteria, fungi (mainly <i>Aspergillus</i> and <i>Candida</i>), HSV CMV
Early postengraftment (day ≈ 30-100)	Allogeneic ^a	Abnormal cell-mediated immunity, abnormalities of anatomical barriers	Acute GvHD (and its prophylaxis and treatment), development of donor-related immune function	<i>Pneumocystis carinii</i> , <i>Toxoplasma gondii</i> , gram-positive and gram-negative bacteria fungi (mainly <i>Candida</i> and <i>Aspergillus</i>) other viruses (papovavirus, RSV, adenovirus, rotavirus, coxsackievirus, parainfluenza, HHV6, VZV) <i>Clostridium difficile</i>
Late postengraftment (day > 100)	Allogeneic ^a	Delayed recovery of immune function (cell-mediated and humoral), functional asplenia, abnormalities of anatomical barriers	Chronic GvHD (and its treatment)	VZV, encapsulated gram-positive and gram-negative bacteria, <i>Clostridium difficile</i> , fungi (mainly oropharyngeal candidiasis), chronic viral hepatitis, EBV, CMV, polyoma-virus, adenovirus, rotavirus, coxsackie virus

^a Patients receiving allogeneic bone marrow transplantation from a matched unrelated donor or from a mismatched related donor and after T-cell depletion present a more severe and prolonged immunosuppression.

chemotherapy is administered [23]. Patients with prolonged granulocytopenia show an increased incidence of fungal infections, especially in association with prolonged periods of broad-spectrum antibacterial therapy [24,25], with *Candida* and *Aspergillus* spp. as the most frequently observed fungal pathogens. Interestingly, by comparing human immunodeficiency virus (HIV)-infected patients with granulocytopenic cancer patients, it appears that the former, usually affected by defects in cellular immunity, tend to develop superficial mucocutaneous candidiases, while the latter seem to be more predisposed to deep, visceral candidiasis. This suggests that phagocytic mechanisms are essential in protecting against deep-seated candidal infections, while cellular mechanisms are pivotal for superficial mucocutaneous forms. The development of and recovery from aspergillosis, as well as from other mold infections, is so dependent on granulocyte counts that some authorities doubt that survival is possible in the absence of an effective phagocytic response [25].

In contrast to granulocytes, mononuclear phagocytes are less sensitive to the toxic effects of antineoplastic therapy, thus maintaining a rudimentary defense mechanism in neutropenic patients. Granulocytopenic patients also have an impaired inflammatory response, the consequence of which is a characteristic paucity of signs revealing the existence of an infection. For example, in the fifth therapeutic trial of the IATCG of the EORTC, more than 50 percent of patients presented at randomization without any sign of infection other than fever [26]. Sometimes even fever is absent, and a severe infection can present with dyspnea, oliguria, and hypotension, without fever. For example, 17 (44 percent) of 39 single-agent bacteremias identified in a cohort of 124 severely immunodepressed recipients of bone marrow transplant from unrelated donors occurred in the absence of any inflammatory response, including fever [14]. In addition to quantitative defects, cancer patients also have functional phagocyte abnormalities [27]. For example, patients with chronic myelocytic leukemia, myelodysplastic diseases, and preleukemic states were shown to have significant impairments in neutrophil functions, including defects in bacterial killing and decreased spontaneous migratory and chemotactic leukocyte responses [27]. However, the practical effect of these functional defects is poorly understood.

Defects of humoral immunity and opsonization. Patients with defects in immunoglobulin synthesis and opsonization may develop infections with a number of pathogens, especially encapsulated bacteria, which require opsonization to be phagocytized (mainly pneumococci) and certain types of viruses (mainly enteroviruses). This defect has rarely been associated with intensive chemotherapy, while it is far more common after prolonged immunosuppressive therapy [28]. For example, patients undergoing allogeneic bone marrow transplantation usually undergo prolonged, chronic immunosuppressive therapy for prophylaxis of GvHD. Even in ideal conditions (i.e., absence of GvHD) these patients may require 1 year to restore their ability to synthesize IgG and IgM, while synthesis of IgA may remain depressed for years [29,30]. If chronic GvHD develops, these patients may fail to switch from IgM to IgG production in the secondary response and may have functional asplenia [30,31].

Defects of opsonization were also common in patients whose spleens were removed for staging of Hodgkin's disease and also in patients who received splenic irradiation with consequent irreversible damage of splenic B lymphocytes. Despite the fact that solid tumors are not supposed to be able inherently to cause defects of humoral immunity, patients with solid tumors may be at risk for infections due to intracellular pathogens, especially in those of pediatric age, correlating with the intensity of the antineoplastic therapy. Other subgroups of cancer patients with disease-related defects of humoral response are those with chronic lymphocytic leukemia and multiple myeloma. Because of the availability of immunoglobulin preparations for intravenous use, the practical importance of hypogammaglobulinemia in facilitating infections in cancer patients has probably decreased, since we can now replace this deficit. However, different from granulocytopenia, no precise cut-off limit of gammaglobulin counts has been established for defining the risk of infection. In addition, the cost effectiveness of immunoglobulin administration in patients with chronic lymphocytic leukemia has been questioned [32]. Moreover, a recent trial of Ig administration in patients undergoing bone marrow transplantation (BMT) did not show any advantage in the prevention or treatment of infectious complications [33].

Defects in cellular immunity. Defects in cellular immunity are common in cancer patients and may lead to infections with organisms that differ from those seen in granulocytopenic or hypogammaglobulinemic patients. Also in this case, the immunodeficiency can result from the underlying disease [34], its treatment, or a combination of both. Patients with hematological malignancies usually have an inherent depression of cell-mediated functions, while patients with solid tumors have normal immunological defenses that are subsequently damaged by cytotoxic therapies. Many antineoplastic drugs may actually depress cell-mediated mechanisms. For example, cyclophosphamide depresses the proliferation of B and T lymphocytes (in addition to monocytes and neutrophils) [35], while cyclosporin has a specific inhibitory effect on T cells, leaving the other components of host defenses intact [35,36]. Corticosteroid therapy reduces cell-mediated immunity by affecting the function of the mononuclear macrophage [37].

The commonest pathogens involved in infections related to cell-mediated deficiency are thought to be the intracellular pathogens, such as mycobacteria, *Pneumocystis carinii*, *Cytomegalovirus*, *Listeria*, and *Salmonella*. In some patient populations, the risk of developing these infections has been correlated with a quantitative limit of the CD4-positive absolute T-lymphocyte count. For example, Masur et al. [38] showed that in adult patients with AIDS, the risk of developing *Pneumocystis carinii* pneumonia was higher when the absolute CD4-positive T-lymphocyte count fell to below $200/\text{mm}^3$ or 20 percent of the total lymphocyte count. However, this was not confirmed in children with the same underlying condition, in whom pneumocystosis developed with a total CD4-positive T-lymphocyte count higher than $450/\text{mm}^3$ [39]. The correlation between absolute CD4+ count and the risk of developing (PCP) or any other infectious complication related to cellular defects has not been studied extensively in cancer patients [39a]. However,

Pneumocystis carinii pneumonia was thought to be more common after prolonged maintenance therapies, especially in children with acute lymphoblastic leukemia or BMT, than in other conditions [13,40]. Recently, however, *Pneumocystis carinii* pneumonia has been described in unusual settings, such as in patients with metastatic brain neoplasms [41,42]. We also observed two cases of *Pneumocystis carinii* pneumonia in unusual settings. The first patient was receiving an allogeneic bone marrow transplantation from an unrelated donor. She developed *Pneumocystis carinii* pneumonia very early after bone marrow transplantation (day 23), with an absolute CD4-positive T-lymphocyte count of $45/\text{mm}^3$ [43]. The second [43a] developed *Pneumocystis carinii* pneumonia 3 months after an autologous bone marrow transplantation with pulmonary irradiation for a solid tumor, with an absolute CD4-positive T-lymphocyte count of $5/\text{mm}^3$. In conclusion, the correlation between the absolute number of CD4-positive T-lymphocytes and infection deserves further studies in cancer patients in order to determine if a limit exists under which the risk of infection increases substantially. [39a,43a,43b]

The other common pathogens encountered in patients with cell-mediated immunodeficiencies are viruses. Cytomegalovirus infection, in particular, is frequently seen among patients undergoing allogeneic bone marrow transplantation, with pneumonia the most important clinical manifestation, strongly associated with acute GvHD. The role of viral infections is poorly understood in leukemic patients receiving first induction chemotherapy, and it is commonly considered to be of secondary importance because in this early phase granulocytopenia is the predominant immune defect. However, we remember well an instructive case of cytomegalovirus disseminated infection in an 11-year-old girl with acute nonlymphoblastic leukemia during the first course of induction chemotherapy. This patient received broad-spectrum empirical antibacterial and antifungal therapy for several episodes of fever, in the absence of any clinical or microbiological documentation of infection. On day 70 of antineoplastic chemotherapy, she developed clear signs of intestinal perforation, rendering surgery inevitable. Ileostomy with intestinal resection was then performed and several samples of the intestinal wall, lymph nodes, and liver tissue showed evidence of intranuclear inclusions typical of cytomegalovirus. This case suggests that infections with intracellular pathogens are also possible in early phases of antineoplastic treatment in leukemic patients.

Mechanical defects. Mechanical barriers are effective measures that are able to defend organisms from infections and can be modified by both cancer and its treatment. For example, patients with leukemia, lymphoma, and solid tumor may experience malignant cellular infiltration of normal tissues, facilitating bacterial or fungal superinfections. In addition, solid tumor masses may cause mechanical obstruction of body fluid passages, with stasis and consequent overgrowth of microorganisms. This is commonly seen in the gastrointestinal tract, lungs, and urinary and biliary tracts. The consequence may be postobstructive pneumonia, enteritis, urinary tract infection, and colestitis. Even without complete obstruction, many clearance mechanisms can be altered. For example, impaired ciliary motion, ventilation, and coughing caused by lung cancer may facilitate pulmonary infections,

whilst impaired bladder voiding caused by prostatic adenoma or carcinoma may increase bacterial and fungal colonization of the urinary tract, with a consequent risk of urinary tract infection. In the biliary tract, unconjugated bile, with its antibacterial properties, helps to decrease bacterial colonization of the small intestine. Partial obstruction of the biliary tract secondary to neoplastic disease may cause ascending colangitis. Intestinal motility inhibits bacterial outgrowth, but neoplastic infiltration with development of ileum can disrupt this defense mechanism. Central nervous system neoplasms causing a neurological deficit may also increase the risk of infection. For example, complete or partial loss of the gag reflex can lead to aspiration pneumonia, changes in micturition with residual retained urine are conducive to urinary tract infection, and impaired mobility can lead to decubitus infections. Finally, virtually every tumor, by compressing blood vessel walls, may cause ischemia, which in turn predisposes to infection [27]. The treatment of neoplastic diseases can cause disruption of mechanical barriers in several different ways. Radiotherapy and chemotherapy, particularly with cytosine arabinoside, anthracyclines, methotrexate, 6-mercaptopurine, and 5-fluorouracil, are the leading causes of gastrointestinal mucositis, with stomatitis as the most clinically recognizable symptom. By damaging mechanical barriers, mucositis increases the risk of bacterial, fungal, and viral superinfections and may facilitate the entrance of microorganisms into the bloodstream. The clinical interpretation of oral mucositis is difficult, because it is often unclear to what extent mucositis is just the expression of drug-related toxicity, which facilitates infection or is associated with an infection from the beginning. For example, it has been shown that adult and pediatric herpes simplex virus (HSV)–seropositive patients [44,45] present frequent viral reactivations at the oral cavity after antineoplastic chemotherapy and that prophylactic acyclovir, by decreasing the number and severity of reactivations, can also improve drug-related oral mucositis. This suggests that at least in these patients oral mucositis is multifactorial in origin. In addition, some authors have suggested that both toxic and viral mucositis can contribute to the development of streptococcal bacteremia and that the risk of this bacterial infection could be higher in HSV–seropositive patients, thus giving an example of the complex interrelationships between toxic and infectious effects [46] (see also later).

Other treatments

Surgery. Surgery is an essential therapeutic tool for cancer patients. However, especially when extensive, it can result in anatomical barrier disruptions and displacements of material either already containing bacterial flora or supporting bacterial growth. In patients with solid tumors, surgical infections do not differ from those seen in normal patients, but both the risk and management can be influenced by several disease-related mechanisms, including malnutrition and chemotherapy-related mucositis and immunodeficiency [47]. Surgeons may sometimes be involved in the supportive care of a cancer patient. This may occur in three major instances: (1) with insertion of a long-term venous access device; (2) in the management of a surgical emergence, such as, for example, acute abdomen; and (3) in obtaining

a tissue sample for the diagnosis of fungal infections. Problems related to the use of long-term indwelling venous devices will be dealt with later. The surgical management of the acute abdomen and neutropenic enterocolitis is a controversial issue and it is not our intent to discuss it in this chapter. Obviously, surgery in a thrombocytopenic and neutropenic patient with a severe abdominal infection carries a relevant risk of death, which should be balanced against the possible advantage in the treatment of the infectious process for which surgery is performed [48]. The same caution should be used when asking the surgeon to perform biopsies with the aim of obtaining specimens for the diagnosis of bacterial or, more often fungal, infections. Also in this case, the possible advantage for the patient and for future patients in achieving a diagnostic documentation of a specific infection should be weighed against the risk inherent in the invasive procedure required for diagnosis.

Other drugs. Other drugs administered for various reasons during the management of cancer can increase the risk of infection. For example, bacille Calmette-Guérin (BCG) immunotherapy has been used as direct or adjuvant treatment in a variety of malignant neoplasms. It has been administered with the multiple puncture tine technique, by scarification, by aerosolization, and by intratumor injection. Depending upon the degree of prior sensitization and the route of administration, local and systemic reactions may follow. Disseminated BCG infections are rare and have been described, especially in association with intralesional inoculation. In these cases hematogenous dissemination can occur, with development of granulomata in various organs [49,50]. In recent years interleukin-2 has found a role for immunological treatment of neoplasia. Unfortunately its administration has been associated with an increased risk of infection, especially due to staphylococci [51,52], probably in relation to defects of the neutrophil function induced by the drug itself [51,53]. For example, Pockaj and coworkers found a 13 percent incidence of documented infections in 935 interleukin-2-based treatments, with two septic deaths. The majority of infections were urinary tract infections or infections related to the intravenous catheter, and the pathogen most commonly involved was *S. aureus*, which caused 56 of 181 (31 percent) single-agent episodes. Desferoxamine has recently become part of investigational trials of antineoplastic chemotherapy of neuroblastoma, and it has been used in other hematological conditions [54]. However, this drug has been associated with an increased risk of bacterial infections and zygomycosis in dialysis patients, probably because of the increased availability of free iron necessary for fungal growth [55]. Although no causal relationship could be shown, we have recently observed a case of fusariosis in a child with neuroblastoma treated with desferoxamine [56]. Finally, the use of histamine type 2 antagonists and high-dose ara-C has been associated with an increased risk of viridans streptococcal bacteremias. Viridans streptococci are increasingly being isolated as a cause of severe bacteremias in cancer patients. The reason for this is unclear and probably multifactorial. Indeed, in multivariate analyses of factors predisposing to this type of infection, several variables have been identified, including gastrointestinal toxicity, use of histamine type 2 antagonists, antimicrobial prophylaxis, profound neutropenia, high-dose ara-C, and oral mucositis. The hypothesis is that the use of

antibiotics intrinsically inactive against viridans streptococci leads to an overgrowth of these bacteria in the gastrointestinal tract and that the stomach alkaline pH facilitates the colonization of the esophagus, pharynx, and mouth. Oral mucositis secondary to ara-C toxicity facilitates the entrance of these microorganisms into the bloodstream, where septicemia develops due to the impairment of phagocytic defenses [57].

Supportive therapies and diagnostic procedures

Among factors predisposing cancer patients to infection, an important role is played by a number of procedures aimed at improving the patients' quality of life and allowing them to survive chemotherapy-related toxicity. Four issues should be discussed: (1) the role of diagnostic procedures, (2) malnutrition and the use of parenteral alimentation with long-term indwelling venous catheters, (3) the use of blood transfusions, and (4) the use of broad-spectrum antibiotics for antiinfective prophylaxis and therapy.

Diagnostic procedures. Diagnostic procedures are well-recognized factors increasing the risk of infectious complications [9,18,27]. Biopsies, bone marrow aspirations, endoscopy, and any other procedure that breaks the barrier between the internal and external environment may allow bacteria and fungi to enter into the bloodstream. Diagnostic procedures might also contribute to the process of bacterial and fungal colonization, in which potential pathogens may become part of the patient's flora and cause infection concomitant with immunosuppression. This emphasizes the need for applying aseptic procedures in any invasive maneuver performed for diagnostic purposes.

Malnutrition, parenteral alimentation, and the problem of central venous catheters. Patients receiving anticancer therapy are at risk of developing malnutrition and wasting, with consequent impairment of immune defense mechanisms and increased risk of infection [58]. The patient's ability to maintain an adequate calorie intake is severely damaged, through several mechanisms that prevent the patient from swallowing, processing foods, and absorbing nutrients. As shown in figure 2, the dynamic relationship between infection, malnutrition, and immunodeficiency is complicated. Every factor can influence the contiguous one in both directions. In addition, malnutrition and immunodeficiency, which result from underlying disease and chemotherapy, may facilitate the process of bacterial translocation, in which bacteria may migrate from the intestinal lumen into the mesenteric lymph nodes and then into the bloodstream in the presence of conditions of malnutrition, immunodepression, and stress [59]. With the aim of overcoming malnutrition and related immunodeficiency, total parenteral alimentation, generally through a central venous catheter, has become a common and generally successful practice. Unfortunately, a dark side of the coin exists, because parenteral alimentation and the use of central venous catheters are associated with infections secondary to impaired mechanical defenses. The net result is that for preventing malnutrition and infections

Infection, Malnutrition and Immunodeficiency

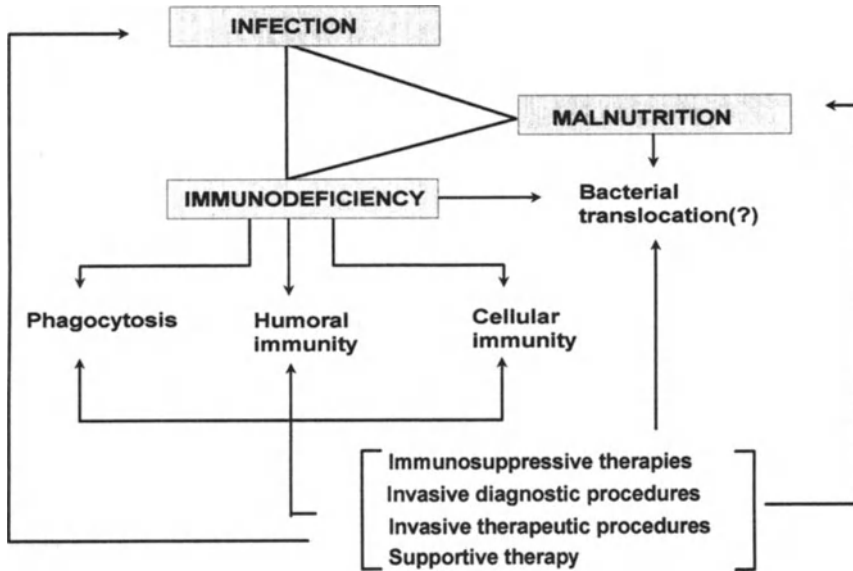


Figure 2. A complex relationship exists between infection, malnutrition, and immunodeficiency and every factor can act on the contiguous one in both directions. Microorganisms that are part of the endogenous flora may cross the mucosal barriers and enter lymphatics and blood vessels (bacterial translocation) as a result of malnutrition and invasive procedures. Once in the bloodstream, in the presence of impaired immunological functions, microorganisms can readily proliferate and disseminate.

related to malnutrition, we open the field to infections related to infusates and to central venous lines.

High-concentration carbohydrate solutions and lipid administration have been incriminated as able to favor the development of fungal and/or bacterial infections, especially bacteria of the KES (*Klebsiella*, *Enterobacter*, *Serratia*) group, *Pseudomonas cepacia*, *Citrobacter freundii*, coagulase-negative staphylococci, *Flavobacterium*, *Candida parapsilosis*, and rare fungal pathogens, such as *Malassezia furfur* [60–64]. Indwelling central venous catheters have many advantages for the patient receiving antineoplastic chemotherapy, since they free the patient from repeated venipunctures and allow administration of drugs, blood products, fluids, and other supportive medications. However, these devices can easily become colonized by skin bacteria and fungi, traveling along the internal or external surface [65–67]. It is likely that all long-term intravenous devices become colonized after a few days from insertion. However, only in a limited proportion of cases, in 15 percent to 20 percent of catheters, does an infection develop. On the average, when correlated with the number of catheter days, the incidence of catheter-related infections (Hickman-Broviac type) is estimated to be 1.37 episodes per 1,000 patient days of long-term catheter use [68]. A catheter-related infection can either

remain localized at the catheter site or proceed along the catheter in the subcutaneous tunnel, giving rise to a neck or thoracic wall abscess and to bacteremia, with or without endocarditis.

Several studies have documented that the most commonly involved pathogens are gram-positive microorganisms. Indeed, a multivariate analysis of factors predicting bacteremia in febrile, granulocytopenic cancer patients (see later) showed that the presence of signs of infection at the catheter site was significantly associated with a diagnosis of gram-positive, but not of gram-negative, bacteremia [22]. However, recent studies have reported clusters of catheter-related gram-negative infections in cancer patients [69–71], suggesting the need for continuous surveillance of the microbiology of this complication. In addition, increased awareness of hospital personnel and parents/tutors of their pivotal role in preventing this complication should be encouraged. Finally, the development of new materials less prone to facilitate bacterial and fungal adhesion is highly desirable. Totally implanted devices (Port-a-cath) are thought to be less likely to cause infection than Hickman-type catheters, probably due to the more frequent manipulation of Hickman-Broviac catheters when not in use [71,71a].

Blood transfusions (including bone marrow infusion). Blood products represent an effective vehicle for transmission of infectious diseases, especially of viral etiology [hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus] [72–75]. Even if nowadays the risk of HBV, HIV, and HCV transmission has been greatly reduced by blood bank controls, the risk of cytomegalovirus transmission remains an important concern. This risk depends on the source of blood (commercial donors carry higher risks and Mediterranean countries have usually a higher incidence of seropositivity within the population [76]) and on the procedure used for filtration (which appears to reduce the chance of transmission) [77]. In addition to viruses, bacteria and protozoa have also been transmitted by means of blood products, especially platelets, through contamination during collection, processing, preparation, or storage [74,78,79]. Among bacteria, pseudomonads, achromobacters, and coliforms—able to grow at 4–8°C or at room temperature, but not at 37°C, and to use citrate as a source of energy—have been described as the cause of severe infections related to contamination of blood [78]. Staphylococci have been rarely reported as contaminants of blood transfusions, probably because their growth is impaired by anti-coagulants and cold storage [78].

There are also reports of transmission of *Salmonella* or *Yersinia* infections in patients receiving platelet concentrates, probably due to the fact that platelets are stored at 20–22°C, a temperature at which these bacteria can readily grow [78]. Finally, gram-positive infections have been described in patients receiving platelets from random-donor pools stored for a long time, but not from single-donor apheresis units [79]. Other diseases, such as syphilis, trypanosomiasis, visceral leishmaniasis, malaria, toxoplasmosis, and babesiosis, have been transmitted by transfusion [74,78,80], mainly in areas with a high prevalence of these diseases. However, these transfusion-associated infections could also be expected in areas with intensive

immigration from regions where these infectious diseases are endemic, as demonstrated by cases of Chagas disease and malaria secondary to blood transfusions observed in the United States [81–83]. Finally, the increased number of patients receiving transplants raises the question of transmission of infectious diseases through bone marrow and organ donation [84,85]. This possibility underlines the need for severe controls of the health status of the donor and of the procedures of manipulation of bone marrow (autologous or allogeneic) in the time elapsing between donation and transplant.

Anti-infective drugs. Antibiotic-related alteration of the normal intestinal flora is another important factor in predisposing cancer patients to infection. Probably the most widely known example of this interaction is *Clostridium difficile* enterocolitis induced by antibiotics (and by methotrexate) [86,87], but there are other and even more worrisome examples. In recent years, fluoroquinolone antibiotics have been successfully used in the prophylaxis of bacterial infections in neutropenic cancer patients, with a consistent reduction in the incidence of gram-negative bacteremia [88]. Fluoroquinolone antibiotics are usually poorly active against gram-positive cocci, and this explains at least in part why in some studies these microorganisms have been nearly the only pathogens isolated in fluoroquinolone-treated patients [89]. Unfortunately, recent reports suggest that some gram-negative rods are rapidly developing resistance toward the fluoroquinolones. For example, in the trials performed between 1983 and 1993 by the IATCG of the EORTC, the proportion of neutropenic cancer patients receiving fluoroquinolone prophylaxis increased from 1.4 percent to 45 percent.

During this time 1118 bacterial strains were isolated from blood and were sent at the reference laboratory of the group, in Lausanne, Switzerland. All 92 strains of *Escherichia coli* isolated from 1983 to 1990 were susceptible to ciprofloxacin, norfloxacin, ofloxacin, L-ofloxacin, and sparfloxacin. On the contrary, 11 of 40 (27 percent) strains of *Escherichia coli* isolated between 1991 and 1993 were resistant to all fluoroquinolones. The 11 resistant strains were isolated from 10 patients, all of whom were receiving fluoroquinolone prophylaxis, while the 39 sensitive strains were isolated from 29 patients, only 1 of whom had been given quinolone prophylaxis. So, in this case the widespread use of fluoroquinolone prophylaxis seems to have induced the rapid development of resistance to these drugs [90]. The use of antibacterial prophylaxis and therapy with broad-spectrum antibacterial drugs has also led to an increase in the proportion of fungal infections. Multivariate analyses of factors predisposing to fungal infections performed in various populations of cancer patients showed that administration of antibiotics is one of the major predisposing factors, usually in association with factors related to the duration of neutropenia, the type and stage of the underlying disease, cytotoxic and immunosuppressive treatments (especially prolonged administration of high-dose steroids), allogeneic bone marrow transplantation (especially with T depletion and mismatching), use of indwelling catheters, age, high level of candidal colonization, and presence of other concomitant immunodeficiencies (e.g., GvHD) or diseases (e.g., cytomegalovirus infection, previous aspergillosis, bacteremia) [25,91].

The issue of resistance is a major concern in the area of fungal infections as well. Indeed, antifungal drugs are increasingly used to prevent systemic fungal disease in patients with neutropenia. Recent studies have demonstrated that absorbable triazoles, especially fluconazole, are effective in reducing fungal infections, especially in recipients of allogeneic bone marrow transplantation [92]. Unfortunately, the use of fluconazole has been associated with the emergence of infections due to resistant *Candida* species [93–95] or *Torulopsis glabrata* [97]. Partially as a result of antifungal prophylaxis, unusual molds have become important pathogens for cancer patients. In addition to *Aspergillus*, also *Zygomycetes* and *Fusarium* species have been increasingly isolated in disseminated and often fatal infections in these patients [91,98]. Antiviral drugs can work as a factor predisposing to infections. For example, the emergence of herpes simplex virus, varicella-zoster virus, and cytomegalovirus resistant to acyclovir, foscarnet, and ganciclovir is now well documented, although the clinical relevance of this phenomenon is poorly understood [99]. In addition, the administration of ganciclovir can predispose to bacterial infections. During a trial of ganciclovir versus placebo in cytomegalovirus infection prophylaxis, an increased incidence of bacteremias was reported in patients receiving ganciclovir, due to the increased duration of granulocytopenia, which represents the major side effect of ganciclovir [100]. These are instructive examples of how antibiotics can work as a sword with two edges. The problem of multidrug-resistant pathogens will surely be a major concern in the next years in the treatment of infections in both immunocompromised and immunocompetent hosts [101–103].

Other factors

Two less recognized but not less important factors able to predispose cancer patients to infection that are unrelated to the underlying malignant disease, to its treatment, and to the supportive care, should be discussed: The role of preexisting conditions related to patient history and lifestyle, and the role of the environment where the patient lives or has lived.

Patient history and lifestyle. In addition to the main underlying disease, cancer patients may have other pathological conditions able to influence their infectious risk [9,18,104]. These include noninfectious diseases, such as diabetes and hepatic cirrhosis, as well as infectious diseases, such as tuberculosis (or asymptomatic tubercular infection), toxoplasmosis, and viral infections due to herpes viruses, hepatitis viruses and retroviruses. Diabetes mellitus is considered to be associated with a higher risk of bacterial and, especially, candidal infections. This is probably related to abnormalities of first-line defense mechanism (the integument), due to vascular disease and neuropathy, and to a reduction in chemotactic and phagocytic functions. In addition, the high glucose concentration present in urines of diabetic patients may favor pathogen colonization and disease. Hepatic cirrhosis has been often associated with severe infections, mainly due to the impairment of the hepatic barrier counteracting dissemination of bacterial pathogens coming from the gastrointestinal tract.

Reactivation of tuberculosis has been observed in patients with both hematological malignancies and solid tumors, usually with development of atypical or disseminated disease [105]. Toxoplasmosis in patients receiving antineoplastic therapy is unusual. However, it can present with protean manifestations, including dissemination [106]. Reactivation of cytomegalovirus is a well-known cause of severe disease in patients receiving allogeneic bone marrow transplantation [13,107], and the same is true for varicella [13] and genital herpes [108]. Epstein Barr virus has been associated with lymphoproliferative diseases in patients receiving immunosuppressive treatment, for example, after bone marrow transplantation [109]. Reactivation of hepatitis B after immunosuppressive therapy has also been described [110,111], while at the present time there is no information about this possibility with C hepatitis. Retroviral infections are associated with neoplasia and opportunistic infections [112]. Patients with acute leukemia due to human T-cell lymphotropic virus type I present with T-cell deficiency, which has been associated with an increased risk of *Pneumocystis carinii* pneumonia and disseminated strongyloidiasis and histoplasmosis, while patients with human immunodeficiency virus (HIV) infection and HIV-related tumors treated with cytotoxic therapy are at risk of HIV-related opportunistic infections, which can be unresponsive to any antimicrobial therapy, due to the overlapping of viral and iatrogenic immunodeficiencies. Reactivation of human herpes virus 6 has been described after bone marrow transplantation, with development of fever and skin rash, resembling GvHD [113], and severe pneumonia [114]. Finally, patients with congenital immunodeficiencies may develop neoplastic diseases, the course of which will obviously be complicated by overlapping of the underlying immunodeficiency with the effects of cytotoxic chemotherapy [115]. Patient lifestyle may also be important in some instances. For example, alcoholism, drug addiction, and smoking have been associated with an increased risk of infection. In particular, cocaine inhalation has been associated with a potentially increased risk of colonization with *Aspergillus* spores. The same has been suggested for certain occupations and hobbies, such as gardening, wood cutting, masonry, and tobacco rolling (see later) [23].

The environment. The term *normal microbial flora* refers to the population of microorganisms that inhabit the internal and external surfaces of healthy normal humans. Microorganisms that live in the skin and mucous membranes are supposed to be able to counteract colonization by foreign organisms through bacterial interference (competition for receptor or binding sites of the host cell; competition for nutrients; mutual inhibition by metabolic or toxic products, or by antibiotic materials or bacteriocins; or other mechanisms) [116,117]. Suppression of the normal flora can lead to transient or permanent colonization by microorganisms from other parts of the body or from the environment, which, in turn, can proliferate and produce an opportunistic disease. In the immunocompromised host, the underlying disease and its general management, in combination with long periods of hospitalization and repeated cycles of broad-spectrum antibiotics for prophylaxis or treatment, are all factors concurring in the modification of the endogenous microbial flora [118], with possible acquisition of aggressive and resistant pathogens.

Approximately 80 percent of pathogens causing infections in granulocytopenic cancer patients come from the intestinal flora, and half of them are acquired soon after hospitalization [119]. Passage of pathogens from the hospital environmental flora into the body may occur through various routes, including patient-to-patient contacts, doctor/nurse-to-patient contacts, and device-to-patient contact [120–122]. In addition, certain types of microorganisms can be transmitted by dust, water, foods, and air. Exposure to dust during work or leisure time may lead to inhalation of fungal spores (e.g., *Aspergillus*, *Zygomycetes*, *Coccidioides*, *Histoplasma*), which can represent a risk factor for development of disease when the patient receives cytotoxic therapy. In the hospital, exposure to dust can occur during building renovation or construction inside or near the hospital, with consequent contamination of air-conditioning filters, as well as because of the use of housekeeping equipment that tends to redisperse microorganisms into the air, especially *Aspergillus* spores [123–125]. Fungal spores are also common inhabitants of plants and flowers. For this reason, cut flowers and potted plants should probably be banned from the room of immunocompromised patients, especially if at risk of neutropenia [125,126]. Water may represent another important source of pathogens and a vehicle of transmission in neutropenic hosts. Outbreaks of nosocomial legionellosis associated with contamination of water and cooling systems are well documented [127–129]. The organisms can be dispersed from the main water supplies, where they used to live in the sediment at the bottom of large hot-water tanks, throughout the water system, contaminating plumbing fixtures and pipes. Food is another important source of colonization, and cooked food has been recommended by several authors for immunocompromised hosts [130–132]. However, at the present time sterile diet is no longer considered as indispensable for immunocompromised patients, including those undergoing allogeneic bone marrow transplantation. Many centers either leave patients free to eat whatever they want or limit the restriction to uncooked fruits and vegetables (low bacteria diet) [130,132,133].

Factors associated with diagnosis and outcome in febrile and granulocytopenic patients

Classical teaching in infectious disease classifies febrile episodes in granulocytopenic cancer patients according to the presence or absence of a microbiological documentation of infection and according to any identified site. When granulocytopenic cancer patients become febrile and receive empirical antimicrobial therapy, a microbiological cause for the febrile episode can be demonstrated in only about 30–40 percent of patients, the majority of whom will have bacteremia [15]. Given the poor outcome of infections in cancer patients with fever and granulocytopenia and the delay between onset of fever and the reporting of culture results, it is common practice to start intensive antibacterial treatment in all febrile and granulocytopenic cancer patients, on the assumption that all these patients are potentially at risk of developing life-threatening infections. However, patients with cancer, granulocytopenia, and fever are not all the same, and both the clinical

course and the diagnosis of febrile episodes vary considerably. Indeed, some authors showed that early discharge, outpatient treatment, and short-term antibacterial therapy are feasible and safe in selected groups of patients [134–137]. For example, in a pragmatic, randomized study, Rubenstein and coworkers [134] showed that outpatient treatment was as safe as the traditional in-hospital approach in a selected group of febrile and neutropenic cancer patients, staying in a range of 30 miles from the cancer center and free of any type of comorbidity. However, in this study the choice of the patient to be given outpatient care was not based on any risk assessment or the result of clinical prediction rule.

The problem remains, indeed, how to scientifically identify a priori (i.e., before diagnosis of the febrile episode and at the development of fever) the subgroups of patients susceptible to outpatient treatment in order not to put some patients at unacceptable risk. With this in mind, Talcott and coworkers [138] analyzed data from episodes of fever and granulocytopenia, which were available within the first 24 hours, in order to identify patients at lower risk of an unfavorable course and, therefore, most likely to benefit from early discharge and outpatient care. In these analyses the dependent variable was defined as the development of severe medical complications, including infection. A long list of these complications was provided. Judgements were based on a prospective evaluation, partially combined with a blind review performed by an independent physician. Patient risks of developing complications were classified according to control of cancer, presence of comorbidity factors, and type of care (outpatient or inpatient), and four risk groups were built. Outpatients with controlled cancer and without any comorbidity factor were more likely to recover easily and rapidly from their episode of fever and granulocytopenia.

The results were validated on an independent set of data and confirmed the previous analysis. As expected, complications occurred less frequently among outpatients with a controlled cancer and without any comorbidity than in other patients, and a multivariate analysis of factors associated with a favorable outcome showed that the predefined risk groups were independently significantly correlated with the development of complications. Unfortunately, in this study the individual patient risk of complication calculated on the basis of the mathematical model was not evaluated, and sensitivity and specificity of the model (i.e., its discriminant capacity) were not calculated [139].

Another approach aimed at identifying low-risk patients has considered a hematological parameter, that is, the appearance of monocytosis as an early sign of hematological recovery. This parameter seemed to correlate well with favorable outcome in a population of granulocytopenic children with cancer, and these patients underwent safe, early dismissal. However, no methodologically correct validation of this approach has been published so far [135,136]. A third approach has been the one proposed by our group [22]. In this study, we choose to focus on a simpler, more objective dependent variable, a diagnosis of bacteremia, making the assumption that bacteremia carries an increased risk of unfavorable outcome. This assumption may not be completely true because some studies have found that bacteremias are more likely to respond to antibacterial therapy than are other infections, especially pneumonias [140,141]. However, bacteremia is known to be

associated with some incremental risk of complication and clinical deterioration [15,25,142–149].

In addition, comparative clinical trials of empiric therapy usually base their conclusions on data stemming from the subgroup of bacteremic patients, since the response to empiric antimicrobial therapy is usually similarly good in the other febrile and neutropenic patients. Our aim was to create a clinical prediction rule for diagnosis of bacteremia and to identify factors more predictive of a specific diagnosis of gram-positive or gram-negative bacteremia. Demographic information and data on history, symptoms, signs, and laboratory tests available at the onset of fever were collected prospectively from febrile and granulocytopenic cancer patients entered into the fifth trial of empirical antibiotic therapy performed by the IATCG of the EORTC from 1986 to 1988 [26]. A total of 834 episodes of fever developing in 771 neutropenic patients were divided into two groups. The first group of 558 episodes (70 percent) was used to derive the multivariate model and to evaluate factors associated either with a diagnosis of gram-positive or of gram-negative bacteremia (derivation set). The second group of 276 episodes (30 percent) was used to assess the discriminating ability of the model (validation set). In the derivation set, baseline characteristics of patients with a final diagnosis of bacteremia (either single-agent or polymicrobial) were first compared with those of all other patients (including those with microbiologically documented bacterial infections without bacteremia, viral, fungal, and mixed infections; clinically documented infections; possible infections; and noninfectious fevers) using the standard chi-square test for heterogeneity or, when appropriate, Fisher's exact test, or the chi-square test for trend.

Characteristics evaluated for association with a diagnosis of bacteremia were sex, age, presence (and type) of an intravenous line at the onset of fever, underlying disease, number of patients randomized by each institution (reflecting the 'size' of the institution, since larger institutions are used to enroll more patients than smaller institutions), administration of antifungal and antibacterial prophylaxis, duration of granulocytopenia before fever, initial granulocyte and platelet counts, highest temperature before inclusion in the study during the last 12 hours, presence of shock, and, finally, presence and location of an identifiable site of infection at presentation). The probability of bacteremia was then modeled as a function of the above-mentioned characteristics using a multivariate logistic regression analysis. Starting from the full model with all variables included, nonsignificant variables were progressively deleted with a step-down procedure based on a likelihood ratio test. The results of the multivariate analysis in the derivation set were used to develop a clinical prediction model, and the accuracy of this model in discriminating patients with and without a diagnosis of bacteremia was evaluated both in the derivation and in the validation sets using a receiver-operating characteristic (ROC) curve. Sensitivity and specificity were computed using different levels of predicted risk as the cutoff [147].

In addition, in order to understand if variables predicting diagnosis of bacteremia were distributed differently in the subgroups of patients with gram-positive and gram-negative bacteremias, two additional multivariate analyses were performed in

the derivation set, using the same variables as before. Patients with either gram-negative or gram-positive bacteremias (excluding polymicrobial infections) were compared with all other patients. Since the purpose of this second analysis was not to build a predictive model but simply to suggest associations and correlations, no validation was performed. The results showed that shock, very high fever, presence and location of signs of infection, longlasting granulocytopenia, thrombocytopenia, and administration of antifungal prophylaxis were predictive of bacteremia in our patient population. Weaker predictive factors included the institution where the patient was treated, the underlying disease, and the administration of antibacterial prophylaxis. Age, sex, intravenous line, and granulocyte count at onset were not associated with a diagnosis of bacteremia. Presence of shock and lack of antibacterial prophylaxis were associated with gram-negative bacteremia, while signs of intravenous catheter site infection were suggestive of gram-positive bacteremia.

Unfortunately, the clinical prediction rule derived from our data discriminated poorly episodes with bacteremia from other episodes. At best, it allowed a reliable prediction for a small subgroup of patients at lower risk. This might have been because other factors influencing the probability of bacteremia in neutropenic cancer patients were not recorded in our case report form or because some patients classified as having nonbacteremic infections, clinically documented, or possible infections actually had occult bacteremia not detected by standard microbiological methods. Microbiological skills or technical facilities may vary among centers, and this might explain the effect of the 'institution' variable on the prediction of bacteremia. In conclusion, despite its limitations this study provided some interesting information on the management of infection in neutropenic cancer patients and can represent an example of how to deal with the problem of infections in cancer patients in the year 2000. In our opinion, at the present time the development of validated risk profiles for the occurrence of specific types of infections represents the best approach to the study of infectious complications in cancer patients, with twin aims of improving our understanding of this clinical condition and of rationalizing patient care.

Conclusions

This review has drawn attention to the importance of the infection factor in the management of cancer patients and a number of factor predisposing these patients to infection. The role of the underlying disease and its treatment, the role of other ancillary treatments, the role of supportive care, and aspects related to the environment and to the individual patient's history have been discussed. A constant level of attention should be maintained in this field, because new syndromes emerge, antibiotic resistance develops, and new pathogens cause severe infections. At the same time, oncologists and hematologists tend to increase the intensity of antineoplastic therapies on the assumption that this correlates with better outcome. A better understanding of the practical effects of these therapies on the patient's clinical course should be warranted, with the aim of individualizing treatments and levels of care. This is also very important in terms of cost containment, an issue

that has become crucial nowadays throughout the world. Reserving sophisticated approaches to very high-risk patients, while treating other patients with standard care, requires the identification of these subgroups of patients with adequate scientific methodologies. In the 1970s, the empirical approach for the management of infection in cancer patients changed the natural history of these patients. Now it is likely that more attention should be given to early diagnosis and reliable prediction rules, trying to proceed toward improved recognition of why and what we treat.

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2 Signs and symptoms of infections and differential diagnosis from noninfectious conditions

Robert Hemmer

Lower respiratory tract

Infection of the lung is one of the most frequent infections seen in cancer patients, or at least it is one of the most frequently diagnosed on radiography or computed tomography (CT) scan. Aspiration of oropharyngeal bacteria is the usual mechanism by which patients acquire lung infection, and the hematogenous route is more exceptional. Lung infection is favored by local obstruction, for example, a tumor mass caused by lung cancer or, less frequently, metastatic cancer.

In patients with alteration of cell-mediated immunity, the most frequent etiologic agents are *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and viruses, especially cytomegalovirus (CMV). In patients with altered humoral immunity, encapsulated bacteria are major sources of infection: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*. In patients who are neutropenic, either because of the underlying illness (leukemia) or because of chemotherapy, gram-negative bacteria and fungi are the main etiologies.

Signs and symptoms

Cough, fever, dyspnea, and sputum production are the major symptoms and signs suggesting the presence of lung infection. Alteration in mental status, rales, pleuritic pain, and hypoxemia may be present. The characteristic pattern of dry cough and orthopnea—patients breathe well when supine but are dyspneic when sitting or even unable to speak one whole sentence without interruption—suggests *Pneumocystis carinii* pneumonia. Onset of cough and fever in the neutropenic patient, even in a nonhospital setting, suggests pneumonia with either gram-positive or gram-negative organisms, and prompt treatment should be directed against both, pending culture results. Persistence or recurrence of fever in the presence of x-ray evidence of pneumonia in the neutropenic patient suggests fungi: *Aspergillus* spp., *Mucor* spp., and less frequently *Candida* spp. [1]. *Aspergillus* spp. should be particularly suspected if the hospital or ward undergoes reconstruction [2]. Adult respiratory distress syndrome (ARDS), especially when associated with viridans streptococci, has been described in neutropenic patients [3–5].

Diagnostic procedures

Chest radiography will usually confirm clinically suspected pneumonia and show more or less typical radiographic patterns: focal lesions, interstitial lesions, and atelectasis. In a review of the role of chest radiography in febrile neutropenic patients, pulmonary disease could be found in 30 percent of febrile episodes despite the presence of a normal chest radiogram [6]. The radiogram may appear normal in deeply neutropenic patients, especially when the granulocyte count is under 100/ μ l, because these patients are unable to produce an inflammatory reaction that would be visible on chest radiography.

Some radiographic signs have been described as being more or less specific for definite etiologic agents. The radiographic air crescent representing air interposed between a radiodense parenchymal lung lesion and the surrounding normal lung is most frequently seen in angioinvasive aspergillosis [7], less commonly in pulmonary mycetomas caused by other fungi, such as mucormycosis [8], and also in infection caused by *S. aureus* [9]. Patients who have normal chest radiograms or radiograms interpreted as demonstrating nonspecific changes may have infiltrates detected only by chest CT scans [10].

Sputum examination

The only proof of infection is isolation of the etiologic agent. Obtaining a valuable sample for microbiological examination is essential for distinguishing infectious from noninfectious conditions, for sensitivity testing, and for allowing correct treatment. Demonstration of tissue involvement is essential to prove invasive fungal disease. But even though every effort should be made to establish a definitive diagnosis, invasive procedures are often contraindicated in the presence of marrow aplasia. Gram stain and sputum culture are of less diagnostic value in neutropenic than in non-neutropenic patients, because there will not be sufficient polymorphonuclear leukocytes to validate the sputum specimen. Other immunocompromised patients fail to produce sputum at all, for example, patients with *Pneumocystis carinii* pneumonia. For *Aspergillus* there tends to be a consensus that if in the presence of a radiographic finding suggestive of invasive *Aspergillus* infection an *Aspergillus* spp. is isolated in the sputum, the probability of infection is very high [11].

Invasive procedures include transtracheal aspiration (TTA), bronchoscopy associated with bronchoalveolar lavage (BAL) and bronchial brushing, and transbronchial transpleural or open lung biopsy. All procedures have their adepts, and probably each center has the best results with the procedure the center is most used to and performs most often. It also depends on the kind of patient. For example, TTA is most useful for recovering anaerobic bacteria, but these infections are not common in the setting of cancer patients. Bronchoalveolar lavage and bronchial brushing are most useful for the diagnosis of *P. carinii* pneumonia. This technique is thus very useful in AIDS patients. Refinements of the BAL technique to avoid possible contamination by oropharyngeal bacterial flora have been described by Wimberly et al. [12] and others [13].

Quantitative bacteriology on samples obtained by bronchoscopy has also been attempted for greater diagnostic accuracy [14]. Obtaining a correct sputum sample for microbiological analysis is not only important to establish a diagnosis of infection but also to differentiate between infection and tumor invasion or radiation pneumonitis. For this differential diagnosis, biopsy, together with a negative microbiology exam, is the procedure of choice.

None of the procedures is 100 percent diagnostic, and often a combination of more than one only gives an approximate guess. More than one diagnosis may also coexist: a patient can have a mixed infection (e.g., *P. carinii* and CMV), superinfection, or a combination of a noninfectious process with an infection. Blood cultures are occasionally helpful in establishing the diagnosis.

Noninfectious causes mimicking lung infection in cancer patients are mainly neoplastic lung disease causing obstruction and secondary bacterial infection (lesions from lung cancer or from metastatic cancer, leukemic infiltrates, invasion of the mediastinal lymph nodes), pulmonary emboli, congestive heart failure, radiation pneumonitis, pulmonary hemorrhage, drug-induced pneumonitis (many cytostatic agents, including methotrexate, bleomycin, busulfan), and leukoagglutinin reactions during or in the 24 hours following blood transfusions. Leukoagglutinin reactions are rarer today because of the use of red blood cells rather than whole blood, containing leukocytes, and because of the use of filters [15].

As in the case of infectious causes, fever and dyspnea may be the only symptoms and signs present in the noninfectious conditions, and often consideration of the clinical setting will provide the clue to diagnosis: Previous radiation therapy, drugs administered, fever pattern according to the time schedule the drugs are administered, dissociation of fever and pulse rate, clotting abnormalities, and epidemiological patterns of *Legionella* or *Aspergillus* infections in the hospital.

Sinus infections

Pain, often unilateral, involving the frontal, temporal, or occipital area; dysesthesias over the face; and occasionally nasal discharge suggest sinusitis or spread of an ear, nose, and throat (ENT) tumor. The paucity of signs and symptoms often delays diagnosis and treatment. Sinusitis may mimic tumor or may accompany tumor or proton beam therapy [16]. Radiography or CT scan may differentiate between infection and tumor; aspiration or biopsy of the sinus will establish the definitive diagnosis, and in the case of sinusitis may demonstrate the etiologic agent. Gram-positive bacteria, including *S. pneumoniae* and *S. aureus*, gram-negative bacteria, and anaerobic bacteria may be the cause. If, however, after antibiotic treatment the symptoms do not improve, fungal infection should be strongly suspected; aspirated material will be positive by the potassium hydroxyde wet mount method if a sufficient fungal load is present. Cultures will be positive for *Aspergillus* spp. or *Mucor* spp., the most frequent fungi. *Alternaria* spp. have been isolated in six cases of localized sinonasal infection in a series of 1186 patients who underwent bone marrow transplantation [17,18].

Skin

Skin infections should be easy to diagnose because they are easily seen and are readily accessible for diagnostic procedures [19]. They can be divided into localized or regional infections, hematogenous infections, and infections around an implanted device. Localized infections include, especially in neutropenic patients, carbuncles, cellulitis, and abscesses. Clinical clues are often only pain and redness; the typical fluctuation, even in the presence of an abscess, is missing in those patients not able to produce an inflammatory local reaction. Other types of lesions are hemorrhagic or vesicular, or resemble subcutaneous nodules. Localized skin infections are rarely misdiagnosed; thrombophlebitis is a differential diagnosis of cellulitis. Particularly frequent are abscesses of the perianal region, which should be looked for systematically to avoid their resulting in life-threatening bacteremia.

Etiologic agents of localized infections include *S. aureus* and coagulase-negative staphylococci, gram-negative bacteria, or mixed gram-negative and anaerobic infections (especially in the perianal region), and also fungi and Herpes simplex virus. Skin infections as a manifestation of disseminated infection are often the long expected clue to make a correct diagnosis of an obscure fever in cancer patients. Sometimes the diagnosis is easy: Varicella or Herpes-zoster infection in patients with lymphomas are easy to recognize and can be treated effectively. Ecthyma gangrenosum is a lesion that is necrotic and ulcerates in its center, while ecchymotic in the periphery. It is classically a sign of *Pseudomonas aeruginosa* infection, but necrotizing skin lesions have also been described with other pathogens, including other gram-negative organisms. *Aeromonas hydrophila*, marine vibrios, *Nocardia* spp., and fungi have been described [19–21]. Cutaneous septic emboli of bacteria, and also of *Candida* spp., *Cryptococcus*, *Mucor* spp., and *Aspergillus* spp., have been reported [22–24].

Bacterial, mycobacterial, and fungal cultures, as well as histological examination of aspiration material or punch biopsy material, should actively be undertaken and will distinguish those maculopapular lesions from the true ecthyma gangrenosum lesions and also from pyoderma gangrenosum, a noninfectious lesion [25], and from Sweet's syndrome [26].

Skin infections presenting as abscesses, furuncles, nodules, or papules due to *Mycobacterium haemophilum*, accompanied sometimes by septic arthritis, osteomyelitis, pneumonia, or bacteremia, have recently been described in patients with lymphoma, after bone marrow transplantation for aplastic anemia or for acute myelocytic leukemia, as well as in renal transplant patients and patients with AIDS [27]. When acid-fast bacilli are observed in a sample recovered from a cancer patient with skin infection, special culture media and incubation at 30°C for 4 weeks should be utilized [28].

Punctures of the skin, and venous and arterial access devices

In the neutropenic patient venipunctures or punctures associated with invasive procedures can result in localized or disseminated infection. Short-term peripheral

intraarterial and intravenous catheters, as well as insertion of foreign bodies, such as Ommaya reservoirs for the treatment of meningeal infection or carcinomatosis, may also cause localized or generalized infection. For repeated courses of chemotherapy, administration of blood products, antibiotics, or parenteral nutrition, semi-permanent venous access lines are now commonly used. Two types are currently available: tunneled silicone catheters exiting the skin (Hickman type) and totally implantable, subcutaneous infusion ports. Hickman-type catheters may result in exit-site infection, which is defined as erythema, induration, pain, or purulent discharge at the exit site or within 2 cm of the skin exit site. Erythema, tenderness, or induration along the subcutaneous tract of the catheter on a length greater than 2 cm defines tunnel infection [29]. Port pocket infection is defined as induration, erythema, and tenderness around the port with a culture-positive material aspirate from the port pocket [30]. Atypical mycobacterial infections have been described as exit-site infections around devices [31,32].

In granulocytopenic patients inflammatory signs may be discrete. All localized infections may be associated with bacteremia or fungemia. Site infection can sometimes be easily managed with local care and topical antibiotics. Catheter-associated bacteremia or fungemia can often be treated with antibiotics without removal of the catheter [33,34]. If, however, tunnel infection or port pocket infection is present, if there is evidence of systemic emboli, or if fever persists in spite of appropriate antibiotic treatment, removal is mandatory [34]. In a nonrandomized series comparing Hickman-type devices with ports, the incidence of infections per device day was 12 times greater with catheters than with ports, and the difference was 21-fold for bacteremia and fungemia [30].

Gastrointestinal tract and intraabdominal infections

Apart from the presence of a gastrointestinal or intraabdominal cancer itself, chemotherapy is the main factor predisposing cancer patients to develop infections. Intensive cytostatic treatment produces mucositis and ulceration of the gastrointestinal mucosa that allows invasion by microorganisms. Neutropenia favors infection with bacteria present in the mouth or gut, and alteration of cell-mediated immunity favors infection with CMV and *Salmonella* nontyphi. Both favor infections with parasites, especially the hyperinfection syndrome due to invading *Strongyloides* infection.

Mouth and pharynx

Stomatitis and pharyngitis may be noninfectious, due to chemotherapy, or infectious, due to the resident streptococcal or anaerobic flora, or to HSV. They may also first be noninfectious and then become infectious after colonization by resident bacteria or hospital flora. Symptoms of stomatitis, pharyngitis, and gingival infection are pain and difficulties with chewing and swallowing. If inspection of the oral cavity shows white plaques, *Candida* infection is suspected. Less frequent

manifestations of *Candida* infection are erythematous lesions on the dorsal surface of the tongue, called *acute atrophic candidiasis*, and involvement of the angles of the mouth (*perleche* or *angular cheilitis*). One should note, however, that true *Candida* infection is difficult to differentiate from *Candida* colonization: Biopsy, rarely performed, would prove tissue invasion.

Infectious mucositis in granulocytopenic patients may be caused by anaerobes, streptococci, and hospital-acquired gram-negative bacilli. A clinical presentation of necrotizing gingivitis is a more reliable diagnosis than a culture result, which may mean only colonization. Herpes simplex virus is another agent of mucositis and should be isolated by microbiological techniques, since successful treatment is now possible.

Esophagus

Candida oesophagitis is a common finding in neutropenic patients or in patients with altered cell immunity. It often accompanies or follows oral thrush. It should be suspected if pain on swallowing, retrosternal burning pain, or meallic taste or impression of food stop at the end of the esophagus or, less commonly, gastrointestinal bleeding is present. To confirm the diagnosis we prefer endoscopy to classical radiography of the esophagus, because it enables one to obtain a biopsy specimen at the same time and because radiographic specificity is lower. The endoscopic appearance of white plaques usually provides sufficient evidence to start antifungal treatment; culture is not useful because it does not distinguish between invasion and colonization; only biopsy proves fungal invasion. *Candida* infection may also present as ulcers or vesicles and must be distinguished from HSV infection or, more rarely, CMV, bacteria, or noninfectious causes such as reflux [35].

Stomach, small intestine, and colon

Gastric infection is rarely diagnosed in cancer patients but should be suspected in cases of nausea, vomiting, epigastric pain, and bleeding, especially when patients are receiving chemotherapy or corticosteroids. Endoscopy or radiologic exams may reveal an ulcer, and biopsy may show evidence of either CMV infection or gastric candidiasis [36–39]. Radiography shows a bull's-eye appearance, and the differential diagnosis is submucosal metastasis or lymphoma [39].

Small intestine and colon infection is suspected in patients with diarrhea, abdominal pain, small bowel or colon ulceration, or focal or diffuse colitis on radiography or endoscopy, which may lead to massive gastrointestinal bleeding and/or perforation. CMV is a major cause of small bowel and colon infection [36], but the role of *Candida* spp. is less well established. The 'usual' enteric pathogens should be considered: *Giardia lamblia*, especially in patients with dysgammaglobulinemias, *Salmonella* spp. in patients with alterations of cellular immunity, and *Cryptosporidium* [40]. Diarrhea and pseudomembranous colitis may also be due to *Clostridium difficile* following chemotherapy [41–43]. *Strongyloides stercoralis*, usually causing mild or inapparent symptoms in the immunocompetent host, in the

immunocompromised host may lead to the hyperinfection syndrome, which is life threatening and consists of intestinal obstruction, gastrointestinal bleeding, and diffuse peritonitis [44,45]. The clinical presentation is one of acute surgical abdomen, due to perforation of the bowel by the parasite and subsequent bacterial infection, causing peritonitis and septicemia.

To prevent this life-threatening syndrome, examination of concentrated stool, especially in patients who have traveled to endemic areas or with a history of blood eosinophilia, should be performed prior to the administration of chemotherapy and corticosteroids. Acute abdominal pain should raise the suspicion also of appendicitis and of another entity mimicking appendicitis, neutropenic enterocolitis, an infection caused by *Clostridium septicum*, occurring in patients with neoplastic disease. Mucosal ulcerations of the gut seem to be the portal of entry. It also follows cytotoxic drug therapy for leukemia and lymphoma, and progresses rapidly to peritonitis, septicemia, and shock [46].

Another clinical entity causing intraabdominal infection should be mentioned, hepatosplenic candidiasis, also called chronic disseminated candidiasis [47,48]. It occurs most frequently in leukemic patients following prolonged neutropenia, which suggests that the gastrointestinal tract is the site of entry via the portal circulation. The clinical presentation is essentially fever without any detectable focus of origin, and sometimes abdominal or pleuritic pain, not responding to broad-spectrum antibiotics. The fever persists or recurs even when the patient recovers from neutropenia. Alkaline phosphatase is elevated, and the other liver function tests may be normal or abnormal. Ultrasonography, CT scan, or magnetic resonance imaging (MRI) showing multiple lesions in the liver and spleen suggest the diagnosis. Confirmation of the diagnosis should be obtained by liver biopsy before treatment is initiated with prolonged amphotericin B in high doses with or without flucytosine, or with liposomal amphotericin B. Biopsy will rule out other diagnoses, such as disseminated tuberculosis [49].

Central nervous system

Neutropenia as well as alteration of cell-related immunity predispose to central nervous system (CNS) infection. Symptoms and signs may be very subtle, and one should not let them worsen until obtundation and agitation occur. The subtle signs are sudden-onset or progressive headache and/or slightly modified mental status. Sometimes focal neurological signs may be present. Even if symptoms and signs are subtle, due to a diminished inflammatory response by immunosuppression, diagnostic procedures should be started immediately. They consist of CT scan or MRI and lumbar puncture. If lumbar puncture is performed before CT scan or MRI, papilloedema should be excluded on fundoscopic examination. Computed tomography scan or MRI will exclude mass lesions such as brain abscess, toxoplasmosis, or noninfectious causes, such as solid tumor or metastasis. Cerebral spinal fluid (CSF) examination will confirm or exclude meningitis or show leukemic meningitis with the presence of blast cells.

Which kind of meningitis do we expect in immunocompromised patients? Encapsulated bacteria (*S. pneumoniae*, *Neisseria meningitidis*, *H. influenzae*, *S. aureus*) are possible, especially in myeloma patients or in patients who have undergone splenectomy. *Staphylococcus aureus* and gram-negative bacilli (Enterobacteriaceae and *Pseudomonas* spp.) are frequent in neutropenic patients and cause meningitis by either the hematogenous route or by superinfection of surgical wounds. Cerebrospinal fluid shunt infections or infections resulting from implantation of devices, such as an Ommaya reservoir, are caused mainly by coagulase-negative staphylococci and *S. aureus*, but corynebacteria and gram-negative bacilli may be encountered [50,51]. *Listeria monocytogenes* is an important pathogen in patients with deficiencies of T-lymphocyte functions [52]. Cerebrospinal fluid findings are extremely variable: In a series of 78 patients white blood cell counts ranged from 6 to 12,000 cells/mm³, and differential counts varied from 99 percent polymorphonuclear leukocytes to 98 percent mononuclear cells. Glucose levels may be low or normal, and the organism, a gram-positive rod, may not be seen on Gram stain and should not be mistaken on culture for a diphtheroid [53].

Fungal CNS infections occur in patients with a decrease of cell-mediated immunity. *Cryptococcus neoformans*, although less frequent than in AIDS patients, has been isolated in some cancer centers, quite often among patients with CNS disease [52,54,55]. Cerebrospinal fluid examination may show normal glucose and proteins, and only a slight pleocytosis. India ink examination may or may not show budding yeasts, and cultures are usually positive. The best diagnostic procedure, however, is the detection of cryptococcal antigen in CSF and in serum, which is positive in nearly all cases of cryptococcal infection. Other fungi that cause more rare CNS infections are *Aspergillus* spp. and *Mucor* spp. [56], which may both cause the rhinocerebral syndrome with infiltration of the brain from the sinus, causing proptosis and cellulitis around the eye, progressing to ophthalmoplegia and coma. The CNS infection is often associated with lung infection. Biopsy is needed to confirm the diagnosis.

Only one parasite causing CNS disease in cancer patients will be mentioned: *Toxoplasma gondii*. Excluding AIDS patients, who are much more frequently infected, 120 published cases of toxoplasmosis have been reviewed by Ruskin in 1989 [57], the majority of them occurring in patients with lymphoma and leukemia, and 65 presenting as a major neurologic syndrome. The ultimate diagnostic procedure is brain biopsy. Computed tomography scan or MRI may, however, as in AIDS patients, suggest the diagnosis strongly enough to allow a therapeutic trial, and only if there is no improvement will biopsy be undertaken [58]. Clinical presentation includes patients with headache, lethargy, confusion, fever, or seizures. Serology is rarely helpful in the immunocompromised patient, and CT scan and MRI suggest the diagnosis by showing enhancing lesions, typically the ring-enhancing lesions [58,59].

One would expect an increased incidence of viral diseases, especially of the genus Herpes in cancer patients with diminished T-cell function, but there is no evidence in the medical literature to firmly support this hypothesis. This may only be due to inadequate diagnostic methods at present.

Sepsis without a focus of origin

One of the greatest challenges to the oncology patient is isolated fever without microbiological or even clinical evidence of infection. We admit as a rule that fever in the neutropenic patient must be considered as having an infectious origin, unless proven otherwise, and be treated with antibiotics. A vigorous attempt should be made to establish the infectious focus and to document the microbiological etiology. Organ-oriented signs and symptoms that have been described and analyzed earlier must be carefully looked for, and diagnostic procedures that look most promising in a given situation should be undertaken. Common infections, such as urinary tract infections, should not be forgotten, and rare infections, such as babesiosis [57,60], must be kept in mind.

Fever can be due to noninfectious causes. We have already mentioned, in the differential diagnosis of lung infection emboli, atypical pulmonary edema, leucoagglutinin reactions, radiation pneumonitis, and drug-induced pneumonitis. Drug fever without pneumonitis is also frequent. Transfusion of blood products, hematomas, noninfectious infarcts of the spleen, graft-versus-host disease after bone marrow transplantation, and neoplasms themselves, especially Hodgkin's lymphoma, acute leukemias, hepatoma, and hypernephroma, can also cause fever, but these diagnoses must be accepted only if infections are ruled out. Recent studies seem to show a decline in the incidence of documented infections, probably due to the administration of prophylactic absorbable antibiotics, mostly quinolones, and perhaps also due to quicker empirical antibiotic treatment in the case of fever [61]. The latest published EORTC study [62] analyzing 858 febrile episodes in 677 patients found 29.5 percent of episodes were microbiologically documented infections (83 percent being bacteremias), 27.5 percent were clinically documented infections, and 43 percent were unexplained fevers. Some infections may not be recognized until autopsy. Many patients with or without documented infection respond to antibiotics.

Can laboratory parameters distinguish between fever of infectious and noninfectious origin? The best proof of an infection remains a positive blood culture, and the sooner the blood cultures detect the bacteria or the fungi, the sooner an appropriate treatment can be started. Some microorganisms only rarely grow in blood, such as *Aspergillus* spp., while others may have a fastidious growth, and blood cultures may become positive only after several days of incubation. The newer blood culture systems, such as lysis centrifugation, yield an earlier growth and detect more fungi than conventional broth systems [63]. Other systems, such as the infrared nonradiometric resin system (Bactec 660), or a system based on colorimetric detection, known as the BacT/Alert Microbial Detection System, may detect bacteremia and fungemia earlier.

Viral cultures should also be undertaken. They quite often yield positive results, especially for CMV, when using newer techniques, such as the shell vial assay and the polymerase chain reaction (PCR) [64,65]. PCR is a promising new tool, which, however, still yields too many false-positive results [66,67].

Because bacterial sepsis is accompanied by metabolic changes, referred to as

acute-phase responses, that are mediated by cytokines, the serum concentrations of tumor necrosis factor, interleukin-1 beta, interleukin-6, serum amyloid A (SAA), and C-reactive protein (CRP) have been measured in children with cancer who had fever and neutropenia to determine if these parameters could differentiate between bacterial infection and fever due to other causes. None of these variables correlated with documented bacterial etiology; they were not helpful for clinical decisions, neither on admission of a neutropenic child with fever nor after 2 days. The sensitivity of CRP determination proved to be poor [68,69].

A retrospective study [70] found CRP determination to be more helpful because it showed a statistically significant difference in patients with septicemia compared with patients without positive blood cultures. A significant difference was also found between CRP levels in patients with major infections and those in patients with minor infections. No difference was found between patients with microbiologically versus those with clinically documented infections. The authors concluded, however, that a prospective epidemiological study is needed before concluding that CRP is really helpful for predicting and diagnosing infection.

Bacterial serology using antigens for *S. aureus*, *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, and Enterobacteriaceae, in a prospective study of 91 episodes of fever in neutropenic children with cancer, seemed helpful according to the investigators [71]. They found, however, that there may exist cross-reactions between *S. aureus* and *S. viridans*; the study also was not designed to rule out false-positive or false-negative antibody reactions. Even if bacterial serology becomes a promising tool in the future, this author believes that, for the moment, it does little to help the clinician make an appropriate decision when faced with a febrile neutropenic patient.

Fungal serology has also not made tremendous progress in recent years, especially in those infections in which it is most needed, *Aspergillus* spp. and *Candida* spp. infections. One remarkable exception is antigen detection of *Cryptococcus neoformans* (see earlier). Detection of anti-*Candida* antibodies or antigens, detection of *Candida* metabolites and cell-wall components, and amplification of *Candida* DNA by PCR reaction are being investigated in several laboratories, but no system has yet been standardized enough to allow regular clinical use [72,73].

Fungal infections are probably the most frequent cause of fever of unknown origin in cancer patients [74]. In autopsy studies demonstrating candidiasis, the fungi were isolated when the patients were still alive by blood cultures in less than 50 percent of cases [75]. The role of fungi in infections of cancer patients has probably become even more important because of the widespread use of catheters. The significance of catheter-associated fungemia has not been clarified. Earlier investigators suggested that removal of the catheter is sufficient [76]. This may be true in some cases, but it is equally true that it is very difficult to distinguish between those patients who will have tissue invasion after fungemia and those who will not [75]. Probably all immunocompromised patients who have catheter-associated fungemia should be treated by systemic antifungal antibiotics to avoid serious complications, either clinically patent, such as endophthalmitis, endocarditis, or arthritis, or occult, which are discovered only at autopsy [77].

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3 Chemoprophylaxis for the prevention of bacterial and fungal infections

J. Peter Donnelly

Bacterial and fungal infections contribute significantly to the morbidity of patients with malignancies and can be fatal, thereby frustrating attempts to successfully treat the underlying disease. Consequently, the prevention of infection by every possible means still remains a desirable, if elusive, goal. The armamentarium at our disposal is considerable and includes antimicrobial agents, disinfectants, isolation techniques, low microbial diets, and growth factors. Yet fatal infections continue to occur that might have been preventable had they been recognized earlier and had appropriate action been taken.

The factors involved in the evolution of infection are manifold and complex. Infection can be the culmination of a fairly predictable sequence of events, for instance, chemotherapy → mucositis → neutropenia → fever associated with bacteremia due to *Pseudomonas aeruginosa*; then within a few hours, sepsis syndrome → shock → death. More often, the presence of infection is inferred from the clinical manifestation, which includes fever, elevated proinflammatory cytokines, tachycardia, and little else. Blood cultures are often inconclusive, yielding, perhaps, a skin or oral commensal bacterial species. The patient's condition may continue to worsen despite broad-spectrum antimicrobial therapy, and then death might ensue. Alternatively, the patient might revive rapidly after neutrophil recovery. Given the unpredictability of febrile neutropenia and the constant risk of fulminant infection, prevention through chemoprophylaxis seems far better than cure. However, this issue is far from straightforward and divides infectious opinion into two extremes, ranging from those who believe the benefit far outweighs the cost and those who remain skeptical and eschew any form of prophylaxis. In order to understand how this wide range of opinions evolved, it is necessary to review the risk factors for infection that are present now, in the 1990s, since these are unlikely to be identical to those that were current two decades ago when chemoprophylaxis was first employed.

Sites of infection and potential pathogens

The commonest sites of infection are the oral cavity and the lung (figure 1). Oral infections are rarely straightforward to diagnose since it is usually impossible to

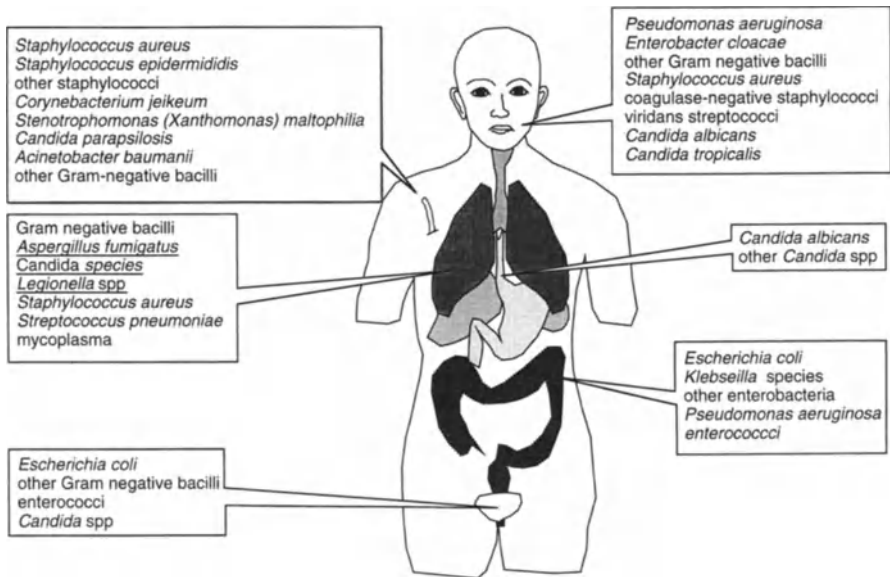


Figure 1. Sites of infection and potential pathogens.

distinguish between different infectious etiologies and between infection and the inflammation and lesions arising with oral mucositis. Nevertheless, when open lesions become colonized with gram-negative bacilli or other potential pathogens, the risk of invasion and dissemination is high. Similarly, oral resident flora, for example the viridans streptococci, have a ready portal of entry when the integrity of the mucosa is impaired, as do any bacteria that colonize as a result of profound disturbance of the normal flora, for example, coagulase-negative staphylococci. With oral mucositis, *Candida* spp. can establish a superficial infection, marked by the presence of pseudo-membranes over the ulcerated tissue, but can also initiate local invasion. Progressive candidosis can also extend to the esophagus.

Potential pathogens that colonize the oral cavity, nasal passages, sinuses, and upper airways are also the principal source of pulmonary pathogens. Aspiration of bacteria and yeasts, together with inhalation of spores of *Aspergillus* spp., allow colonization to extend to the bronchial tree and into the alveolar spaces. Following chemotherapy and irradiation, the lung appears to be exquisitely susceptible, not only to infection but also to immunopathological reactions mediated by the pulmonary macrophages that survive chemotherapy and can lead to various other syndromes, including respiratory distress. Pulmonary hemorrhage as a result of profound thrombocytopenia will further imperil the lung, increasing the risk of infection.

It is even more difficult to diagnose enteric infection, especially when nausea, vomiting, diarrhea, bowel cramps, and melena can all be due to toxicity related to chemotherapy and irradiation. However, the bowel is the major source of gram-negative bacilli, particularly *Escherichia coli*, which forms a normal part of the bowel flora of almost everyone. Simultaneous colonization of the oral cavity and

bowel with the same gram-negative bacillus and the same strain of *Candida* spp. is also common and can represent spread by the fecal-oral route via the fingers but can also be the result of hematogenous spread from the gut via the bloodstream to the lungs and then the mouth. Urinary tract infections, although rare, can also be initiated via perianal or vaginal contamination as well as through hematogenous spread from the gut.

Infections associated with intravenous catheters more often represent colonization of the lumen, which gives rise to bacteremia and occasionally candidemia. Whilst many, if not most, cases of intraluminal colonization do not represent a threat to the patient, metastatic infection can occur when *S. aureus*, *Candida* spp., and gram-negative bacilli are involved and when colonization with coagulase-negative staphylococci or *Corynebacterium jeikeium* persists, leading to repeated bacteremia. Colonization of the external surface of a catheter may lead to infection of the catheter-tissue interface. This can be restricted to the exit site or may be associated with cellulitis along the tract of a tunneled catheter such as the Hickman device.

Factors that influence infection

Treatment for malignancy inevitable leads to collateral damage to healthy tissue. Even when the tumor is localized in a single area, relatively superficial, and readily removed, any surgery and local irradiation will nonetheless extend impairment of the normal defenses. Irradiation and intensive chemotherapy cause mucosal damage (oral mucositis, stomatitis), which, in turn, provides a portal of entry for any potential pathogen, such as gram-negative bacilli, that is either a member of the normal resident flora or has established colonization after being acquired exogenously. Any reactivation of herpes simplex will exacerbate the risk of infection, particularly candidiasis [1,2], while dead or dying tissue will alter the local microbial ecology, thereby creating a nidus for infection. Such infections rarely prove fatal, are usually readily apparent and relatively short lived, and can generally be managed simply. However, when hypoplastic bone marrow is present at the same time, the lack neutrophils allows any potential pathogen that has invaded the tissues or translocated to the bloodstream to disseminate readily. Infection then extends to the major organs, with the attendant risk of fulminant sepsis and ultimately death. The trend towards more intensive chemotherapy and the increasing use of allogeneic and autologous transplantation augments the number of patients who will experience the double jeopardy of profound neutropenia and damage to the natural barriers of the skin and mucosa. Consequently, the transition from colonization to disseminated infection is likely to require fewer steps and to involve much lower inocula than is necessary in patients whose immunity is not so comprehensively compromised.

Influence of chemotherapy and irradiation on hematopoiesis

When treating malignancies with intensive chemotherapy, bone marrow function is profoundly impaired. Myeloid cells and megakaryocytes are principally affected,

giving rise to absolute and functional neutropenia and thrombocytopenia. The lack of neutrophils deprives the host of a primary defense mechanism against invading microorganisms, which are able to readily establish themselves, initiate local infection, and disseminate unhindered, leading to fulminant sepsis and death unless treated promptly and effectively. When preparing for bone marrow transplantation, it is necessary to completely ablate the hematopoietic system by using total body irradiation combined with chemotherapy or a comprehensive cytoreductive regimen. Thus profound neutropenia is an unavoidable consequence of the treatment of malignancy and may be either transient or persist for 3–4 weeks or even longer. However, neutropenia is almost invariably just one of the components of compromised immunity. Humoral immunity is often depressed, and the coordination of cellular immunity is often lost so that instead of arresting infection, any paracrine mediators released induce the sepsis cascade, eventually resulting in systemic evidence of sepsis, which may culminate in multiorgan failure [3].

Bone marrow transplant recipients require prophylaxis with cyclosporin and occasionally intermittent methotrexate to suppress the development of graft-versus-host disease. This results in impairment of cell-mediated immunity by reducing the number and functions of various T-cell subsets and lowering interleukin-2 levels, the blastogenic response to CD4 cells, and the response to recall antigens. Immunoglobulin (Ig)G and IgM are also depleted; IgA responds less well to antigenic stimuli, and opsonization of encapsulated microorganisms is impaired. The neutrophils present are less mobile, the alveolar macrophages become indifferent to chemotactic stimuli, ingest fewer bacteria and fungi, and kill them less efficiently. Should graft-versus-host disease occur, corticosteroids or immunoglobulins such as antithymocyte globulin are given. Consequently, both the prevention and treatment of graft-versus-host disease places patients at additional risk for infections that are normally controlled by cell-mediated immunity, such as legionellosis, and salmonellosis, and augments their predisposition to mycosis and viral infection.

Physical barriers against microbial invasion and their impairment

The skin and mucosal surfaces of the alimentary tract form the two principal barriers against microbial invasion. Both surfaces are normally colonized with a variety of microorganisms, including many different genera of bacteria and yeasts, which have an intimate association with a particular ecological niche and help maintain the function and integrity of this first line of defense. When intact and healthy, both the mucosa and skin are capable of resisting colonization with the allochthonous organisms found in the immediate environment and of maintaining an ecological balance within the indigenous microbial flora.

Skin

Healthy skin provides an effective barrier against invasion by microorganisms, and its main defense is achieved by remaining intact. Desquamation also helps limit the

opportunities for transient organisms to establish residence. Sweat contains secretory IgA and also sufficient salt to create a high osmotic pressure. This limits the range of organisms that can withstand these conditions and compete successfully for binding sites and nutrients to the gram-positive bacteria, including various members of the coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, *C. jeikeium*, and other coryneforms, *Propriosebacterium* spp. and certain yeasts, *Pityrosporum* spp. [4]. These organisms further modulate the microecology of the skin by releasing fatty acids from the sebaceous secretions, producing a hydrophobic milieu as well as short-chain lactic and propionic acids, which help to maintain a low pH. Many of the bacteria also elaborate bacteriocins that inhibit other microorganisms. Consequently, healthy skin is particularly hostile to allochthonous colonization, especially by gram-negative bacilli.

Factors that erode the effectiveness of the skin barrier. The composition of the skin microflora is influenced by general factors, including climate, body location, age, sex, race, and occupation, as well as by the use of soaps, detergents, and disinfectants. Any antibiotics secreted in sweat will disturb the balance within the commensal flora, leaving the surface vulnerable to colonization by exogenous gram-negative bacteria. Antibiotics will also exert selective pressure on the skin flora, causing resistance to emerge, as has been observed during treatment with ciprofloxacin [5]. Chemotherapy and irradiation can bring about radical changes in the normal skin, causing hair loss, dryness, and loss of sweat production. Needle punctures and catheters provide a ready means of access for microorganisms to both the stratum corneum and the bloodstream. When the skin is broken, the release of fibronectin is thought to assist colonization with *S. aureus*, and other changes facilitate colonization with gram-negative bacilli such as *Acinetobacter baumannii* and enterobacteria. Abraded skin can lead to local infection, as well as providing a reservoir that assists further spread to the oral cavity and intravenous devices. When the balance is lost between the host defenses and commensal flora around the hair follicles, these can become inflamed and necrotic, forming a potential nidus of infection. Clinical infection therefore results from breaks in the skin, loss of local immunity, and disturbances within the resident flora.

Impact of intravenous catheters on the integrity of the skin. Vascular devices, particularly Hickman's right atrial catheter, have gained widespread acceptance as a safe form of long-term venous access. Regular use, however, is associated with a marked increase in the incidence of bacteremia due to coagulase-negative staphylococci, which frequently colonize the lumen [6,7]. These staphylococci are commonly resistant to tobramycin, trimethoprim, and methicillin, and may also be resistant to ciprofloxacin [8]. Unless the catheter ends in an implanted port, skin commensals have open access directly into the bloodstream, depending upon how frequently it is used [9], since the hub is the most likely source of contamination [10]. Infections related to the external surface of the catheter, particularly exit site infections and tunnel infections, occur much less frequently than does intraluminal colonization and involve other gram-positive bacteria, such as *C. jeikeium* and

Stomatococcus mucilaginosus, and gram-negative bacilli, such as *Acinetobacter* spp. and *Stenotrophomonas (Xanthomonas) maltophilia*. Once established, these infections are often very difficult to treat without removing the device [11]. The catheter is also a portal of entry for *Candida parapsilosis* [12] and other *Candida* spp. [13,14], and even molds such as *Aspergillus* spp. and *Mucor* spp.

Alimentary tract

The alimentary tract is the major reservoir of gram-negative bacilli and *Candida* spp. Normally, the alimentary tract flora contains in excess of 10^{14} microorganisms, amounting to several grams, but only very few of the organisms are capable of establishing infection, even in the most profoundly immunosuppressed patient. Most of the microbial flora is densely distributed around the surfaces of the oral cavity and the large bowel, where scores of different microorganisms, including various bacteria, for example, spirochaetes, spore formers, bacilli, cocci, and yeasts, compete for the available surfaces and nutrients supplied to them daily. Anaerobic bacteria predominate and play a crucial role in maintaining a healthy commensal flora by providing the facility to withstand the establishment of exogenous or allochthonous organisms, which is known as colonization resistance [15,16].

Colonization resistance of the alimentary tract. This facility of colonization resistance, or rather its loss, is inferred from the phenomenon of yeast overgrowth or oral thrush, ready colonization with nosocomial gram-negative bacilli, and the predominance of enterococci. It has also been defined for mice and human volunteers by their ability to resist colonization after challenge with gram-negative bacilli [16,17]. Yeast overgrowth corresponds to low concentrations of short-chain fatty acids [18], indicating suppression of anaerobe metabolism. Similarly, increasing yeast and enterococcal populations are usually accompanied by failure to detect anaerobes by culture, short chain fatty acid analysis [19], or the presence of β -aspartyl-glycine [20]. The normal commensal flora also attaches to the surfaces of the epithelial cells, thereby restricting access to exogenous organisms. The loss of the normal bowel flora would therefore create an ecological vacuum, which would allow other organisms to establish colonization by occupying the vacant cell surfaces or by taking advantage of the surfeit of nutrients. However, the microbial flora are not the only participants in the establishment and maintenance of colonization resistance. Host factors are also involved and include the integrity of the mucosa, the production of saliva and mucus, peristalsis, gastric pH, and the levels of secretory IgA [21].

Impact of antibiotics on the microflora of the alimentary tract. Many antibiotics exert a negative influence on the commensal flora, particularly the gram-positive nonsporing, lactic acid-producing bacilli, such as bifidobacteria, that are the likely contributors to colonization resistance, since these bacteria are peculiarly susceptible to antibiotics which significantly impair colonization resistance, including the penicillins, rifamycin, clindamycin, erythromycin, bacitracin, and vancomycin [21–26]. Certain cephalosporins, for example, cefoperazone and cefotaxime, are

also detrimental to colonization resistance, whereas the quinolones, including nalidixic acid and ciprofloxacin, pefloxacin, and the β -lactams aztreonam, moxalactam imipenem, and meropenem, have been declared 'friendly' [18,22,27–31]. Cotrimoxazole has been thought neutral [21,22,32–36] and is the most widely used agent for prophylaxis in neutropenic patients but may be deleterious after all [37]. Individual antibiotics that appear to spare colonization resistance, such as ceftazidime and piperacillin, might have a marked impact when given in combination, leading to an increase in both *Clostridium difficile* as well as yeasts [38].

Very susceptible bacteria, such as the oral *Neisseria* spp., will be suppressed by a wide range of antimicrobials, whereas oral viridans streptococci, such as *Streptococcus mitis* and *S. oralis* (formerly *sanguis* II), and other unusual oral commensals, such as *Streptococcus mucilaginosus* and *Capnocytophaga* spp., are likely to be selected for antimicrobial agents, such as a quinolone, to which the bacteria are only marginally susceptible, if at all. The chlorhexidine mouthwashes used to minimize infective complications arising from the oral toxicity induced by cytostatics also influence the microflora [39–41].

Influence of chemotherapy and irradiation on the alimentary tract

Effect of chemotherapy and irradiation on the oral cavity. Neutropenic patients will experience varying degrees of mucosal damage depending upon the nature of their therapy since some agents used for the chemotherapy of malignancy and regimens used to prepare for autologous transplantation also cause profound damage to the oral mucosa, with the production of thick mucus, for example, methotrexate and melphalan [42,43]. Oromucositis can also be particularly severe when anthracyclines are combined with total body irradiation and cyclophosphamide to condition patients for an allogeneic transplant [44]. Once established, oromucositis provides a portal of entry for a variety of oral commensal, including members of oral viridans streptococci, *mucilaginosus* and *Capnocytophaga* spp. [45–50], as well as *Candida albicans*.

It is likely that as conditioning regimens become more intensive, oromucositis will increase, leading to a commensurate increase in the number of unusual bacteria, especially endogenous gram-positives bacteria. Moreover, while bone marrow recovery can be accelerated by the use of the growth factors granulocyte–colony-stimulating factor (GM-CSF) and granulocyte-macrophage–colony-stimulating factor (GM-CSF) [51,52], these agents do not appear to have any influence on oromucositis [53]. However, despite the frequent morbidity associated with gram-positive infections, the attributable mortality is negligible [54–59].

Effect of chemotherapy and irradiation on the gastric acid barrier. Nausea and vomiting are frequent side effects of chemotherapy and irradiation, which can be ameliorated by antiemetics such as chlorpromazine and, more recently, ondansetron. However, dyspepsia is sufficiently commonplace for antacids like H_2 -histamine receptor antagonists to be regularly prescribed. Reduced gastric acidity inadvertently destroys the natural barrier that prevents transit and bowel colonization by oral commensals, many of which are resistant to the majority of antimicrobial agents

used for prophylaxis currently available. When patients swallow large amounts of mucus as a result of severe oromucositis, any oral commensals will survive passage to the bowel. The loss of the gastric barrier therefore effectively extends the area of potential sites for colonization of oral commensals and any organism with marginal susceptibility to prophylactic agents, for example, lactobacilli and *Bacillus* spp., to the full length of the alimentary tract.

This extensive colonization might explain why only a minority of patients with viridans streptococcal bacteremia develop the signs and symptoms of the so-called alpha-strep syndrome, which is associated with gut toxicity [60] and the use of H₂ histamine receptor antagonists [47,61]. Although much less potent than endotoxin, the cell wall material of gram-positive bacteria is capable of inducing tumor necrosis factor (TNF) and other cytokines [62], and the sudden appearance in the bloodstream of overwhelming numbers of bacteria from multiple sites of mucosal damage may provide the mechanism for inducing shock. Antacids such as sucralfate have a lesser impact on gastric pH [63] and appear useful in minimizing oromucositis [64], but, like other aluminium-based antacids, may alter the absorption of fluoroquinolones, especially when administered at the same time [65–67].

Effect of chemotherapy and irradiation on the intestinal tract. The alimentary tract was shown to be the major reservoir for gram-negative rods as a result of colonization with endogenous bacteria, for example, *E. coli* or exogenous species such as *Klebsiella pneumoniae* and *P. aeruginosa*, which had been originally acquired from the environment [68–70]. The ecology of the bowel flora will be altered markedly by diarrhea induced by treatment with certain cytostatics, for example, cytarabine [71], graft-versus-host disease [72], and total body irradiation [73]. Gut permeability also markedly increases following conditioning therapy for bone marrow transplant and viral infection of the gut [74]. Agents used either for the treatment of neoplasm or supportive care may even exert an influence on the gut and oral flora, either alone or in combination. Some cytostatics have been shown to have antibacterial activity and even to enhance the effects of antimicrobial agents [75–80], and the antifungal, miconazole, is also inhibitory to gram-positive bacteria [81]. Parenteral nutrition leads to a low amount of fiber, which, together with a reduced microbial biomass, results in dilute feces, which will affect gut motility and also allow some antimicrobial agents that normally barely affect the anaerobic microflora because they are inactivated by feces, for example, aztreonam and imipenem [82,83], to destroy what remains of colonization resistance. Even if the ‘anaerobic wallpaper’ were to remain intact, the gut would still not function normally and, without a protected environment and selective oral antimicrobial prophylaxis, the patient is especially vulnerable to acquiring nosocomial pathogens.

Intervention steps for chemoprophylaxis

Infections in neutropenic patients derive from two principal sources, the endogenous flora and the exogenous or environmental flora. The resident commensal

flora found on the skin and mucosal surfaces contains potential pathogens, but organisms can also be acquired exogenously by ingestion of contaminated fluids and food, or through direct contact. Such organisms may prove transient, being unable to establish a foothold and hence colonize. Their opportunity to infect is therefore limited unless there is repeated exposure and prolonged transit and a ready-made portal of entry is available, such as an ulcer or abrasion or direct access via a catheter. Under conditions of reverse barrier isolation, high-efficiency particulate air [HEPA] filtered air, and a diet of low microbial content, chemoprophylaxis is directed at the potential pathogens that have become resident on the skin, the airways, and in the alimentary tract.

Chemoprophylaxis of bacterial infection in patients with cancer

Antimicrobial agents were first given to cancer patients and those with hematological malignancy in the early 1970s to try to reduce the infectious complications arising during neutropenia [68,69,84,85]. Nonabsorbable regimens, particularly gentamicin plus vancomycin plus nystatin (GVN), were employed to sterilize the gut [25,86]), but this proved futile, the compliance was fragile, and the risk of selecting resistant bacteria was actually higher. This was explained by impairment of the putative colonization resistance brought about by the antibiotics destroying the anaerobic flora of the alimentary tract, such that much lower doses of allochthonous gram-negative organisms were required for colonization than was seen under normal conditions [17]. It therefore seemed more appropriate to aim for partial or selective decontamination rather than to attempt complete sterilization of the body sites.

Selective oral antimicrobial prophylaxis

Co-trimoxazole. Partial or selective decontamination can be achieved with non-absorbable agents, such as framycetin or neomycin together with either colistin (polymyxin E) or polymyxin B plus one of the polyene antifungals, nystatin or amphotericin B [87], but these regimens have to a large extent been superseded by absorbable agents, particularly co-trimoxazole alone or as a hybrid with non-absorbable agents to provide systemic antimicrobial concentrations while effecting local decontamination of the gut. Co-trimoxazole seems the ideal agent because it prevents infection with *Pneumocystis carinii*, is effective against a wide range of respiratory pathogens, including *Streptococcus pneumoniae* and *Haemophilus influenzae*, and offers protection against with *S. aureus* and enteric gram-negative rods [88]. Placebo-controlled trials, albeit with small numbers of patients, indicated a clear benefit for co-trimoxazole as selective prophylaxis (figure 2) [89–97], as did comparative studies [84,98–105]. However, the risk of resistance emerging, causing bacteremia, was apparent [89,106], as was co-trimoxazole's lack of activity against *P. aeruginosa*, necessitating the addition of colistin [104].

Co-trimoxazole has been used at various doses, but 960 mg twice daily together with 100 mg colistin four times a day appears the optimum. Generally, the drug is

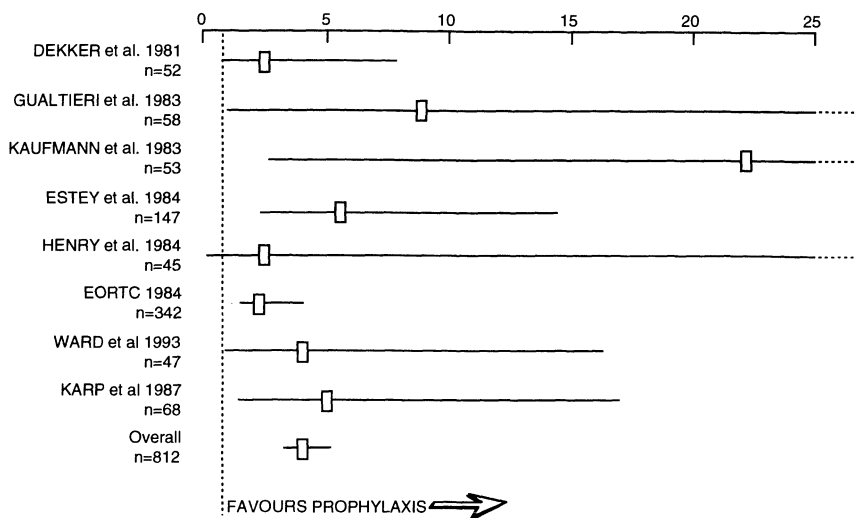


Figure 2. The impact of selective oral antimicrobial prophylaxis in the prevention of gram-negative infection. The boxes represent the odds ratios and the lines represent the 95 percent confidence intervals. An odds ratio that exceeds and is significantly different from unity indicates a result that favors prophylaxis, although it need not be clinically important. This depends, among other things, on the prevalence of infection, the presence and magnitude of prognostic risk factors, and the attributable morbidity and mortality. All authors employed co-trimoxazole at 960, 1920, or 2,880 mg/day, except Karp et al., who employed norfloxacin 800 mg/day. Overall, prophylaxis prevents gram-negative infection, although the odds ratios vary widely from as little as 2.6 to as much as 22.3. Clearly, prophylaxis would be of significant benefit if a patient is 22 times less likely to develop infection but much less attractive if there is only a twofold benefit, unless the cost of infection was high, for example, associated with a high mortality, or if the regimen is inexpensive, well tolerated, and not prone to induce or select resistance.

well tolerated but induces skin rash in 2–5 percent of patients. This incidence rises to 15 percent when patients are receiving remission induction therapy, particularly when cytarabine is included [107]. Moreover, the onset of skin rash frequently coincides with allergy to allopurinol and cytarabine, as well as oral mucositis, nausea, and diarrhea, for example, after remission-induction of acute myeloid leukemia. This leads to less compliance and interruption if not total discontinuation of prophylaxis. Co-trimoxazole has also been associated with delaying hematopoiesis in bone marrow transplant recipients [108].

Fluoroquinolones. The introduction of the newer fluoroquinolones, norfloxacin [109] ciprofloxacin [110], ofloxacin [111], and pefloxacin [112], further expanded the range of agents available for prophylaxis. Moreover, compliance is better and side effects are lower with these drugs than with co-trimoxazole, and fluoroquinolones do not seem to have any deleterious effect on hematopoiesis [113]. Their spectrum of activity includes the most common causes of infection due to gram-negative bacilli, *S. aureus*, and many of the coagulase-negative staphylococci [114,115]. The viridans streptococci and enterococci are only marginally susceptible, if at all.

Although only one of the many prophylactic trials with the fluoroquinolones has been placebo controlled (figure 2) [109], it is clear that they all provide better protection against infection due to gram-negative bacilli than does co-trimoxazole [111,116–125]. However, of the drugs studied so far, only ciprofloxacin offers the most complete protection against gram-negative bacilli, including *P. aeruginosa* [120–122,124].

Concerns about fluoroquinolones for prophylaxis. The use of fluoroquinolones for prevention raises several important concerns, not the least being that by employing them for prophylaxis effectively precludes them from being used as therapy in the same patient population. They also select for multiply resistant gram-positive cocci, including staphylococci and enterococci [5,8,121,126–128], and also predispose certain patients to viridans streptococcal bacteremia, probably by giving a selective advantage to these organisms [60], although severe mucositis induced by anthracycline conditioning therapy for bone marrow transplantation also plays a role [45], as does cytostatic chemotherapy with cytarabine [129]. However, it should be remembered that bacteremia due to viridans streptococci was first observed in patients given co-trimoxazole and that most of the strains involved were resistant to the drug [130,131]. Bacteremia might occur as a result of the plasma levels of the quinolones being lower than the rather high minimal inhibitory concentration (MIC) for gram-positive cocci such as viridans streptococci [114], making it more likely that they will be detected in blood cultures of patients receiving these drugs.

There are also doubts about the bioavailability of the fluoroquinolones, since their absorption can be impaired by antacids, cations, and milk [65–67,132–135]. Moreover, the C_{\max} serum levels of both ciprofloxacin and ofloxacin decrease from approximately 4 mg/l to 2 mg/l and from 6 mg/ml to 5 mg/l during neutropenia, when mucosal damage is most apparent [136,137], levels that are lower than the MIC_{median} for ‘viridans’ streptococci [138]. Fluoroquinolones have been developed with an enhanced spectrum of activity against gram-positive cocci, but none is likely to be available for clinical use for some time [139–145].

Specific indications for decontamination

There may be indications to continue selective oral antimicrobial prophylaxis with a regimen of colistin combined with co-trimoxazole in neutropenic patients during systemic empiric therapy with certain single agents, such as ceftazidime and imipenem. Patients colonized with *Enterobacter cloacae* are at risk of bacteremia and rapidly fulminant sepsis if treated with ceftazidime alone since there is a risk of both inducing resistance as a result of de-repression of a chromosomally mediated gene for β -lactamase, giving selective advantage to these bacteria [146]. Similarly, patients treated with imipenem may be at risk when colonized with *S. maltophilia* [147]. Persistent colonization of the alimentary tract with *P. aeruginosa*, which occurs much less frequently nowadays, may also be an indication to administer locally active agents such as the polymyxins.

Chemoprophylaxis of skin infections

Specific chemoprophylaxis for skin infections is rarely practiced since it is not thought necessary. Besides, most antimicrobials agents will find their way to the skin surface in the sweat. If necessary, colonization with gram-negative bacilli can be suppressed by applying povidone iodine or chlorhexidine, whilst mupirocin ointment is very effective against nasal carriage and colonization with *S. aureus* [148]. Predictably, this antibiotic will induce selection of resistance among the resident coagulase-negative staphylococci and therefore should be used with caution, especially because interspecies exchange of resistance plasmids occurs among the staphylococci [149].

A single injection of teicoplanin has been shown to reduce the incidence of catheter-related infections when the device was inserted during profound neutropenia [150]. This approach is also supported in an animal model [151], although careful insertion before chemotherapy to ensure the minimum of tissue trauma is the most important factor in preventing clinical infection. Maintaining line patency using heparin blocks was once widespread, but it appears that it is the preservative that produces suppression of colonization rather than the heparin [152].

Since colonization of the catheter is the primary factor that leads to both bacteremia and tissue-interface infection, much work is being directed towards prevention by designing nonstick polymers and modifying their surfaces [153,154]; incorporating antimicrobial agents into the plastic, for example, benzalkonium chloride [155,156]; iodine [157] and antibiotics, for example, fusidic acid [158,159]. Impregnating the cuffs of tunneled catheters with silver reduced tissue infections in one study [160] but not in another [161]. Flushing the device regularly with sodium metabisulfite [152,162], aspirin, and other nonsteroidal antiinflammatory drugs, for example, ibuprofen [163,164], has been shown to reduce colonization in vitro, as has the application of a low electric current [165] and exposure to cations [166]. Novel and ingenious though these approaches are, it remains to be seen whether any will prove beneficial in practice.

Chemoprophylaxis of fungal infection

Candida species and *Aspergillus* species are the most frequent fungal pathogens involved in infection in neutropenic patients. Although it is common practice and quite correct to refer to them both as fungi, it is actually more appropriate to keep them separate because of the differences in biology, epidemiology, and natural history of infection [167]. *Candida* spp. are able to cause both superficial and deep-seated infection at any stage, while *Aspergillus* spp. infections occur mainly in the air-ways and only disseminate at a terminal stage. *Candida* spp. are common residents of the oral cavity and alimentary tract and, occasionally, the skin, whereas molds are not. *Aspergillus* is transmitted in the air by conidiospores, which have to germinate before initiating infection, whereas *Candida* spp. exists primarily as blastospores, which are actively growing, and only some species, for example, *C.*

albicans, produce filaments as hyphae or pseudohyphae. Moreover, there are few distinguishing features that mark out those species among commensal candida that might be pathogenic, with the possible exception of *Candida tropicalis*, which has a relatively high likelihood of proceeding from colonization to infection [168,169].

In contrast, finding evidence of *Aspergillus* spp. in the nasal cavity, sinuses, or bronchi is abnormal and has been found predictive of infection [170–174], although these findings will vary with the spore burden of the air and may only reflect outbreaks. Besides, *Aspergillus flavus* is more commonly involved in sinusitis than invasive pulmonary aspergillosis, which is invariably caused by *Aspergillus fumigatus* and does not predict invasive mycosis [175]. Finally, most *Candida* species are readily accessible to the polyenes and the imidazole and triazole antifungal agents, to which only a minority of species are resistant, whereas *Aspergillus* spp. is only susceptible to itraconazole [176–178]. These limitations, therefore, make the design of a broad-spectrum prophylactic regimen elusive, if not impossible.

Chemoprophylaxis against candidiasis

Nonabsorbable polyenes. Nystatin and amphotericin B have been widely used to provide oral prophylaxis against candidosis, but despite their being highly active in vitro with MICs within the therapeutic range, there are serious doubts about their value as oral prophylactic agents. The rationale behind giving them derives from two separate sources. Firstly, there is a tendency for overgrowth of *Candida* spp. to occur during treatment with antibacterial agents that undermine the colonization resistance [36,179], and even with some agents, for instance, co-trimoxazole, that apparently do not [37]. Secondly, it is reasoned that lowering or suppressing colonization in any case should lessen the risk of infection, since this is invariably preceded by colonization [167–169]. The assumption underlying prophylaxis with nonabsorbable polyenes is therefore that the risk of infection can be reduced by suppressing or reducing colonization. For nystatin to make a significant impact on *Candida* spp. colonization in both the oral cavity and gut, at least 4.5 MU/day must be given [179,180], which makes compliance difficult since the drug is distinctly unpalatable. Still, infections can occur despite as much as 30 MU/day of nystatin [167]. Its close chemical relative, amphotericin B, is more effective in suppressing colonization, provided at least 1.5–2 g/day is given [167,179,181], although the reduction in colonization observed is approximately 30 percent for 600 mg, 3,000 mg, and 6,000 mg, indicating that once a certain threshold is reached there is little profit gained from giving more drug [182].

This drug also tastes unpleasant, especially in suspension form, and is poorly tolerated by patients who have concomitant oromucositis, again raising doubts about compliance. Moreover, given this way neither polyene will offer any benefit against *Aspergillus* spp. since there is no likelihood of drug contact with the organism. Also, there are marked regional differences in the experience and use of polyenes, with nystatin being mainly confined to North America, whereas the converse is true of amphotericin B, which is not licensed in the United States for oral administration.

Finally, there have been no placebo-controlled trials recruiting sufficient numbers of patients to show a significant difference with a power exceeding 80 percent.

Topical clotrimazole and miconazole. Clotrimazole troches are available in North America but not elsewhere and appear to prevent oral candidosis without having any marked effect on colonization [183]. Similar observations have been made for miconazole, which suggests that these drugs can prevent invasion at doses too low to suppress colonization. However, there have been no adequate controlled trails of either of these agents, and neither appear any more effective than the polyenes, probably for the same reason that none of these agents provides systemic levels.

Ketoconazole. When first introduced, ketoconazole seemed to offer the ideal characteristics for an antifungal agent against candidiasis. The drug is active in vitro and is absorbable, so is able to deliver effective concentrations both systemically and locally. Not surprisingly, most prophylactic studies have been conducted with this drug [167,184–208]. The drug is effective only against superficial candidiasis of the oral cavity, and possibly the esophagus, at a dose of 400–600 mg/day, which is two to three times more than initially anticipated, partly because absorption is variable and is impaired by H₂ receptor antagonists. While treatment with ketoconazole reduces colonization with *C. albicans*, there is an increase in fecal overgrowth with *Candida (Torulopsis) glabrata* [188,191]. Moreover, only one of the four placebo-controlled studies indicated a significant impact on proven systemic candidiasis (figure 3), although there was no difference in fungal infections overall [185]. Ketoconazole also interacts with P₄₅₀ cytochrome oxidase enzymes, causing the release of cyclosporin, with the consequent risk of nephrotoxicity. The drug is therefore not recommended for use in allogeneic transplantation. So, although compliance is better than that obtained with polyenes, there does not seem to be a place for this drug in the prevention of candidiasis.

Fluconazole. The introduction of fluconazole, a triazole, made it possible to properly consider the issue of prophylaxis against *Candida* spp. infections because the drug has the right characteristics, namely, excellent activity and flexible dosing, with the oral preparation achieving similar bioavailability as the parenteral form. The drug is effective for the prevention of oral candidiasis at 50 mg/day, but while oral colonization is diminished, amphotericin B is more effective in suppressing fecal carriage [209,210].

Two placebo-controlled studies in adults, one in bone marrow transplant recipients and the other in patients undergoing chemotherapy for acute leukemia, showed the benefit of 400 mg/day fluconazole in reducing both superficial and systemic candidiasis infections (figure 3) but not other fungal infections [211,212]. The incidence of superficial candidiasis was lowered from 15 percent to 3 percent among those given the placebo to 6–8 percent after fluconazole prophylaxis, and systemic candidiasis was reduced from 5–14 percent to 1–2 percent. By the end of prophylaxis, yeasts, mainly *C. albicans*, could still be recovered from the body sites of two-thirds of patients assigned to placebo compared with 9–30 percent given fluconazole. A more detailed account of the impact of fluconazole on colonization

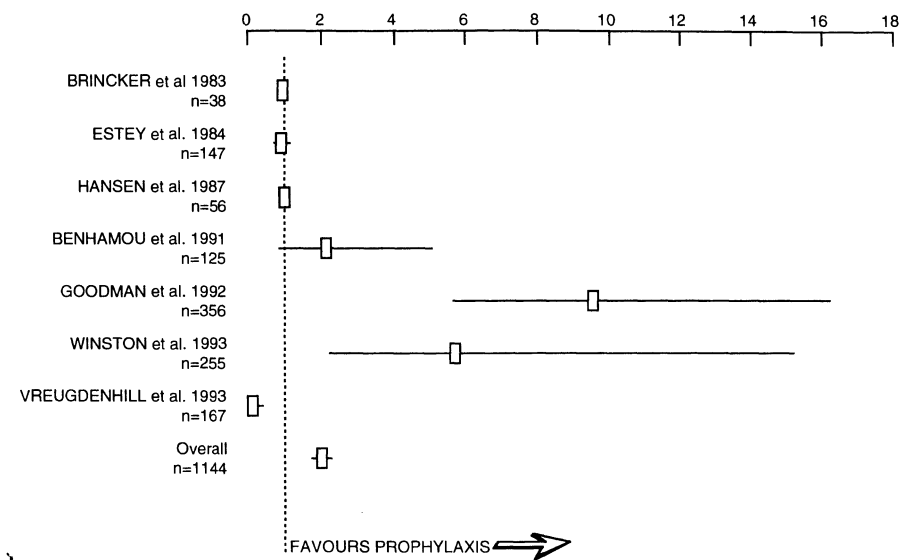


Figure 3. The impact of azole antifungals on the development of systemic candidiasis. The boxes represent the odds ratios and the lines represent the 95 percent confidence intervals. An odds ratio that exceeds and is significantly different from unity indicates a result that favors prophylaxis, although it need not be clinically important. This depends, among other things, on the prevalence of infection, the presence and magnitude of prognostic risk factors, and the attributable morbidity and mortality. Brinkner et al., Estey et al., and Hansen et al., placebo versus 400 mg ketoconazole; Benhamou et al., placebo versus 100, 200, 300, or 400 mg ketoconazole; Goodman et al. and Winston et al., placebo versus fluconazole 400 mg; and Vreugdenhill et al., oral amphotericin B plus placebo versus itraconazole 400 mg. Unlike fluconazole, neither ketoconazole nor itraconazole appeared to have any effect on the development of disseminated candidiasis. While the odds ratio favoring fluconazole prophylaxis suggests that the risk of infection might be reduced by a factor of 6–10, the wide confidence intervals reflect the low rate of infection and demonstrate that the benefit could be either much lower or much higher than observed in these studies, depending upon the prevalence.

in a subset of 23 patients showed that there had been a marked reduction in colonization by the second week of treatment, whereas the number of colonized individuals increased to two thirds of the 23 given the placebo [213]. The carriage of *C. albicans* in the oropharynx was reduced from half to less than 10 percent, *C. glabrata* was recovered from the perianal region in approximately one third of patients in both groups, while *Candida krusei* was found exclusively in patients given fluconazole. Thus fluconazole achieved a rapid reduction of colonization of the alimentary tract, thereby eliminating the major reservoir for infection with the yeast *C. albicans* during the critical period of neutropenia.

Concerns about the use of fluconazole. Fluconazole, however, did not lower the perceived need for empirical intravenous amphotericin B in either study, which was similar for the placebo and fluconazole groups, 56–74 percent and 64–66 percent, nor was survival improved. Moreover, the results of a recent study of the GIMEMA (Gruppo Italiano Malattie Ematologiche Maligne dell 'Adulto) group involving 820

adults undergoing treatment for leukemia suggest that a similar reduction in candidiasis can be achieved with either the lower dose of 150 mg/day fluconazole or 2 g/day oral amphotericin B [214]. Compliance was 20 percent higher among patients treated with fluconazole and side effects were fewer. These results call into question the need for 400 mg/day fluconazole when, at under half the dose, similar efficacy was achieved and survival rates were alike, yet three times fewer patients were thought to require empirical intravenous amphotericin B in the Italian study than was found to be the case in the North American studies. The patients involved in these studies were also comparable in terms of age, neutropenia, and risk of mycosis, suggesting a major divergence in perception and practice.

Like the polyenes, fluconazole offers no protection against aspergillosis and may even lead to the development of superinfection by this fungus [215]. Fluconazole also selects natively resistant non-*albicans* *Candida* spp., including *C. glabrata* and *C. krusei*, although concomitant prophylaxis with fluoroquinolones may also play a role [216]. This has aroused some concern since if the use of fluconazole as prophylaxis becomes widespread, primary and breakthrough infection with these organisms might increase [217]. There is also anxiety that resistance might emerge among *C. albicans*, albeit slowly, just as has been observed in patients with AIDS following long-term treatment for oral candidiasis [218–221]. However, neutropenic patients are unlikely to require such prolonged treatment and do not generally have persistent or recurring oral candidiasis. Nevertheless, fluconazole should only be given prophylactically to those most at risk of candidiasis. These are most likely patients who are persistently colonized at a single site or who show colonization at multiple sites [168,169], or who have in excess of 400 colony-forming units (CFU)/ml saliva [222], since candidiasis rarely occurs in patients who are not carriers of *Candida* spp. It is also not at all clear when the drug should be given and, just as important, when it should be stopped. Furthermore, if persistent fever develops despite broad-spectrum antibacterial therapy and fluconazole, should empiric intravenous amphotericin B be given and, if so, when [223]?

Chemoprophylaxis against aspergillosis

Amphotericin B aerosol intranasal spray. Recognizing that *Aspergillus* spp. are airborne, some workers have experimented with aerosols of 5–20 mg amphotericin B delivered over 15 minutes once or twice a day [224–228]. While this seems a reasonable approach to lowering the risk of aspergillosis by exposing the upper airways to amphotericin B, there have been no adequate placebo-controlled trials to demonstrate efficacy. Such trials are vital in this context since air quality fluctuates markedly with the seasons, and building activities are associated with high spore counts. Therefore, it is difficult to prove that a downward trend in infection over a prolonged period of time is due to a particular intervention rather than simply lower levels of spore contamination.

Broad-spectrum chemoprophylaxis against fungi

Intravenous amphotericin B. Amphotericin B has been given prophylactically to consecutive allogeneic bone marrow recipients at the low dose of 20 mg/day or

0.15–0.25 mg/kg/day from the first day of conditioning therapy until the day before transplant and has been given on alternate days thereafter [229]. These patients had all been treated in laminar flow rooms, as had a cohort of 48 patients treated during the 16 months preceding the prophylactic study. A further group of 28 patients treated before the implementation of laminar flow was included for comparing the impact of controlled air supply. All these patients were treated empirically with up to 1 mg/kg/day intravenous amphotericin B when fungal infection was suspected, and regimens for conditioning and prophylaxis against graft-versus-host disease bacteria, viruses, and *P. carinii* remained essentially the same throughout the 5 year period. The cumulative incidence of aspergillosis was 9 percent of the 110 patients given low-dose amphotericin B prophylactically, 23 percent for the cohort managed under laminar flow, and 25 percent for the group nursed in ambient air. A similar trend was observed for deaths occurring before 120 days contributed to by *Aspergillus* spp. infection, which had affected 6 percent, 13 percent, and 18 percent, respectively. However, it is difficult to evaluate these results since the use of historical controls is fraught with difficulties, especially where *Aspergillus* spp. is concerned. Moreover, despite taking care to accommodate confounding factors, several key factors were overlooked, including the use of corticosteroids, the type of empirical antibacterial therapy, and the incidence of aerosolized pentamidine, which is known to have antifungal activity [230]. In contrast, a placebo-controlled trial of low-dose amphotericin B (0.1 mg/kg/day) has been conducted in 182 autologous bone marrow transplant recipients [231]. The number of patients colonized and the degree of colonization were significantly reduced, but there was no difference in oral candidiasis. Moreover, similar numbers of patients were given the higher doses of amphotericin B (0.6 mg/kg/day) at similar rates. However, *Candida* spp. were isolated from sterile sites (blood, urine) of fewer patients given amphotericin B prophylactically. Nevertheless, the authors decided that the costs, including infusion-related complications, did not justify this approach. The nephrotoxic potential of amphotericin B also precludes its use when cyclosporin is being given to prevent graft-versus-host disease in allogeneic bone marrow transplantation. However, the benefit probably outweighs any risk when intravenous amphotericin B is given for secondary prophylaxis for patients whose lungs are not yet healed following aspergillosis but who risk becoming neutropenic as a result of chemotherapy or bone marrow transplantation.

The broad spectrum of amphotericin B given intravenously at 0.5 mg/kg three times a week did not offer any advantage over 400 mg/day fluconazole in a smaller series of neutropenic patients [186]. Proven mycosis developed in 3 of the 36 evaluable patients given amphotericin B and in 2 of the 41 given the triazole, probable or possible mycosis developed in eight and five cases, respectively, whilst four patients had to discontinue the polyene due to toxicity, compared with a single patient who had to stop the triazole for the same reason. Thus prophylactic intravenous amphotericin B did not fulfil the expectations of offering effective prophylaxis, and the related toxicity was discouraging, even at these low doses. There might be some advantage in preventing aspergillosis, but there are as yet no real data. The lipid formulations of this drug might have something to offer since

much higher doses are tolerated, but their costs are prohibitive and likely to remain so [232].

Itraconazole. The principal advantage of itraconazole over fluconazole is its activity against *Aspergillus* spp. [233], and it should therefore prove useful for broad-spectrum prophylaxis, but as yet there have been no placebo-controlled studies of similar size to those conducted for fluconazole. Moreover, experience to date has been limited and disappointing for many reasons. Itraconazole can only be given orally, and absorption appears to be erratic, especially during neutropenia [234]. Although some uncontrolled studies suggest benefit [183], a recent double-blind trial of 400 mg/day together with oral amphotericin B failed to confirm this for either candidiasis or aspergillosis [235]. There have been no controlled trials comparing itraconazole with fluconazole, and the optimum dose has yet to be established. Nevertheless, 200–400 mg/day itraconazole may prove effective as secondary prophylaxis for pulmonary aspergillosis [236,237]. Itraconazole also might offer some protection to bone marrow transplant recipients [183], even although interaction with cyclosporin has occurred with 200 mg/day [238], although others have not noted any nephrotoxicity with the same dosage [239]. Nevertheless, itraconazole can influence cyclosporin metabolism, requiring a reduction of up to 50 percent of the normal dosage [240], so it is advisable to monitor levels of both drugs to ensure adequate absorption of the triazole and safe levels of cyclosporin, especially if 400 mg or higher doses are being used [183,240].

Hybrid prophylaxis. To prevent aspergillosis, it might be better to decontaminate the airways locally using aerosolized amphotericin B and to provide systemic concentrations by given itraconazole. Such a combination of 10 mg/day amphotericin B and 200 mg/day itraconazole has been evaluated for prophylaxis of invasive aspergillosis in 164 patients with hematological malignancies over for a period of 2 years [241]. For comparison, the authors used a historical control group of 290 similar patients admitted 3 years before the study. Against a background of constant aerial contamination, the incidence of proven invasive aspergillosis and the attributable mortality rate fell from 12 to none and from 8 to none, respectively. Probable aspergillosis affected 22 patients in the control group and 8 in the study group, with corresponding mortality rates of 3 and 2, respectively.

Problems with prophylaxis

Lack of impact on mortality and remission rates

Despite the variety of studies undertaken, antibacterial and antimycotic prophylactics have had no measurable impact on overall survival; mortality attributable to target organisms, such as gram-negative bacilli, *Candida* spp., or *Aspergillus* spp.; or remission rates [242,243]. Moreover, the fall in mortality due to gram-negative sepsis probably owes more to the prompt institution of broad-spectrum therapy

empirically as soon as neutropenic patients become febrile and more effective treatment of the underlying disease. Indeed, the mortality attributed to gram-negative sepsis remains around 10–15 percent, whether or not prophylaxis had been employed. However, only 10 percent or so of patients develop this type of infection so that the global mortality is 1–2 percent [244,245]. Similarly, although there is considerable concern that systemic mycosis is increasing, there are few reliable data on the actual prevalence partly because diagnosis is usually made postmortem [246], and autopsy rates are low, particularly in Europe [183]. The most recent figures for disseminated candidiasis have to be gleaned from prophylactic studies mentioned earlier, which suggest a prevalence of less than 10 percent despite prophylaxis, and approximately twice this figure when none is used. The prevalence of invasive pulmonary aspergillosis is even more difficult to ascertain, since it depends upon local factors, including seasonal variation and building activity [247]. Finally, prophylaxis can actually diminish the quality of life because of side effects and the effort often needed to comply.

Conflicts of interest and differences in perceptions and practice

The lack of oral amphotericin B in North America has already been alluded to in explaining why nystatin was chosen for prophylaxis. Similarly, the dose of fluconazole is higher than used in Europe, and empirical intravenous amphotericin B is used more frequently and sooner. Conversely, antibiotic resistance is seen in North America as a risk that should be avoided at all costs [248], unless clearly outweighed by the benefit. It is conceded that the use of the fluoroquinolones for selective oral antimicrobial prophylaxis during neutropenia is likely to lead to emergent resistance, which has already been seen among staphylococci [249] and is now becoming apparent among *E. coli* [250]. Similar problems should be anticipated if fluconazole becomes widely and indiscriminately used, especially at the low dose of 50 mg/day.

The flexibility afforded by the parenteral and oral formulations of fluoroquinolones and fluconazole is one of their most attractive features, since it allows patients to leave the hospital while continuing therapy, but their use in prophylaxis precludes their employment for therapy. The loss of this facility may therefore have serious cost consequences, since, should a patient require therapy, alternative agents will have to be employed that will inevitably necessitate admission into the hospital.

Bioavailability

The bioavailability of oral drugs needs to be confirmed for any drug proposed for prophylaxis, since experience has shown that even when absorption is normally good, it may be impaired during chemotherapy, the neutropenia that follows, and when mucosal damage and gut toxicity are at their height. Moreover, the need for avoiding concurrent medications, such as antacids and H₂ histamine receptor antagonists, should be established. Decontaminating the oral cavity is difficult, even when drugs are excreted into saliva, since its production will be impaired by irradiation and chemotherapy. Moreover, few drugs bind to the mucosa, which poses

the problem of how to maintain adequate drug concentrations. Lozenges, gels, pastes, troches, and continuous gargling have all been tried with varying degrees of success, but recently antifungals have been successfully incorporated into chewing gum and seem to offer a better solution [251]. Drug availability also affects the gut, since feces can inactivate or bind antibiotics, including the quinolones and polyenes [29], so that their effective concentrations are diminished, which will increase the risk of emergent resistance. Ensuring adequate concentrations locally and systemically should therefore be considered part of any investigation of prophylaxis.

Selection of natively resistant microorganisms

The application of selective pressure on natively resistant microorganisms is one of the inevitable consequences of employing any antimicrobial agent for prophylaxis for decontaminating body sites and providing adequate systemic concentrations. Thus, oral 'viridans' streptococci are selected by co-trimoxazole [61,129,252] and more so by fluoroquinolones [45,47,59,60,253–259]. Similarly, *S. mucilaginosus*, *Bacillus* spp., lactobacilli, enterococci, and coagulase-negative staphylococci are easily selected by exposure to fluoroquinolones because of their marginally susceptibility, as are gram-negative bacteria, such as *S. maltophilia*; *C. krusei*, and *C. glabrata*, will also have a selective advantage when fluconazole is employed. Prophylaxis therefore shapes the patterns of infection that will be encountered, sometimes in unpredictable ways, but more often in directions that can be anticipated by knowledge of the dominant flora of the neutropenic population.

Changes in the epidemiology of infection

Many changes in the patterns of infection have been noted over the last decade. The gram-negative bacilli have been replaced by the more benign gram-positive cocci in many centers and seems to have been due to the use of intravenous catheters and antimicrobial prophylaxis of any form. However, similar changes have been noted in countries where neither catheters nor prophylaxis are employed [58,260,261]. Moreover, some centers report only modest shifts over the last two decades, with gram-negative bacilli still accounting for up to 50 percent of bacteremic isolates [262]. As yet, those centers reporting an increase in *C. krusei* infections after introducing fluconazole for prophylaxis have been unfortunate to have suffered an outbreak. Nevertheless, a gradual shift away from *C. albicans* towards *C. krusei*, *C. glabrata*, and some of the more unusual *Candida* species, such as *Candida inconspicua*, *Candida norvegensis*, *Candida famata*, *Candida humicola* and *Candida lambica*, has already been observed [263]. It is therefore difficult for any particular center to determine a role for prophylaxis unless it knows and continually updates its own infectious epidemiology.

Lack of impact of prophylaxis on the occurrence of fever

Despite antibacterial prophylaxis, only a minority of neutropenic patients progress to bone marrow recovery without being given broad-spectrum antimicrobials, so

selective oral antimicrobial prophylaxis is usually only given for a relatively short period of time, for example, a median of about 2 weeks after starting chemotherapy [117]. Thus, the principal advantage of this approach, namely, the preservation of colonization resistance to reduce the risk of acquiring nosocomial organisms, is only seen in a minority of cases since it is likely to be impaired whenever parenteral antibiotics are given that are known to be deleterious to the ecology of the gut and, to a lesser extent, the upper respiratory tract. The combined effects of antibacterial and antifungal prophylaxis have rarely been investigated, but there appears to be a 20–30 percent lower incidence of fever when 150 mg/day fluconazole is given routinely with fluoroquinolones, suggesting that candidiasis, albeit subclinical, does play a role in febrile neutropenia [120,124]. However, the combination of fluoroquinolones and fluconazole might lead to greater selection of *C. krusei* [223].

Impact of prophylaxis on empirical regimens

It is a common experience that, irrespective of whether or not prophylaxis is used, the usage of antimicrobial agents remains the same, although treatment is delayed by a few days. Consequently, the stay in hospital is just as long. Oral prophylaxis with one of the fluoroquinolones and probably co-trimoxazole actually comprises pre-emptive therapy, since the drugs are given at therapeutic doses [243]. Decontamination of the digestive tract then becomes of lesser importance, given that systemic concentrations are adequate for treating incipient infection due to susceptible organisms and arresting their dissemination. The issue of appropriate empirical therapy, given the use of selective oral antimicrobial prophylaxis, particularly with quinolones, also needs to be addressed since infection due to gram-negative bacteria is highly unlikely if ciprofloxacin is given, whereas bacteremia due to gram-positive cocci is more likely. Prophylaxis actually buys time to attempt diagnosing the cause of fever so that empiric treatment can be delayed. Moreover, provided the patient can still tolerate oral medication, it is actually more logical to extend the spectrum of activity of therapy with a specific agent such as penicillin or a glycopeptide [118,264], provided cultures indicate this or there is a very high likelihood of gram-positive infection.

As mentioned earlier, prophylaxis with fluconazole has not altered the need for empiric antifungal therapy with amphotericin B in one or another formulation, which actually appears more a matter of perception, policy, and practice. Nevertheless, some patients are at risk of co-infection or superinfection with *A. fumigatus*, so this issue requires careful investigation [215]. In any event, pulmonary infiltrates developing during prophylaxis should warn of this possibility, and it may be prudent to adopt the current guidelines for instituting intravenous amphotericin B.

Prophylaxis equals pre-emptive or early therapy

In many ways, the more usual practice of replacing oral prophylaxis with empirical therapy with β -lactams alone or in combination with an aminoglycoside simply

represents a switch from oral to parenteral therapy since the prophylactic regimen is given at therapeutic doses, and fever often coincides with oral and gut toxicity, which impairs both compliance and absorption. It can be reasonably argued that since that the majority of these patients will become febrile anyway, it might be more relevant to omit prophylaxis altogether and administer therapy that is effective against gram-negative rods pre-emptively as soon as chemotherapy ends or when profound neutropenia begins. This seems feasible for patients who are also given growth factors to encourage rapid bone marrow recovery [265]. Similar considerations apply to the use of triazoles for prophylaxis. Indeed, when given together with cotrimoxazole plus colistin or a fluoroquinolone, the need to treat empirically becomes even less compelling. Rather, drug levels should be monitored and, if absorption is inadequate, the parenteral formulations should be used. The occurrence of fever and other signs of infection should also prompt attempts at diagnosis.

Therefore, when a patient develops fever, it is probably more logical to continue treatment with the oral regimen while attempting to diagnose the cause of infection rather than simply replace 'prophylaxis' with a broad-spectrum regimen designed to cover the same pathogens. Both co-trimoxazole and the fluoroquinolones can be given parenterally whenever necessary, and so specific agents can be added to treat suspected viral and fungal infection. Thereafter, treatment would only be changed if and when there is a clear clinical or microbiological indication to do so. Fluctuations in the temperature chart would not be an indication to change therapy since fever is not a reliable index of infection [244]. Rather, appropriate therapy should be given if the offending pathogen proves resistant to the oral regimen. However, since gram-positive cocci now predominate as pathogens, it might be preferable to consider giving a carbapenem or a so-called fourth-generation cephalosporin such as cefepime, either immediately after neutropenia ensues or earlier to cover both these organisms and gram-negative bacilli, rather than wait for fever to develop. In either case, further antimicrobial interventions would then be necessary only when the primary infection is refractory to treatment or when a new infection is clinically manifest or diagnosed microbiologically. With strict guidelines for the initiation and discontinuation of treatment, the pre-emptive approach to therapy should help restrict the antibiotic use and lead to better overall management of infection.

Selection of patients

Detecting colonization. Several studies have indicated that surveillance cultures can allow patients to be identified who are unlikely to be at risk of infection because they are not colonized. Thus, failure to detect *S. aureus* in the anterior nares, axillae, and groin or perineum and the absence of gram-negative bacilli [266] and yeasts in the oral cavity or stools [166,167,266] could be used to decline giving antibacterial prophylaxis with a fluoroquinolone or co-trimoxazole plus colistin and antimycotic prophylaxis with amphotericin B or fluconazole, respectively. This would reduce the number of patients needing prophylaxis by 50–70 percent. Such surveillance would have to be done regularly once or twice a week when a

definition of colonization would be applied on each occasion. Once patients are receiving broad-spectrum antimicrobial therapy, whether empirically or pre-emptively, surveillance cultures become of less use but should be continued in order to detect resistant gram-negative bacilli, particularly *E. cloacae*, and nonfermentative bacilli, including *S. maltophilia* and non-albicans *Candida* spp.

Defining risk groups. It has been fashionable for some time to apply sophisticated statistical techniques to identify risk factors for various infections, but there have been almost no attempts to apply them prospectively. Some of the factors are common sense and even banal, such as oral colonization with viridans streptococci being a risk factor for bacteremia when everyone carries several species. Others, for instance, seronegativity for herpes simplex, should be used to preclude acyclovir prophylaxis. Similarly, there is no point in attempting prophylaxis against gram-negative infection when neutropenia is likely to be shorter than 7 days or neutrophils are unlikely to drop below $0.5 \times 10^9/l$ since co-trimoxazole and the quinolones require at least a week before the bacilli are effectively suppressed [29,267,268].

Patients given selective oral antimicrobial prophylaxis who develop bacteremia due to gram-positive cocci and who are colonized with *Candida* spp. are at higher risk of candidiasis than other patients [269]. Similarly, bone marrow transplant recipients are at greater risk of aspergillosis if they have been given methotrexate for prophylaxis against graft-versus-host disease and have experienced other nosocomial infections before the diagnosis of pneumonia [270]. Prolonged neutropenia is also a major risk factor [175], which might be reduced by using hematopoietic growth factors [271]. Physical exclusion of spores by high-efficiency filtration and avoidance of dried foodstuffs such as pepper also significantly lower the risk of nosocomial aspergillosis but do not have any impact upon patients whose airways are already colonized.

Risk factors also change with time. Thus development of pulmonary infiltrates elevates the patients to a different order of risk. Moreover, the radiological pattern may offer a clue as to the etiology, since the appearance of an aspergilloma is often characteristic [272]. Segmental infiltrates are associated with pulmonary aspergillosis, usually only occur late in the infection, and are the result of infarction [273]. In contrast, diffuse pulmonary infiltrates are rarely due to fungi or bacteria [274] but are frequently due to viruses or *P. carinii*, or might indicate acute respiratory distress when associated with high doses of cytarabine, particularly when preceded by bacteremia due to 'viridans' streptococci [255].

Options for prophylaxis

Assuming that prophylaxis is desirable, what should be the criteria for selecting a particular regimen and how should it fit into to an overall strategy for managing infection? For preventing infections due to *S. aureus* and gram-negative bacilli, either a ciprofloxacin or co-trimoxazole plus colistin appear equally effective. The quinolone will provide more reliable protection against infection due to gram-negative bacilli

Table 1. Prevention of infection

Organism	Preventing acquisition	Suppressing colonization	Inhibiting translocation and invasion, and arresting dissemination
<i>Staphylococcus aureus</i>	Reverse isolation	Mupirocin, neomycin	Co-trimoxazole, fluoroquinolone
<i>Escherichia coli</i>	—	Aminoglycoside, polymyxin	Colistin or polymyxin B with co-trimoxazole or nalidixic acid, fluoroquinolone
Other gram-negative bacilli	Reverse isolation, low microbial intake, prohibit plants	Aminoglycoside, polymyxin	Colistin or polymyxin B with co-trimoxazole or nalidixic acid, fluoroquinolone
<i>Candida albicans</i>	—	Polyene, fluconazole	Fluconazole
Other <i>Candida</i>	Reverse isolation?, low microbial intake?,	—	—
<i>Aspergillus fumigatus</i>	HEPA air, prohibit dried foodstuffs	Aerosol amphotericin B	Itraconazole, IV amphotericin

during the early days of neutropenia, but later on co-trimoxazole plus colistin gives better overall prophylaxis since fewer patients become febrile and fewer infectious episodes occur [117]. Because of the increased risk of streptococcal bacteremia, some have advocated including a penicillin [47,275,276], although it is not entirely clear whether the drug simply suppresses bacteremia without altering the clinical course. There is also a high probability of selecting strains with decreased susceptibility to penicillin, which will limit its use.

The choice of antifungal agent to prevent candidiasis still remains open, since fluconazole and oral amphotericin B appear equally effective. However, if compliance is likely to be poor or mucositis is anticipated, fluconazole will prove more reliable, although the dose remains unclear, since 50 mg, 150 mg, and 400 mg have each been recommended. Nevertheless, if the suppression of colonization and the prevention of candidiasis is required, then 150 mg/day would seem sufficient. Which prophylaxis to employ for aspergillosis remains a conundrum. High-risk patients, such as bone marrow transplant recipients, might benefit from aerosolized amphotericin B of 10–20 mg/day in two to four divided doses accompanied by 200–400 mg/day itraconazole, which should be monitored weekly to ensure that serum levels remain above 250 mg/l [183].

Options for prophylaxis

The suggestions shown in Table 1 are a summary of the effective options available for prophylaxis. New agents designed to compensate for deficiencies in the spectrum of activity, bioavailability, or safety are always welcome but, as with every tool, unless employed judiciously within the framework of an overall strategy for prevention and therapy, any advantages afforded by chemoprophylaxis could be

easily nullified. The design and operation of such a strategy requires close cooperation between the various specialities involved in the care of neutropenic patients and good channels of communication so that all parties are kept apprised of any new developments, including plans for changing primary or supportive care, so that any that are likely to have an impact on infectious complications can be identified. Efficient systems for monitoring microflora and their patterns of resistance need to be implemented and kept up to date since the continued success of prophylaxis can only be assessed if such surveillance data are available.

Conclusions

Chemoprophylaxis has been too often a matter of faith rather than science. The studies undertaken so far tend to show benefit for prophylaxis against *Candida* spp., *S. aureus*, and gram-negative bacilli. However, despite the variety and volume of studies undertaken, there are still too few data to prove conclusively that prophylaxis is beneficial in either the long term or even the short term. Given the greater availability of suitable agents, a more comprehensive understanding of the prognostic factors for infection during neutropenia, and an increasingly better means of identifying those at most risk, it should now be possible to undertake statistically valid studies to evaluate prophylaxis and finally provide a definitive answer, one way or the other.

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4 Infection control for oncology

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A program to prevent nosocomial infections is vital for the cancer patient. As has been thoroughly illustrated in prior chapters, infection is a major cause of morbidity and mortality (Table 1). Soon after admission, hospital-acquired organisms, mainly gram-negative bacilli, rapidly replace patients' endogenous flora [1–3]. These colonizing organisms are responsible for one half to two thirds of infections occurring during hospitalization [1,2,4,5]. Between 9 percent and 12 percent of cancer patients as a whole develop nosocomial infection. Infections of the bloodstream, respiratory tract, urinary tract, and surgical wounds predominate [6,7]. Patients with leukemia, neutropenia, or recent bone marrow transplants are especially susceptible. Carlisle et al, found a rate of 46.3 infections per 1,000 days at risk in neutropenic patients, corresponding to 48.3 percent of these patients developing a nosocomial infection [8]. In some series, between 18 percent and 20 percent of patients with leukemia or undergoing bone marrow transplant developed nosocomial bacteremia [7,9]. Twenty percent of bone marrow transplant patients acquire nosocomial pneumonia [10]. Although mortality from infection has improved from earlier very high levels (70–90 percent) with better antibiotics and supportive care [1,11,12], it nevertheless remains a significant burden. Cancer patients with nosocomial bacteremia have a crude mortality of 31 percent [13], whereas bone marrow transplant patients with pneumonia have a crude mortality of 75 percent and a direct (attributable) mortality of 61.8 percent [10,14].

As medical technology advances, more and more immunocompromised cancer patients survive longer, enlarging the high-risk population. According to the National Center for Health Statistics, cancer patients accounted for 1,594,000 discharges from acute care hospitals in the United States in 1991. Their average length of stay was 9.2 days [15]. In addition, the number of bone marrow transplants has grown rapidly from 200 worldwide in the early 1980s to 41,764 performed from 1989–1991 [16,17].

Antimicrobial tools have become less effective, even as the population in need of them has grown. Microorganisms have acquired resistance to most classes of antibiotics. This has included the development of extended spectrum beta-lactamases in gram-negative bacilli; intrinsic aminoglycoside, beta-lactam, and glycopeptide resistance in enterococci; and quinolone resistance in methicillin-resistant *Staphylococcus aureus* [18,19]. Resistance usually follows on the heels of increased use

Table 1. Importance of nosocomial infections in oncology

-
- Affects 9–12 percent of cancer patients
 - Affects 48 percent of neutropenic patients
 - 20 percent of leukemic patients develop nosocomial bacteremia or pneumonia
 - Oncology patients with nosocomial bacteremia have 31 percent crude mortality
 - Bone marrow transplant patients with nosocomial pneumonia have 62 percent attributable mortality
-

Table 2. Purposes of surveillance

-
1. Recognize outbreaks
 2. Plot secular trends of pathogens and resistance patterns
 3. Identify problem areas to focus infection control efforts
 4. Provide feedback on effectiveness of infection control program
-

[20]. Not surprisingly, several studies have documented the emergence of resistant organisms, both bacteria and fungi, when investigators have treated cancer patients with repetitious antibiotic regimens [21–25]. Patients who subsequently developed sepsis with multiply resistant organisms did poorly [26].

The importance of infection control practices increases as physicians must manage larger numbers of immunocompromised cancer patients with fewer effective antimicrobial therapies. If caregivers can prevent infections, they can minimize morbidity and mortality. This chapter explores infection control methods with specific reference to oncology. It presents an overview of surveillance, data analysis, and outbreak investigation, followed by an examination of multidisciplinary measures particularly important for the cancer patient population.

Surveillance

Surveillance is the process of systematic observation to determine the incidence and prevalence of a disease, in this case, nosocomial infection [27]. The information gathered by surveillance allows recognition of the most pressing nosocomial infection problems (Table 2). It points to clusters of infections and permits the plotting of the occurrence of particular pathogens or antimicrobial resistance patterns over time (secular trends). It provides data useful for the formulation of goals for infection control and monitors progress toward those goals [27,28]. Surveillance enabled investigators to determine the nosocomial infection rates in cancer patients cited earlier. Furthermore, the analysis of such data often brings to light information that would not otherwise be suspected. For example, when Robinson et al. began surveillance at their cancer center, they discovered that surgical patients were almost twice as likely to develop a nosocomial infection as medical patients (14.9 percent vs. 9.3 percent) [7]. This encouraged them to allocate additional resources to examine surgical patients more closely.

Surveillance is usually performed by a trained infection control practitioner

Table 3. Kinds of surveillance

-
1. Site specific (wounds, catheters)
 2. High-risk areas (oncology units)
 3. Rotating
 4. Comprehensive (entire health care center)
-

(active surveillance). Relying on personnel with other primary duties to report infections (passive surveillance) results in under-reporting [29]. The infection control practitioner determines the presence or absence of nosocomial disease based on standardized definitions, often following national guidelines [27,30]. Surveillance can be carried out prospectively or retrospectively. Following patients prospectively during their hospitalizations usually allows earlier recognition of epidemics but may miss infections documented by information that reaches the chart after discharge. Retrospective review after discharge usually finds such infections but may miss the pattern of clustering infections [31]. Both methods are reliable when performed by adequately trained personnel [32,33].

In most health care settings, there are insufficient infection control practitioners to follow every patient for signs of infection. Hence, a surveillance system must be organized to identify patients most likely to develop nosocomial infections so that they can be given closer scrutiny. Surveillance targets should be selected in a way that meets specific infection control goals (Table 3), committing resources to areas where the most infection, morbidity, and mortality can be prevented [34]. For example, surveillance can be site specific, covering surgical wounds or central lines. It can be directed toward high-risk areas, such as one for bone marrow transplant units. It can even be rotated through different hospital units to allow the whole institution ultimately to be covered. Once the infection control practitioners have selected an appropriate target, they can further screen patients for review by using 'clues.' They may gather clues from microbiology laboratory reports, patient diagnosis lists, or nursing notes. For example, if patients carry the diagnosis of leukemia, lymphoma, or granulocytopenia, they can be monitored more closely than others. If patients receive surgical wound care or have had new fevers or blood cultures, their charts can be retrieved and examined. Several hospitals have developed successful screening systems based on information found in the nursing 'Kardex,' a collection of care plans kept near the nursing station [29,35]. In units where nurses are reliable and motivated, they may report screening clues directly through standardized 'sentinel sheets' [36]. At other institutions in which nursing documentation is frequently unavailable, laboratory-based clues have been more helpful [37]. Some clues may be particularly useful when screening oncology wards, where bloodstream and central catheter infections are a main concern. These include fever curves, new antibiotics, the performance of blood cultures, and the presence of erythema at catheter insertion sites [27].

Once infection control practitioners have found a patient with a nosocomial infection, they complete a standardized work sheet. Work sheets include such information as patient age, diagnosis, procedures, infections, microorganisms, and

Table 4. Purposes of data analysis

-
1. Calculate incidence
 2. Calculate prevalence
 3. Plot infection rates over time
 4. Adjust for confounding variables
-

susceptibility profiles. They later collate these data into line lists (lists of patients with infections) and often enter them into a computer database [29,35].

No matter which system is used to gather data, it is only as reliable as the infection control practitioners who do the gathering. The accuracy of the system and practitioners must be periodically validated. For validation, surveillance results are compared to a gold standard, usually intensive concurrent surveillance performed by a physician [27]. Both a prospective and retrospective review of all patients in a given area may be required to find all nosocomial infections present [33,35]. More representative comparisons are often possible when the practitioners being validated are unaware they are being monitored [27]. Well-performed surveillance in the past has generally had a sensitivity (true infections detected as infections) of 75–80 percent and a specificity (noninfections recorded as noninfections) of 95–98 percent [33,35].

An issue that often emerges in oncological infection control surveillance is the utility of routine patient or environmental surveillance cultures. Numerous studies have documented the colonization by pathogens of both hospitalized cancer patients [1,2,21,26,38] and their environment [39–42]. Generally, routine culture have not been predictive of either nosocomial infection or of a specific etiologic pathogen [2,26]. A possible exception is nasal colonization with *Aspergillus*. Aisner and colleagues showed this predicted disseminated aspergillosis in neutropenic patients [43]. While this test had a high positive predictive value during an aspergillosis outbreak (9 out of 11 patients), its sensitivity was low (50 percent), and 2730 cultures were required to detect the nine cases [43]. Surveillance cultures may be very useful during outbreak investigation, however. By identifying the implicated strain, they may lead to the discovery of the reservoir of infection [44]. Oncology unit surveillance cultures have documented environmental sources of *Corynebacterium jeikeium* [45] and *Legionella* [46]. Similarly, surveillance of patients and staff identified carriers of *Clostridium difficile* [47] and epidemic pneumococci [48].

Data analysis

Once surveillance has provided data on nosocomial infections in oncology patients, infection control practitioners must analyze the data to make it meaningful (Table 4). Most basic analyses should include calculation of the incidence and prevalence of the nosocomial infections of interest, such as central line infections, bacteremia, and others. The incidence is the number of occurrences (infections) per unit time,

adjusted for the size of the population at risk. Since those at risk are easily estimated by those admitted or discharged, the number of admissions or discharges is conveniently used in the denominator. The incidence (I) can then be expressed as

$$I = \frac{\text{number of infections/month}}{\text{number of discharges/month}} \times 100.$$

This yields the number of infections per hundred discharges. Alternatively, incidence can be expressed in terms of the number of patient-days at risk:

$$I = \frac{\text{number of infections}}{\text{number of patient days}} \times 1000.$$

This yields the number of infections per thousand patient-days. This method is especially desirable in populations where the number of admissions is low and the average patient stay is long [49].

For example, to calculate the incidence of nosocomial bacteremia on an oncology unit, one would first obtain the number of bacteremias from surveillance data for the month. This number would then be divided by either the total discharges for the month, or in the second method, by the total number of patient days at risk. The days at risk can be calculated by summing the number of patients on the unit on each day of that month. For device-related infections, the denominator can be adjusted to device-days at risk. This permits better comparison between units and over time [50]. For example, to calculate the incidence of Hickman catheter infections, the total number of Hickman catheter infections that month would be divided by the sum of the number of days each patient had a Hickman catheter. For convenience, rates are usually expressed as the number per 100 patients or per 1,000 patient-days.

The incidence is generally the most helpful calculation when following infection rates over time (secular trends) because it specifically identifies new infections. However, when long-term data are unavailable or when it is difficult to determine the onset of a particular disease, the prevalence may be used. The latter rate provides a snapshot statistic of the amount of a particular disease present at a given point in time. The prevalence (P) is

$$P = \frac{\text{number of infections}}{\text{number of patients present}} \times 100.$$

For example, the prevalence of colonization with vancomycin-resistant enterococci on a bone marrow transplant unit would be calculated by dividing the number of patients colonized by the total number of patients present and multiplying by 100.

Determining the incidence and prevalence allows the infection control practitioner to follow the endemic rates for nosocomial infections and provides a starting point for effective intervention. When monitoring rates over time or comparing rates between units, one must be aware of the many confounding variables that interfere with analysis. Nosocomial infections usually have multiple, interrelated risk factors. The differences in risks between groups must be accounted for when

Table 5. Key personnel for infection control

-
1. Surgeons
 2. Nurses
 3. Housekeepers
 4. Dietitians
 5. Hospital engineers
 6. Microbiologists
-

comparing them [51]. One way to accomplish this is to stratify and risk-adjust infection rates. For example, rates can be calculated separately for men versus women or for patients with neutropenia versus those without neutropenia. Then when the number of women or the number of neutropenic patients fluctuates from month to month, the infection rate can still be meaningfully compared. More complicated nosocomial infections, such as vancomycin-resistant enterococcal bacteremia, may have too many risk factors to allow simple risk adjustment. The degree of neutropenia, prior antibiotic exposure, colonization with enterococci, and many other factors may need to be considered. In these cases, logistic regression models using multivariate analysis usually provide a more valid method [51].

Intervention and reporting rates

Once infection control practitioners have determined and analyzed endemic nosocomial infection rates, they can appropriately target basic infection control interventions. For instance, if wound infection rates are high in patients undergoing oncological surgery, they can give priority to reducing wound infections. It is important to realize that different kinds of nosocomial infections require targeted interventions with specific personnel (Table 5) [34]. Key personnel for wound infections are not surprising—surgeons. Likewise, intervening with nurses who perform urinary catheterization may help to reduce urinary tract infections. Several specific infection control interventions that are important for oncology will be discussed subsequently. One intervention that has broad applicability to many infections is the simple reporting of infection rates to the appropriate personnel. In the Study on the Efficacy of Nosocomial Infection Control (SENIC) performed by the Centers for Disease Control in the mid-1970s, hospitals that reported surgical wound infection rates to the operating surgeon were able to reduce their surgical wound infection rate by 20–40 percent. While such a direct relationship was not as obvious for other infections, reporting rates seemed to contribute to decreasing urinary tract infections, nosocomial pneumonias, and nosocomial bacteremias [52].

Outbreak investigation

Nosocomial epidemics represent only about 3 percent of nosocomial infections [34,53]. While this fact emphasizes the importance of lowering baseline rates, it

Table 6. Steps in outbreak investigation

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1. Determine timing of outbreak
 2. State case definition
 3. Save microbiology specimens
 4. Review literature
 5. Document everything
 6. Institute initial control measures
 7. Analyze data (case-control studies)
 8. Revise control measures
-

does not account for the moral and political impact an outbreak can have. Epidemics disproportionately involve the sickest patients, such as those in intensive care units [53,54]. Most oncology patients probably fall into this high-risk category whether or not they actually reside in an ICU. Thus, early identification and termination of nosocomial epidemics may particularly benefit oncology patients.

An outbreak can be defined as a cluster of infections at a specific anatomic site due to a specific pathogen that, when compared with the endemic incidence of disease, is significantly greater than expected [54]. Traditionally, significance is determined by comparing current rates with endemic rates by Fisher's exact test or a chi square test and finding a $p < 0.05$ [54–56], though clinically important increases may occur at higher p values. Recall that the p value defines the probability that the difference observed occurred by chance alone. A probability less than or equal to 5 percent is considered significant.

Case finding and laboratory methods must be the same for the time periods being compared, and confounding variables must be accounted for, as noted earlier, in order for valid rate comparisons to be made [55]. For example, Heard and associates discovered an epidemic of *Clostridium difficile* infection on their oncology ward. Twenty-two out of 29 patients culture-negative for *C. difficile* at admission developed infection with the epidemic strain compared with 7 infected with other strains. On chi square testing, their p value was less than 0.005 [47].

When investigating an outbreak, infection control practitioners must perform several tasks simultaneously (Table 6) [55]. They must determine the timing of epidemic and pre-epidemic periods. They must agree on a clear case definition. In the earlier example, a case definition could be 'any initially *C. difficile* negative patient admitted after May 1983 who became culture positive for the epidemic strain.' The microbiology laboratory should save all possibly relevant specimens. The medical literature should be reviewed for etiologic and management factors found important in prior similar outbreaks. Initial infection control measures should be instituted.

Everything should be carefully documented for medicolegal purposes as well as for purposes of the investigation. Each case, along with its important associated facts (location, risk factors, mode of transmission, time course), should be entered into a master database or 'line list.' The course of the epidemic can be followed by plotting case occurrence over time to obtain an epidemic curve. This can yield valuable clues about transmission and incubation periods [55]. When sufficient data

Table 7. Odds ratio table for calculating relative risk for disease

	Cases	Controls	Total
Antibiotics	8	5	13
No antibiotics	9	63	72
Total	17	68	85

have been gathered, hypotheses can be generated regarding the epidemic's source and risk factors. For example, in the *C. difficile* outbreak, hypothetical risk factors could include receiving care from nurses who care for known *C. difficile*-infected patients, occupying a room with positive environmental cultures for *C. difficile*, or receiving antibiotics. Graphical analysis of risk factors is often helpful.

One way to test hypotheses is to perform a case-control study [57]. This allows a formal test of the association of a risk factor with infection. Cases are compared with controls chosen from the uninfected members of the population of interest who were present at the time of the outbreak. Controls should be loosely matched, usually only for age, sex, and service. Two to four controls are needed for each case, particularly if the number of cases is small [55]. Data are arranged in a 2×2 table, and the odds ratio for each variable is calculated. The odds ratio is an approximation of the relative risk for disease that a variable conveys. It is calculated by dividing the odds of exposure to the variable in cases (number of cases exposed/number of cases unexposed) by the odds of exposure in controls (number of controls exposed/number of controls unexposed) [57].

For example, an odds ratio for antibiotic use in Heard and associates' *C. difficile* outbreak could be calculated. The 2×2 table could be constructed as illustrated in Table 7. In this table the odds of exposure to antibiotics for cases = $8/9 = 0.88$. The odds of exposure to antibiotics for controls = $5/63 = 0.08$. The odds ratio then would be $0.88/0.08 = 11$. By this estimation, cases with *C. difficile* were approximately 11 times as likely to have received antibiotics as controls (data based on Heard et al. [47]). The strength of association of a variable in matched samples can then be calculated using a Mantel-Haenszel test [57].

Besides documenting the strength of association between a possible etiology and a nosocomial infection, case-control studies can reveal important facts about both the population at risk and the effect of the nosocomial infection. For example, in their case-control study of an aspergillosis outbreak in a new bone marrow transplant center, Rotstein et al. discovered that their patient population had shifted to include more high-risk patients [58]. This realization prompted them to install more high-efficiency particulate air (HEPA) filters in patient rooms. Disease effects can be analyzed most clearly in studies in which cases and controls are tightly matched for diagnosis and severity of illness (retrospective cohort studies) [59]. Mortality directly due to infection (attributable mortality), as well as excess costs and excess length of stay, can be estimated. Pannuti et al. performed a good example of this kind of study, examining pneumonia in bone marrow transplant patients. They found that the overall or crude mortality from pneumonia was 75 percent, and it

Table 8. Examples of oncology unit outbreaks

Author	Ref.	Year	Organism	Setting
Aisner	92	1976	<i>Aspergillus</i>	Construction
Barnes	94	1989	<i>Aspergillus</i>	Construction
Berk	48	1985	<i>Pneumococcus</i>	Open ward
Helms	46	1983	<i>Legionella</i>	New ward
Johnson	62	1985	<i>Legionella</i>	
Martino	77	1988	<i>Cryptosporidium</i>	Cleaning, rags
Rhame	111	1973	<i>Salmonella</i>	Platelets, transfusion
Rotstein	58	1985	<i>Aspergillus</i>	Bone marrow transplantation
Telander	45	1988	<i>C. jeikeium</i>	
Weisfuse	112	1990	Hepatitis A	IL-2 treatment
Wingerd	22	1991	<i>Candida krusei</i>	Fluconazole

was 95 percent for *Aspergillus* pneumonia. The attributable mortality of nosocomial pneumonia was 61.8 percent, increasing to 85 percent if the etiologic agent was *Aspergillus* [14]. Thus only a small proportion of the deaths could be related to the underlying disease; most was due to infection.

Once infection control practitioners have deduced the probable causes of an outbreak, they can adjust interventions to attack the causes directly. The form of the intervention depends on the outbreak. In the *C. difficile* outbreak cited earlier, infection was contained by cohorting or isolating infected patients, treating patients with symptoms early rather than waiting for laboratory documentation, and improving hygiene when disposing fecal material [47]. Other measures that have been effective in other outbreaks on oncology wards (Table 8) include immunization in a pneumococcal epidemic [48], increasing HEPA filtration to prevent aspergillosis [60], and hyperchlorination of water to prevent Legionnaire's disease [61,62].

Specific infection control interventions for oncology

Throughout their care, oncology patients interact with many members of the health care team and are exposed to the hospital or clinic environment. This provides opportunities for people in many departments to assist the infection control practitioner in preventing nosocomial infections. An effective infection control program must coordinate these personnel, despite sometimes conflicting departmental interests [63]. The rest of this chapter examines ways in which all patient caregivers can contribute to infection control.

Hand washing

Since the time of Semmelweis, infection control workers have advocated hand washing as a method of reducing nosocomial infections [28]. Recent studies have shown that many nosocomial pathogens are spread by direct contact [64] and that nosocomial infections can be reduced by increasing hand washing [65]. Hand washing

has long been advocated as especially critical when caring for immunocompromised cancer patients [38,66]. In spite of good intentions and education, staff in intensive care units have had a maximal hand-washing rate between patients of 40 percent, with physician rates being much lower than nurses' rates [65,67]. The lack of success of education programs has led to the consideration of using marketing techniques or even subliminal stimulation to increase hand washing [68,69]. Short of such measures, every effort should be made to encourage hand washing on oncology units. Sinks and disinfectants should be easily accessible in patient care areas. Whereas a variety of soaps and disinfectants has been shown to remove or inactivate hand flora [70], current evidence favors 4 percent chlorhexidine or 60 percent isopropyl alcohol as the most effective agents [65,71]. Significantly, these disinfectants were successful in removing vancomycin-resistant *Enterococcus faecium* in one recent trial, yet soap and water often failed [72].

Nursing

Nurses are perhaps the most important personnel to involve in preventing nosocomial infections in cancer patients. Nurses are responsible for maintaining patients' hygiene, including bathing, skin care, and removal of soiled materials [73–75]. To reduce personnel-related infections, clear nursing protocols should promote hand washing and maintain aseptic technique during any invasive procedures. In addition nurses serve as gatekeepers, intercepting visitors and materials (such as flowers) that may introduce pathogens. They also represent the first line of surveillance. Protocols should incorporate careful observation of vital signs, temperature curves, and catheter sites that might prompt an investigation for infection [73,75]. Nurses should take special care that emergency procedures incorporate appropriate hygiene and sterility [76].

Housekeeping and central services

Together housekeeping and central services are responsible for the day-to-day management of the hospitalized patient's environment. A recent outbreak of cryptosporidiosis on a bone marrow transplant unit in which the protozoa were spread from room to room on shared cleaning rags illustrates their critical role [77]. Rooms should be cleaned regularly and promptly. Housekeepers should eliminate potential reservoirs for pathogens, such as areas of standing water [73,74,78]. They should change cleaning materials between patient rooms. Central services plays its part by maintaining proper sterilization or disinfection of any reusable item [76,79]. When incorporated into the total infection control program, improved housekeeping and central services performance has been shown to reduce colonization with gram-negative bacilli in neutropenic patients [38].

Dietary

Numerous studies have documented that hospital food, particularly fresh fruits and vegetables, may contain pathogenic gram-negative bacilli, including *Klebsiella* and

Pseudomonas [39,41]. Strains found in food have colonized patients [80]. On the basis of on this evidence, dietitians have traditionally served neutropenic cancer patients either a sterile diet or one with a low burden of microbes [66,81,82]. Dietitians should consult with the patient to find a diet that is acceptable. This may be difficult given the usual side effects of radiation and chemotherapy. Maintaining food sterility is a very labor-intensive task: Sterile food must be canned, autoclaved, baked, or irradiated. Cans must be disinfected before opening [83,84]. Many commercially available foods may be suitable to a less restrictive, 'low microbial' diet, though some monitoring of microbial load may be necessary to ensure standards are met [83,85].

Hospital engineering

Hospital engineers are responsible for maintaining protected environments for oncology patients, when needed. For many years, investigators debated the degree of protective isolation required to insulate neutropenic cancer patients from infectious organisms. In the early 1980s, Nauseef and Maki demonstrated that simple protective isolation was no better than hand washing and good hygiene alone [86]. A consensus developed that the more protective environment of the laminar air flow (LAF) room, while effective in reducing microbial colonization [87,88], was limited both by cost and cumbersome logistics. Laminar air flow rooms were reserved for patients with prolonged granulocytopenia [23,89]. Recent studies show that LAF may be particularly useful for preventing disseminated aspergillosis in immunocompromised patients. *Aspergillus* spores fill the air in some areas, especially in the autumn months. Cleaner air, such as HEPA filtered air, clearly decreases the spore count and rates of aspergillosis [60,90,91]. For example, Sherertz et al. found an incidence of aspergillosis of 16.6 percent in one bone marrow transplant unit. After installing HEPA filtration, the *Aspergillus* spore count fell from 0.027 colony-forming units (CFU)/m³ to 0.003 CFU/m³, and the number of cases declined to none [60].

Hospital engineers also need to protect immunocompromised patients during hospital construction. Several outbreaks of aspergillosis have occurred when construction has produced clouds of spore-bearing dust [92–95]. Hospital engineers can institute measures to prevent such outbreaks. Engineers should place airtight plastic and drywall barriers around the construction area. They can then apply negative pressure ventilation at the work site, with venting to the outside. When workers expose spore-covered surfaces, they can decontaminate the area with antifungals. Engineers can install temporary HEPA filters as needed. If dust and spores are contained with these measures, fatal infections can be limited [93–95].

An additional infectious hazard of construction, or even a simple shift in building utilization, is nosocomial Legionnaire's disease. Several outbreaks have occurred in oncology wards when their water supplies became contaminated with *Legionella*. Water systems containing stagnant areas are especially susceptible to colonization with *Legionella* [46,62]. Hospital engineers can control this problem with

hyperchlorination. They can also test stagnant areas for *Legionella* and flush them before patient use [61,62,96].

Microbiology

A good working relationship with the clinical microbiology laboratory is crucial for any infection control program [44,97,98]. The laboratory should provide rapid, accurate identification of significant isolates, as well as their susceptibility patterns. As Trenholme et al. demonstrated, rapid reporting of microbiological data was more likely to affect treatment decisions. Physicians would more often initiate antibiotics or change to a more effective or less expensive regimen [99]. In addition, the microbiology laboratory should provide support for surveillance [44]. It should perform cultures of environmental or employee samples when needed [97]. It should save relevant isolates for later analysis [98]. Such analysis may include detailed characterization by special typing methods. These methods allow differentiation between strains of the same species, particularly important for outbreak investigation. In an outbreak, it may be critical to know if specimens of *Staphylococcus aureus* in wounds of patients operated on by the same surgeon are identical or different [44].

Ideally, typing systems should be standardized, reproducible, sensitive, stable, available, inexpensive, and field tested in epidemic investigations [100]. Needless to say, no methods currently available meet all these criteria. A wide variety of typing methods exist. Some are commonly employed clinically, such as biotyping [97]. Because these methods are designed to identify species, their ability to discriminate strains is limited. Other methods, such as serotyping and phage typing, may reliably differentiate organisms but are limited by availability of reagents [44]. More recently, molecular biology-based techniques, such as plasmid typing and genomic DNA typing, have enjoyed increasing use. Plasmid typing relies on the presence of small, extrachromosomal pieces of bacterial DNA, which are extracted and compared with gel electrophoresis [101–103]. Investigators have successfully used it to type gram-negative bacilli, staphylococci, enterococci, mycobacteria, and many other organisms. Its primary drawback is its limitation to plasmid-bearing organisms. An alternative approach, genomic DNA typing, uses restriction endonucleases to cut chromosomal DNA into fragments that can be separated by gel electrophoresis [103]. Care must be taken when selecting an endonuclease so that an interpretable number of bands are produced on the gel. One variety of genomic DNA typing with better band resolution is pulsed-field gel electrophoresis (PFGE). It has been used to investigate several recent epidemics. Organisms successfully typed by PFGE include *Candida* [104], enterococci [105], and methicillin-resistant *Staphylococcus aureus* [106].

Finally, the clinical microbiology lab can provide surveillance data on the antimicrobial susceptibility patterns of common nosocomial pathogens [97]. With this information, physicians can tailor empiric antibiotic therapy to the particular institution [107]. When possible, producing site-specific or unit-specific susceptibility patterns may permit the identification of resistance trends and changes in predominant organisms that may be obscured by hospitalwide patterns [108,109].

Therapeutic agents

It is important to ensure the purity of any therapeutic agents given to immunocompromised cancer patients. Outbreaks of *Pseudomonas* bacteremia have been traced to mouthwash [110], and *Salmonella* infections have been spread by platelet transfusions [111]. Investigational therapies should receive more intense screening. This was recently emphasized by an epidemic of hepatitis A transmitted by contaminated pooled serum in interleukin (IL)-2 lymphokine activated killer (LAK) cell preparations used in a cancer immunotherapy protocol [112].

Therapeutic agents that may change the resistance patterns of nosocomial pathogens—antibiotics—should be administered with foresight. Recommended antibiotic protocols exist for the treatment of neutropenic fever [11,113], a topic covered elsewhere in this text. When antibiotics are used routinely, resistance develops. This has occurred in immunocompromised patients with anti-pseudomonal penicillins and aminoglycosides [21,23–25], imidazoles [22], and most recently, vancomycin [114]. Physicians should conserve antibiotics they plan to use to treat active infections. For example, when they prescribe prophylactic regimens to prevent infection, if possible they should avoid agents that may later be needed to treat an active infection. Then if resistance develops to the prophylactic regimen, there will be a better chance that infecting organisms will still be susceptible to the most effective antimicrobials.

Efficacy of infection control

While few measures of the efficacy of infection control practices have specifically addressed oncology patients, they have performed well for the overall population. The SENIC study, which included a variety of hospital settings and patients, in a retrospective analysis demonstrated a 33 percent reduction in nosocomial infections among hospitals with an effective infection control program [52]. Reductions were seen in all categories of infections, including surgical wound infections, urinary tract infections, pneumonias, and bacteremias. The authors estimated that infections must only be reduced by 6 percent to offset the cost of the infection control program. Savings appeared to have come both from shortened patient hospital stays and from lower treatment costs. In a similar vein, Miller and associates estimated that they saved their hospital nearly \$4.5 million in 1985 by reducing nosocomial infections [115]. Regardless of the financial benefit patients and institutions may derive, it is the potential savings in lives that matters most. For the immunocompromised cancer patient, an effective infection control program can be life saving indeed.

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5 Empiric therapy for bacterial infections in neutropenic patients

Jean Klastersky

Fever has long been associated with malignancy and remains a common problem in cancer patients. With the advent of cytotoxic therapy, fever in the cancer patient has been closely linked with infection, especially when the patient is granulocytopenic. Since fever can be the only sign of infection in neutropenic patients, its appearance commands a series of diagnostic and therapeutic measures, to be taken empirically, that is, without precise knowledge of the nature and cause of the infection [1]. This approach is quite different from that usually recommended to deal with fever in non-neutropenic patients; under these circumstances, it is important, first, to decide whether fever is caused by infection or another process; then, to determine the site of the infection and to investigate the offending pathogen through a series of microbiological techniques. Finally, when a precise clinical and microbiological diagnosis is available, the choice of therapy can be made on rational grounds. Of course, depending on the acuteness of the disease, these diagnostic steps can be accelerated and, occasionally, presumptive therapy will be also prescribed in non-neutropenic patients. If the diagnostic workup is negative and fever persists for more than 7 days, it is customary to speak about fever of unknown origin (FUO). Then, a series of other diagnostic considerations must be considered.

The pattern of fever is usually unimportant for making a causal diagnosis; in cancer patients, just as in those without malignancies, fever is usually the consequence of infection; in fact, in patients with neoplasms, a series of factors predisposes patients to infection and decreases their resistance to it. Fever, however, can be caused by the cancer itself through tumor-related necrosis, hemorrhage, or pyrogens; this is definitely a less common cause of pyrexia than infection, with the possible exception of certain tumors such as Hodgkin's lymphoma. Because the direct causal relationship between tumor and fever is rarely obvious, these pyrexias are often considered to be FUO [2]. Finally, fever in cancer patients can be caused by any disease, unrelated to infection or cancer, that can affect noncancer patients; here, also, if the causal relationship is unclear, the differential diagnosis of FUO is to be undertaken; moreover, one has to stress that cancer patients are often exposed to various medical interventions that can be responsible, directly or indirectly, for fever.

In neutropenic patients, the pyrexial episode requires prompt intervention, on an

empirical basis, as will be discussed later. Neutropenia and fever should be clearly defined using criteria such as those generally employed [3]. The criteria for fever in a clinical trial should be clearly defined in that trial. One example of fever is an oral temperature above 38.5°C or above 38°C on two or more occasions during a 12-hours period. The major risk of acute bacterial infections occurs when the polymorphonuclear leukocytes (PML) are below 500/mm³. However, patients presenting with more than 500 PML/mm³ but fewer than 1,000 PML/mm³ and whose counts are anticipated to fall below 500/mm³ within 24–48 hours, because of antecedent therapy are also at risk. Any analysis should evaluate patients with fewer than 100 PML/mm³ separately.

Granulocyte–colony-stimulating factor (G-CSF) and granulocyte-macrophage–colony-stimulating factor (GM-CSF) are hemopoietic growth factors now available commercially for use in patients. The predominant effects of G-CSF are to stimulate the survival, proliferation, differentiation, and function of neutrophil granulocyte precursors and/or mature cells. GM-CSF acts not only on cells of the neutrophil lineage but also on cells of the eosinophil and monocyte-macrophage lineages. The hematological effects of G-CSF and GM-CSF alone in cancer patients have also been recently reviewed [4] and provide a basis for understanding their effects when used in conjunction with chemotherapy agents. An illustration of the hematological effects of postchemotherapy CSF comes from an American study of G-CSF given in a preventive manner, commencing the day after a 3-day chemotherapy regimen for small-cell lung cancer and continuing for 14 days [5]. The effects of shortening the duration of neutropenia and elevating the nadir neutrophil level persisted throughout six cycles of chemotherapy. Similar effects of preventive treatment with GM-CSF on neutrophil levels after chemotherapy have been described. GM-CSF also elevates eosinophil levels during leukocyte recovery. Platelets levels have appeared reduced in some studies of postchemotherapy GM-CSF, but this has not clearly been of clinical significance.

Neutropenia predisposes the patient to severe and rapidly progressing infection by bacterial and fungal pathogens; it also interferes with the usual clinical manifestations of sepsis. Therefore, empirical therapy has become an accepted practice and has been designed to cover the most likely pathogens, namely, gram-negative rods and especially *Pseudomonas aeruginosa*, in the earliest studies. Of course, besides ‘microbiologically defined infections,’ in some patients no microbiological or clinical cause for the infection will be found (‘unexplained fever’); in others, only clinical clues will lead to a presumptive diagnosis of infection (‘clinically defined infection’). The criteria for these categories have been established [3] and are widely accepted. In Table 1 the proportion of microbiologically documented and clinically defined infections and that of unexplained fevers is indicated, as observed in recent EORTC trials.

As can be seen in Table 2, during the two past decades we have witnessed a progressive reduction of gram-negative infections and a gradual rise of gram-positive ones, those caused by *Staphylococcus epidermidis* and the streptococci. Table 3 summarizes the nature of the most common pathogens causing fever in neutropenic patients.

Table 1. Infection documentation in IATCG trials VIII and IX

Microbiologically defined		
Bacteremia	314	(24%)
Bacterial-nonbacteremic	61	(5%)
Viral	12	(1%)
Fungal	23	(2%)
Mixed	8	(0.5%)
Clinically defined	332	(26%)
Unexplained fever	493	(38%)
Fever not related to infection	47	(3.5%)
Total	1290	

Table 2. Microbiological nature of febrile neutropenia: Single-organism bacteremia in EORTC trials

Infection	I (1973–1978)	II (1978–1980)	III (1980–1983)	IV (1983–1986)	V (1986–1988)	VIII (1989–1991)
Single-organism bacteremias	145/453	115/419	141/582	219/872	213/749	151/694
No. of febrile episodes (%)	32%	27%	24%	25%	28%	22%
Gram-negative bacteremias	103 (71%)	74 (64%)	83 (59%)	129 (59%)	78 (37%)	47 (31%)
Gram-positive bacteremias	42 (29%)	37 (36%)	58 (41%)	90 (41%)	135 (63%)	104 (60%)

Table 3. Common microorganisms causing infection during granulocytopenia

Gram negative
Enterobacteriaceae
<i>Pseudomonas aeruginosa</i>
<i>Salmonella</i> species
Gram positive
<i>Staphylococcus</i> coagulase-negative
Alpha-streptococci
<i>Streptococcus pneumoniae</i>
<i>Staphylococcus</i> coagulase-positive
<i>Corynebacterium JK</i>
Anaerobic cocci and bacilli
Opportunistic agents
<i>Candida</i> species
<i>Aspergillus</i> species
<i>Pneumocystis carinii</i>
<i>Nocardia</i> species

Coverage for gram-negative microorganisms

Most initial studies concentrated on the coverage for gram-negative infections since they were overwhelmingly more frequent than any other pathogens. Actually, in the princeps paper by Schimpff et al. [6], demonstrating the efficacy of carbenicillin plus gentamicin as empiric therapy for febrile patients with cancer and granulocytopenia,

it was unclear whether the benefit resulted from the choice of those antibiotics or from the early onset of treatment. Most likely both are important, but empiric therapy has become an accepted practice. One prerequisite for successful coverage of gram-negative infection is a broad spectrum of antimicrobial activity. This can be provided by broad-spectrum agents or/and combination therapy but is constantly jeopardized by changes in susceptibility of microbes to antibiotics.

The EORTC studies have clearly indicated that combinations of β -lactam antibiotics with aminoglycosides were superior to β -lactams alone in severely neutropenic patients. A first study indicated that carbenicillin plus gentamicin was superior to carbenicillin plus cephalothin [7], and a subsequent trial found that amikacin added to ceftazidime throughout the therapeutic course was more effective than when given only for 3 days [8]. Although the superiority of the combinations of β -lactams with aminoglycosides might be related to the broader spectrum that the combination provides, there are indications that it may be related to synergistic action, the importance of which in compromised patients has been underlined in several in vitro and clinical studies [9,10]. A more recent study re-examined the role of aminoglycosides in neutropenic patients [11]. Patients were randomly assigned to ceftazidime or imipenem, with or without amikacin; the combination of ceftazidime plus amikacin was superior to ceftazidime alone, whereas imipenem was as effective as imipenem plus amikacin.

It should be emphasized that the beneficial effect of aminoglycoside-containing combinations has been detected primarily in severely neutropenic patients [4,8]. This may explain why ceftazidime was found as effective as ceftazidime plus tobramycin [12] or a triple combination of cephalothin, carbenicillin, and gentamicin [13] in patients, all of whom were not neutropenic and/or had a short-lived and moderate neutropenia.

The emergence of resistance to β -lactams among gram-negative bacilli has been a serious recent problem, related to the production of a large number of β -lactamases, some with unique characteristics [14]. These resistant strains (*Enterobacter* spp., *Citrobacter* spp., *Xanthomonas maltophilia*, *Pseudomonas* spp., etc.) are more likely to emerge in settings in which a single antibiotic has been used consistently for prolonged periods. This has been the case after prolonged use of co-trimoxazole for prevention of infection in neutropenic patients [15] and is now being seen after prophylaxis with quinolones (M. Glauser, personal communication).

The diversity of gram-negative organisms causing infection in neutropenic patients and the variability of their sensitivity to antibiotics makes it increasingly difficult to recommend a single regimen as the best empirical therapy for fever in neutropenic patients to be used for all patients in all institutions. The experience of individual institutions in terms of antibiotic usage and microbiological surveillance is essential to select the optimal regimens. What can be concluded at this time is that although the frequency of gram-negative pathogens has decreased as a cause of infection in neutropenic patients, these pathogens still represent a serious threat and should be covered empirically. In patients with acute leukemia and severe granulocytopenia, especially if it is expected to be longlasting, the combination of a broad-spectrum β -lactam (ceftazidime, cefoperazone, ceftriaxone, etc.) with an

aminoglycoside is probably indicated if there are no contraindications for the use of aminoglycosides. In other instances, single drug therapy is probably sufficient; it should be performed with a broad-spectrum cephalosporin. The experience with quinolones or aztreonam, as single drug empirical therapy, is more limited [16,17]. It should be stressed that if those antibiotics are used, a suitable coverage of gram-positive microorganisms should be associated.

At this point it is important to underline that modifications can be made of the initial regimen in order to cope with potential toxicity and/or the nature and susceptibility of the identified pathogen [13]. An algorithm for antimicrobial therapy adaptation is proposed in figures 1 and 2. There are limited data on restrictive adjustments of therapy once the offending pathogen is known. Most investigators would agree that if a patient is on both anti-gram-positive (vancomycin or teicoplanin) and anti-gram-negative coverages, the former can be discontinued if a gram-negative pathogen is isolated.

On the other hand, under the same condition if a gram-positive organism is isolated, one would hesitate to discontinue anti-gram-negative coverage. Earlier studies have shown that early discontinuation of such a therapy in patients who remain febrile and granulocytopenic can lead to fulminant bacterial infection upon discontinuation of empiric therapy, even if blood cultures taken initially remained negative. Of course, anti-gram-negative therapy can be simplified at this point, and in most cases a single drug (ceftazidime, ceftriaxone, imipenem) would appear sufficient as a companion antibiotic to the anti-gram-positive coverage; the latter can be adapted to the nature and sensitivity of the isolated microorganisms.

The algorithm shown in Figure 2 will probably be helpful in most cases of documented bacteremias occurring in neutropenic patients. It does not take into account the case of bacteremia caused by unusual microorganisms with unexpected sensitivities; in addition, the physician has to take into consideration the changes in susceptibility of more usual pathogens, which often occurs as the result of antibiotic pressure.

Fungal and viral infections

Fungal infection can be documented in 5 percent of patients as the initial febrile neutropenia; that figure has not changed much for years. It is obvious that bacterial and fungal sepsis can coexist and that the bacteremia might overshadow the more difficult to document fungal infection; the latter will manifest itself as a persisting or recurring fever after the eradication of bacteremia by empirically prescribed antibiotics. This explains why it has become accepted to administer amphotericin B empirically to those granulocytopenic patients who remain febrile after a few days of broad-spectrum antimicrobial therapy and in whom no bacteria can be documented [18]. As neutropenia persists, the risk of fungal infection increases; many fevers in patients with prolonged neutropenia will be caused by fungi.

Viral infection is rarely diagnosed in neutropenic patients without concomitant immunosuppression, as it occurs after bone marrow transplantation. Herpes simplex

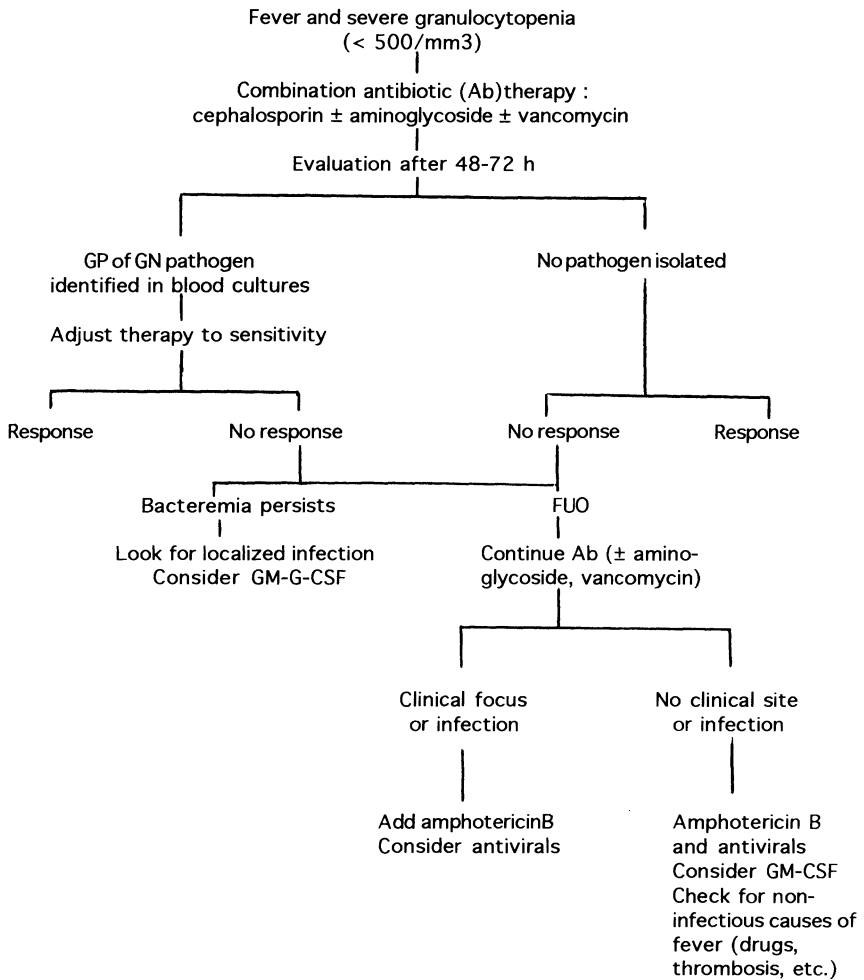


Figure 1. Guidelines for the diagnostic and therapeutic approach of febrile episodes in granulocytopenic patients. FUO = fever of unknown origin; GM-G-CSF = granulocyte-macrophage-colony-stimulating factor; GN = gram-negative; GP = gram-positive.

virus causes fever quite early after bone transplantation during the neutropenic episode; in most centers involved in bone marrow transplantations, prophylactic acyclovir is administered to prevent these infections [19]. Cytomegalovirus (CMV) causes infection, which, in cancer patients at least, most often manifests itself as a diffuse interstitial pneumonitis; these infections occur usually once the patient is no longer neutropenic though still severely immunosuppressed. Fever under these circumstances, especially if associated with pulmonary symptoms, is an indication for bronchoalveolar lavage (BAL) and subsequent therapy based on the findings; if BAL is not available or feasible, CMV and *Pneumocystis carinii* should both be covered with ganciclovir and co-trimoxazole. In fact, in many centers handling

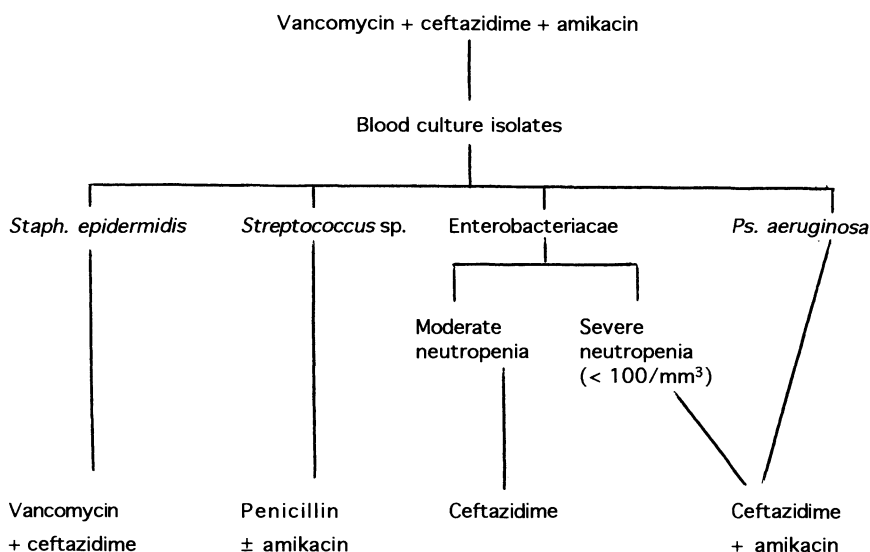


Figure 2. Modification of empirical therapy according to microbiological results.

patients having bone marrow transplants, it has become customary to perform BAL 30 days after the transplant even in asymptomatic patients and, if positive for CMV, to treat the patient at that point [20].

Coverage for gram-positive organisms

Gram-positive pathogens have emerged as significant pathogens in neutropenic patients in the last decade. The most common organisms have been *Staphylococcus epidermidis*, *Corynebacterium jeikeium*, and various strains of alpha-hemolytic streptococci. The widespread use of intravenous catheters has been largely responsible for that increase, as well as the use of prophylactic agents such as quinolones, frequent administration of potent antiacids, and the development of chemotherapeutic regimens leading to more severe mucositis.

Although some of these infections, especially those caused by *Staphylococcus epidermidis*, can be quite indolent, it is not always the case with the streptococci. These infections can be associated with high fever, chills, and rash; some can be fulminant and cause death within hours after the onset of symptoms; they can cause an acute respiratory distress syndrome (ARDS) or renal failure [21,22].

The emergence of gram-positive organisms, some of which are resistant to penicillin and penicillinase-resistant penicillins or cephalosporins, has led to substantial changes in the selection of antibiotics to be used for empirical therapy in febrile neutropenic patients. Because vancomycin and teicoplanin are currently the two only antibiotics that cover all the gram-positive pathogens, it has been proposed

to add such agents to the gram-negative coverage. Several controlled studies demonstrated a benefit from such an approach [12,23–25], although in some of these studies it was felt, in retrospect, that early vancomycin therapy was not necessary for many of these infections, since the mortality rate was small. Other studies did not document a clear benefit from early vancomycin therapy [26,27]. These divergences make the appropriate use of vancomycin a controversial issue. This is most likely due to the fact that many studies lump together all kinds of gram-positive infections. As a matter of fact, *Staphylococcus epidermidis*, which is usually methicillin resistant and thus requires vancomycin or teicoplanin for therapy, causes indolent infections, and delays in appropriate therapy do not jeopardize a favorable outcome. On the other hand, streptococcal infection and sepsis due to *Staphylococcus aureus*, which can be fulminant, rarely require vancomycin as a specific treatment: Many strains are susceptible to antibiotics included in standard regimens or can be treated with broad-spectrum penicillins. A recent study by EORTC indicates that piperacillin-tazobactam plus amikacin is more active on gram-positive infections than ceftazidime plus amikacin; both regimens were equally active on gram-negative infections [28].

At this point it can be concluded that vancomycin should be used empirically only in institutions where fulminant gram-positive infections, caused by methicillin-resistant organisms, is common. In other circumstances it can be added safely once the nature of the pathogen is recognized. Although rarely reported so far, the emergence of vancomycin-resistant strains has been observed [29]. Because there is no substitute for vancomycin or teicoplanin for therapy of some infections due to methicillin-resistant pathogens, caution should be advised as far as the widespread use of these drugs is concerned; this recommendation implies that vancomycin should be promptly discontinued, if used empirically, as soon as its use is not supported by microbiological data. Moreover, its prophylactic use should be discouraged. Finally, alternative empirical regimens, offering a better coverage for gram-positive organisms than the standard regimens, which are designed to cope primarily with the infections caused by the gram-negative pathogens, should be investigated.

Newer aspects and perspectives of empirical antibiotic therapy

More recently, emphasis has been placed on the importance of various prognostic factors for the outcome of febrile neutropenia [30]. It is likely that consideration of these factors will influence the nature and modality of empirical therapy in the future. It seems likely that some neutropenic patients, at low risk for fulminant sepsis, will be more often treated as ambulatory patients or even at home [31]. The availability of orally absorbed regimens, namely, the quinolones and various pumps for intravenous therapy, makes the outpatient approach possible [32].

A more targeted antibiotic therapy is also a possibility for some specific syndromes that occur in patients with neutropenia, such as typhlitis and perirectal abscesses. These infections are usually caused by multiple enteric organisms, and their coverage should provide adequate treatment gains, not only with the usual gram-negative

organisms but also anaerobes and streptococci from the digestive tract. Pneumonia is another frequent infection in neutropenic patients, and the response of its bacteremic form to empirical therapy is often poorer than that of bacteremia not associated with pneumonia [33]. This may be due to the failure to recognize the infecting pathogen. New diagnostic procedures, such as bronchoalveolar lavage and early use of computed tomography scans, might be useful to improve the prognosis of pneumonia during febrile neutropenia.

Superinfection by fungal pathogens or resistant bacteria is often associated with protracted neutropenia and prolonged use of broad-spectrum antibiotics, which suppress the growth of normal gastrointestinal flora, permitting fungal overgrowth. No specific regimen appears to be associated with a peculiar frequency or nature of superinfection [33]; factors other than antibiotic therapy and duration of neutropenia might be important [34]. As already mentioned, what is called fungal superinfection may represent in some cases the delayed appearance of initial fungal infection. Since the early diagnosis of fungal infection is difficult, a special effort should be made to investigate novel diagnostic means and to evaluate prognostic factors, allowing for early recognition of these fungal infections. These developments might alter the choice of empirical therapy for some patients with febrile neutropenia who might benefit from earlier administration of antifungal agents.

Finally, the introduction of cytokines for the management of infectious complications in cancer patients will have an important role in the future of empirical therapy. These agents with hematopoietic growth stimulatory and/or immunoenhancing properties have been shown to have clinical utility in patients with febrile neutropenia. GM-CSF and G-CSF offer a definite benefit for the prevention of infections during neutropenia by restoring phagocytic cells sooner after therapy. The use of these agents in patients with protracted neutropenia will decrease the need for empirical antibiotics and will most likely influence their choice. Moreover, it is likely that some of these cytokines, such as M-CSF, may have activity against specific infections, namely, those caused by fungi. Their early use in some patients with febrile neutropenia may in the future modify our choices regarding empirical antibacterial and antifungal therapy. The use of bone marrow-stimulating agents may also favorably influence the rate of bacterial and fungal superinfections by shortening the duration of severe neutropenia.

Conclusions

There are still problems to be solved with empirical therapy of febrile neutropenia. As summarized in Table 4, these problems mainly consist of

1. Increase in the frequency of gram-positive microorganisms, some of which are methicillin resistant
2. Increase in the number of β -lactamases in gram-negative microorganisms
3. Emergence of new and/or resistant pathogens based on institutional practices
4. Appearance of specific clinical and microbiological syndromes according to novel cancer therapy

Table 4. Problems with empirical therapy

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1. Increase in the frequency of gram-positive microorganisms, some of which are methicillin resistant
 2. Increase in the number of β -lactamases in gram-negative microorganisms
 3. Emergence of new and/or resistant pathogens based on institutional practices
 4. Appearance of specific clinical and microbiological syndromes according to novel cancer therapy
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Table 5. Perspectives for empirical therapy

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1. Constant adaptation of antibacterial regimens to emergence of resistant strains
 2. Definition of prognostic factors influencing the outcome of febrile neutropenia and allowing for adapted therapy
 3. Ambulatory and home therapy for patients with optimal prognosis
 4. Use of cytokines to restore bone marrow function in patients with poor prognosis
 5. Recognition of risk factors for fungal infections and improvement of diagnostic approaches; early therapy with novel drugs and cytokines
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Febrile neutropenia has been a changing syndrome over the last years. The perspectives and goals that we face today are summarized in Table 5. They are mainly

1. Constant adaptation of antibacterial regimens to the emergence of resistant strains
2. Definition of prognostic factors influencing the outcome of febrile neutropenia and allowing for adaptation of therapy
3. Ambulatory and home therapy for patients with optimal prognosis
4. Use of cytokines to restore bone marrow function in patients with a poor prognosis
5. Recognition of risk factors for fungal infections and improvement of diagnostic approaches; early therapy with novel drugs and cytokines

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6 New antifungal compounds and strategies for treatment of invasive fungal infections in patients with neoplastic diseases

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Patients with neoplastic diseases are predisposed to develop invasive fungal infections as the result of impairments host defense, due principally to pharmacological immunosuppression resulting from intensive cytotoxic chemotherapy, ablative radiation therapy, and corticosteroids. *Candida* spp., *Aspergillus* spp., and emerging opportunistic fungal pathogens comprise the principal etiological agents of opportunistic mycoses in neutropenic cancer patients. This chapter will review advances in the development of new antifungal drugs and therapeutic strategies for the treatment of life-threatening mycoses in neutropenic hosts.

Amphotericin B and its lipid formulations

Amphotericin B

The recent introduction of lipid formulations has been an important therapeutic advance in improving the therapeutic index of amphotericin B. In order to understand the potential impact of the recently introduced lipid formulations of amphotericin B, a firm understanding of conventional desoxycholate is necessary.

Amphotericin B is the cornerstone of therapy in critically ill patients with deeply invasive fungal infections. First isolated in the 1950s from *Streptomyces nodosus* (an actinomycete cultured from the soil of the Orinoco Valley in Venezuela [1], amphotericin B is a polyene macrolide that consists of seven conjugated double bonds, an internal ester, a free carboxyl group, and a glycosidic side chain with a primary amino group (figure 1). Amphotericin B is amphoteric, forming soluble salts in both basic and acidic environments. It is virtually insoluble in water. The intravenous infusion is commercially formulated as a desoxycholate micellar suspension consisting of 50 mg amphotericin and 41 mg desoxycholate.

The primary mechanism of action of amphotericin B, as well as other polyenes, is due to binding to ergosterol, the principal sterol present in the cell membrane of sensitive fungi [2]. This binding alters the membrane permeability, causing leakage of sodium, potassium, and hydrogen ions, eventually leading to cell death [3,4]. Amphotericin B also binds to a lesser extent to other sterols, such as cholesterol, which accounts for much of the toxicity associated with its usage [5,6].

**Mechanism of action – inhibition of ergosterol synthesis
by inhibiting C-14-demethylase**

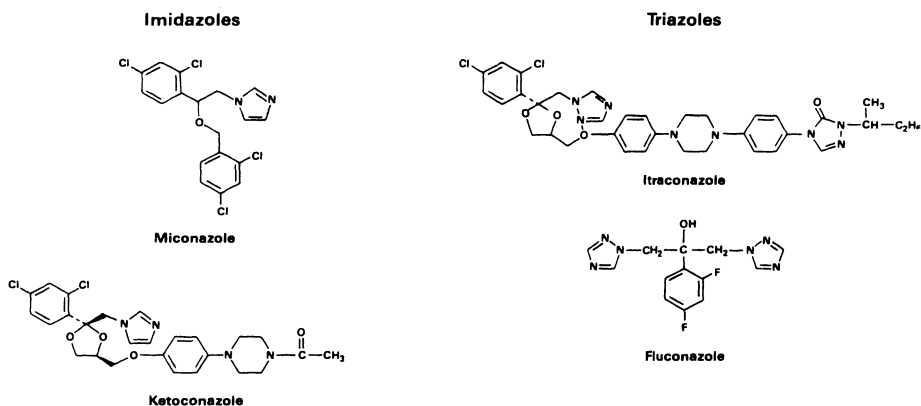


Figure 1. Systemically administered antifungal agents: Azole compounds.

Oxidation-dependent amphotericin B-induced stimulation of macrophages is another proposed mechanism of the chemotherapeutic effect of this polyene [7,8]. This immunomodulation is augmented by oxidative metabolites such as hydrogen peroxide and may be due to auto-oxidation of the drug with the formation of free radicals, or to an increase in membrane permeability, especially to monovalent cations [9]. Thus, in addition to the effect of amphotericin B on fungi, its effect on host cells may contribute to its antifungal properties.

Several studies have investigated the pharmacokinetics of amphotericin B in humans [10–13]. Following intravenous administration, amphotericin B is highly protein bound (91–95 percent), primarily to lipoproteins, erythrocytes, and cholesterol in plasma, and then redistributes from the blood into tissues [14]. It is thought to follow a three compartment model of distribution, with an overall apparent volume of distribution of 4 l/kg [10]. Peak serum concentrations following intravenous administration may be related to dose, frequency, and rate of infusion [15]. In adults, an intravenous infusion of 0.6 mg/kg yields peak serum concentrations of approximately 1–3 mg/l. These levels rapidly decline to achieve a prolonged plateau phase of 0.2–0.5 mg/l. Administration of twice the daily dose on alternate days results in slightly higher peak concentrations with no difference in minimum values [16]. Powderly et al. [17] found a direct relationship between dose and serum concentration, demonstrating peak concentrations of 1.2 and 2.4 mg/l 1 hour after infusion, and trough concentrations of 0.5 and 1.1 mg/l 23 hours postinfusion, following 3 days administration of 0.5 and 1.0 mg/kg, respectively. Increased rates of infusion (i.e., over 45 minutes) result in higher peak serum concentrations but do not affect values measured 18–42 hours postinfusion [18]. Concentrations of amphotericin B in peritoneal, pleural, and synovial fluids are usually less than half of the simultaneous serum concentrations [19], while cerebrospinal fluid (CSF)

concentrations range from undetectable [16] to no more than 4 percent of serum concentrations [20].

Amphotericin B follows a biphasic pattern of elimination from serum, with an initial half-life of 24–48 hours, followed by a long elimination half-life ($t_{1/2}$) of up to 15 days [10], probably because of the extremely slow release of the drug from peripheral tissues. Detectable levels of the drug have been demonstrated in bile for up to 12 days and in urine for 27–35 days following administration [21]. That intravenously administered amphotericin B is concentrated in the bile permits the successful treatment of *Candida* cholecystitis without direct instillation of the compound into the biliary tract [22]. Sufficient levels of amphotericin B can be detected in tissues such as liver and kidney for as long as 12 months after therapy has been terminated, supporting the theory that tissue accumulation accounts for the majority of drug disposition [23]. Since only 5–10 percent of amphotericin is excreted in urine and bile, no modification of the dosage is necessary in patients with renal failure or hepatic failure not attributable to the drug [24,25]. Hemodialysis usually does not alter blood concentrations of amphotericin B, except in hyperlipidemic patients in whom concentrations are decreased, apparently due to binding of the amphotericin B–lipoprotein complex to the dialysis membrane.

The pharmacokinetic profile of amphotericin B is somewhat different in children than in adults. Starke et al. [13] reported a smaller (<4 l/kg) volume of distribution and a larger (>0.026 l/hs/kg) clearance than that usually found in adults. The peak serum concentrations were significantly lower (approximately one half) than those obtained in adults receiving equivalent doses. Benson and Nahata [11] reported a strong inverse correlation between patient age and total clearance of amphotericin B, suggesting that higher dosages may be better tolerated in patients younger than 9 years of age.

Understanding the toxicity of amphotericin B, as well as strategies to prevent or manage it, has been a major area of research in recent years. Toxicity may be classified as acute or chronic. Acute or infusion-related toxicity is characterized by fever, chills, rigor, nausea, vomiting, and headache. The interaction of amphotericin B with mammalian cells is postulated as the primary cause of the chronic toxicity associated with this compound [5]. Fever, chills, and rigors may be mediated by tumor necrosis factor and interleukin-1, cytokines that are released from human peripheral monocytes in response to the drug [26]. These acute reactions may possibly be blunted by corticosteroids, paracetamol (acetaminophen), aspirin, or pethidine (meperidine) [27,28]. Corticosteroids should be utilized only in low dosages, such as 0.5–1.0 mg/kg of hydrocortisone. Pethidine in low doses (0.2–0.5 mg/kg) appears to attenuate the development of rigors. Paracetamol may decrease fever but appears to have little effect on rigors. Aspirin should be avoided in thrombocytopenic patients. Thrombophlebitis is a common local side effect associated with amphotericin B infusion. Slow infusion of the drug, rotation of the infusion site, addition of a small dose of heparin to the infusion, application of hot packs, use of in-line filters, and avoidance of amphotericin B concentrations in excess of 0.1 mg/ml have all been recommended to minimize this reaction

[29,30]. Infusion of amphotericin B through a central venous line avoids these complications.

Nephrotoxicity is the most significant chronic adverse effect of amphotericin B. Nephrotoxicity may be classified as glomerular or tubular. The clinical and laboratory manifestations of glomerular toxicity include a decrease in glomerular filtration rate and renal blood flow, while tubular toxicity is manifest as the presence of urinary casts, hypokalemia, hypomagnesemia, renal tubular acidosis, and nephrocalcinosis [30–32]. While the exact mechanisms involved in amphotericin B–induced azotemia have not been clearly delineated, it has been established that amphotericin B can cause changes in tubular cell permeability to ions both *in vivo* and *in vitro* [33,34]. Thus, one possible explanation for amphotericin B–induced azotemia may be tubuloglomerular feedback, a mechanism whereby increased delivery and reabsorption of chloride ions in the distal tubule initiates a decrease in the glomerular filtration rate of that nephron [35,36].

Tubuloglomerular feedback is amplified by sodium deprivation and is suppressed by previous sodium loading. Burgess and Birchall [31] suggested other possible mechanisms for amphotericin B nephrotoxicity, including renal arteriolar spasm, calcium deposition during periods of ischemia, and direct tubular or renal cellular toxicity. More recent studies implicate roles for prostaglandin and tumor necrosis factor α in mediating amphotericin B–induced azotemia [37]. The actual mechanism is likely a combination of these events. Azotemia is usually reversible, and renal function may return to normal levels following cessation of therapy. However, return to pretreatment levels may take several months in some cases [38]. Tubular defects may also persist and can be further exacerbated by other tubulotoxic agents, such as cis-platinum (diaminodichloroplatinum).

Amphotericin B–induced azotemia may be reduced or prevented by various maneuvers. In laboratory and clinical studies, sodium loading has been effective in attenuating the decrease in the glomerular filtration rate [36,39,40]. Normal saline (1 l/day) administered with amphotericin B (40 mg/day) to leukemic patients reduced the incidence of renal dysfunction [35]. Patients with cancer who are concomitantly receiving antibiotics with a high sodium content, such as carbenicillin, experience less severe nephrotoxicity than patients receiving amphotericin B plus antibiotics with a lower sodium content [41]. However, sodium loading requires close monitoring of patients to avoid hypernatremia, hyperchloremia, metabolic acidosis, and pulmonary edema. Furthermore, sodium loading will not ameliorate, and may indeed aggravate, hypokalemia.

Tubular toxicity is most commonly evident as hypokalemia and hypomagnesemia. Hypokalemia, which occurs in the majority of patients receiving amphotericin B, may require the parenteral administration of 5–15 mEq of supplemental potassium per hour. Amphotericin B–induced hypokalemia appears to be a result of increased renal tubular cell membrane permeability to potassium due to direct toxic effects, or it may be caused by enhanced excretion via activation of sodium/potassium exchange [42,43]. Cautious use of amiloride, the potassium-sparing diuretic, may attenuate the severity of hypokalemia. Magnesium wasting may also occur in association with amphotericin B therapy [44]. Such hypomagnesemia may be more

profound in patients with cancer who develop a divalent cation-losing nephropathy associated with the antineoplastic drug cisplatin [25].

Anemia is another common side effect of amphotericin B therapy. It is characterized as a normochromic and normocytic process that is probably mediated by suppression of erythrocyte and erythropoietin synthesis [30,45]. The anemia is exacerbated by deterioration of renal function due to a decrease in red blood cell production [46]. Maximal decreases in hemoglobin usually reach a nadir of between 18 percent and 35 percent below baseline, with levels usually returning to normal within several months of discontinuing therapy.

A number of important drug interactions with amphotericin B have been described. The renal toxicity caused by aminoglycosides and cyclosporin A are often enhanced by amphotericin B [47]. Acute pulmonary reactions (hypoxemia, acute dyspnea, and radiographic evidence of pulmonary infiltrates) have been associated with simultaneous transfusion of granulocytes and infusion of amphotericin B [48]. While some investigators have disputed the causality of amphotericin B to such reactions [49], a rational approach may be to separate the infusions of amphotericin B and granulocytes by the longest time period possible. In addition, concentrations of amphotericin B of $>5 \mu\text{g/ml}$ have been shown to have deleterious effects on normal neutrophil function in vitro [50].

Amphotericin B is still the drug of choice for treating the majority of deeply invasive mycoses. Among the opportunistic mycoses, amphotericin B is the preferred treatment for most neutropenic patients with invasive candidiasis, invasive aspergillosis, and zygomycosis. It remains the preferred therapy for patients with life-threatening infections due to *Cryptococcus neoformans* and the endemic fungi. The practical questions of daily dosage, total dosage, and duration remain relatively anecdotal and seldom have been studied in a prospective manner. Current recommendations are based upon the type of infection and the status of the host. Essential to the successful treatment of life-threatening mycoses, such as invasive aspergillosis, in neutropenic patients has been the early initiation of high-dose amphotericin B, recovery from neutropenia, and successful induction of remission of the underlying neoplastic process. These principles were well illustrated in the successful treatment of invasive aspergillosis during induction therapy for acute leukemia [51].

Disseminated fungal infections in granulocytopenic patients are difficult to detect and carry a high mortality [52–54]. Thus, empirical antifungal therapeutic strategies have evolved using amphotericin B. In a randomized prospective clinical trial, persistently febrile granulocytopenic patients had significantly fewer invasive fungal infections when they received empirical amphotericin B therapy [55]. These findings were confirmed in a larger trial that demonstrated decreased attributable mortality and fewer infections due to fungi [56]. This approach provides early therapy for occult fungal infections and systemic prophylaxis for patients at high risk of invasive mycoses.

Dosage of amphotericin B varies according to the specific fungus involved and the immune status of the patient. Persistently febrile granulocytopenic patients at the National Cancer Institute receive an initial test dose of 1 mg (0.5 mg in children $<30 \text{ kg}$) followed later by a dose of 0.5 mg/kg infused over 2–3 hours. Empirical

therapy is continued until the patient recovers from their granulocytopenia. Fungemia in a granulocytopenic adult patient is usually treated with a total dose of at least 15 mg/kg over 2–4 weeks, while fungemia in the nongranulocytopenic adult patient is treated with a total dose of at least 7 mg/kg over 2 weeks. Dosage and duration are increased for invasive candidiasis with tissue proven infection. Treatment of hepatosplenic candidiasis often requires several months of therapy. Treatment of invasive aspergillosis is discussed in greater length elsewhere [53].

Lipid formulations of amphotericin B

As toxicity is the major dose-limiting factor of amphotericin B, lipid formulations of amphotericin B have been developed to reduce toxicity and to permit larger doses to be administered [57,58]. Initial studies investigated several lipid formulations of amphotericin B that were prepared in individual laboratories [57–59]. While classically considered as ‘liposomal’ formulations of amphotericin B, the investigational and clinically approved formulations of amphotericin B have a wider diversity of lipid structure. Liposomes, defined as phospholipid bilayers of one or more closed concentric structures, as well as other lipid formulations, have been used as vehicles for amphotericin B with encouraging results. It has been proposed that they may act as a ‘donor,’ carrying the amphotericin B to the ergosterol-containing ‘target’ in the fungal cell membrane [58]. The lipid formulation may provide a selective diffusion gradient toward the fungal cell membrane and away from mammalian cell membrane. The lipid composition, molar ratio of lipid, and liposomal size all play a role in toxicity [60]. For example, when amphotericin B was incorporated into liposomes composed of dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol, there was selective toxicity for fungal cells but not for red blood cells [61]. Early clinical studies revealed remarkably little toxicity with administration of higher doses of the this multilamellar vesicle formulation of amphotericin B [62]. The engineering of lipid formulations of amphotericin B has required extensive investigation of the impact of different lipids and their proportions on safety and toxicity. Indeed, some formulations may augment the toxicity of amphotericin B.

Several carefully developed compounds are being investigated in North America: amphotericin B lipid complex (ABLC) [63], a small unilamellar vesicle formulation (AmBisome) [64], amphotericin B colloidal dispersion (ABCD; Amphocil) [65], and liposomal nystatin (LN). AmBisome was the first lipid formulation of amphotericin B approved for use in Western Europe. Approvals of clinical use are anticipated in Western Europe for ABLC and ABCD.

Each lipid formulation of amphotericin B confers distinct pharmacokinetic properties. As a general principle, however, AmBisome, ABLC, ABCD, and LN distribute to organs rich in reticuloendothelial cells, leading to higher levels in liver, spleen, and lung, and lower levels in kidneys, as compared with desoxycholate amphotericin B [66,67]. In mice and rats, 5 mg/kg of a AmBisome resulted in peak plasma concentrations of 87 and 118 mg/l, and $t_{1/2}$ s of 3–36 hours and 7–56 hours, respectively [68]. Indeed, infusion of AmBisome into rabbits results in strikingly

higher area-under-the-curve (AUC) values and peak concentrations (C_{max}) with this compound than is achieved with conventional amphotericin B or other lipid formulations of amphotericin B [69]. Conversely, the apparent volume of distribution (VD) for compounds such as ABCD and ABLC, following single dose infusion, are larger than that of AmBisome. A single dose of 1.5 mg/kg of ABCD in healthy human volunteers resulted in a mean $t_{1/2}$ of 235 hours and a plasma concentration of 0.10 mg/l at 168 hours [70]. In a comparative study in rats, ABCD resulted in decreased plasma concentrations, increased $t_{1/2}$, and increased volume of distribution as compared with desoxycholate amphotericin B [71]. Given their distinctive properties, the pharmacology of each of the polyene lipid formulations needs to be closely examined as part of their overall evaluation.

Lipid formulations of amphotericin B significantly reduce toxicity to mammalian cells. They are rapidly taken up by the reticuloendothelial system, thereby reducing binding to cholesterol and plasma lipoproteins [72]. This distribution also results in a reduction in the amount of drug taken up by renal tissue, resulting in a reduction in renal toxicity [68,69]. Francis and colleagues found that persistently neutropenic rabbits with invasive pulmonary aspergillosis that received AmBisome 5 mg/kg/day had no significant increase in serum creatinine above baseline in comparison with rabbits receiving amphotericin B 1 mg/kg/day, which was induced significant increase of serum creatinine above baseline [73]. Similar findings were found with ABCD in the treatment of experimental disseminated aspergillosis in immunocompromised rabbits [74] and experimental invasive pulmonary aspergillosis in persistently neutropenic rabbits [75]. Some data suggest that amphotericin B incorporated into liposomes has enhanced and prolonged activity as compared with equivalent concentrations of desoxycholate amphotericin B [76]. Experimental mycoses also were successfully treated at higher doses of ABLC with less toxicity than was achieved with amphotericin B [63].

While associated with less nephrotoxicity, lipid formulations may confer their own patterns of toxicity. For example, the multilamellar lipid formulation of amphotericin B composed of DMPG and DMPC induced reversible hypoxemia, pulmonary hypertension, and depression of cardiac output during infusion [77]. All of the lipid formulations of amphotericin B have been associated with elevated serum transaminases to a level that appears to be more frequent than that associated with conventional amphotericin B.

Lopez-Berestein and colleagues developed extensive experience with a multilamellar liposomal formulation of ABLC in the treatment of deep mycosis patients with refractory infection or azotemia [78]. Amphotericin B lipid complex in 228 cases treated under a compassionate release protocol was found to be active in treatment of immunocompromised patients with refractory mycoses or those with intolerance to conventional amphotericin B [79]. This study found little dose-limiting nephrotoxicity of ABLC. Ringden and colleagues reported successful therapeutic use of AmBisome with minimal nephrotoxicity in neutropenic patients and in those undergoing bone marrow transplantation [80]. Tollemar et al. [81] demonstrated the safety and activity of AmBisome for prophylaxis in a randomized trial in bone marrow transplant recipients. The most appropriate use, however, for the

lipid formulations of amphotericin B is for treatment of proven or suspected infections in profoundly immunocompromised patients.

Larger comparative trials are currently underway to investigate AmBisome in proven invasive fungal infections, empirical antifungal therapy, cryptococcal meningitis, and histoplasmosis. A comparative trial of ABLC versus amphotericin B has recently been completed. ABLC and ABCD are currently undergoing investigation in large clinical trials for treatment of aspergillosis and empirical antifungal therapy. These studies will provide an important foundation of data in understanding the utility of lipid formulations of amphotericin B.

Recently, lipid formulations of other polyenes have been developed. Nystatin, for example, has been incorporated successfully into liposomes, a formulation that would allow the drug to be given systemically [82]. Preliminary results from a murine model are encouraging concerning its toxicity and therapeutic effectiveness [83]. Clinical trials for dose escalation and treatment of candidiasis are currently being pursued with novel lipid formulation.

Flucytosine

Flucytosine (5-fluorocytosine, 5-FC), a fluorine analog of cytosine (figure 1), was first synthesized in the 1950s as a potential antineoplastic agent [84]. It was not effective against tumors but was found to have *in vitro* and *in vivo* antifungal activity [85,86]. Flucytosine is most frequently used as an adjunct to amphotericin B therapy. This combination was originally proposed because of the observation that amphotericin B potentiated the uptake of flucytosine by increasing fungal cell membrane permeability [87].

The mechanisms of action, pharmacokinetics, safety, and antifungal properties have recently been reviewed [88]. Two mechanisms of action have been reported for flucytosine. These are the disruption of protein synthesis by inhibition of DNA synthesis and by altering the amino acid pool by inhibition of RNA synthesis. These occur via a two-step process. Initially, flucytosine is taken up into susceptible cells by cytosine permease [89]. Flucytosine is converted intracellularly by cytosine deaminase to 5-fluorouracil, which replaces uracil in the pyrimidine pool and thus disrupts protein synthesis. In addition, 5-fluorouracil may then be converted through several steps to 5-fluorodeoxyuridylic acid monophosphate, a competitive inhibitor of thymidylate synthetase [90]. 5-Fluorouracil cannot be directly used as an antifungal agent because it is not taken up by fungal cells and it is highly toxic to mammalian cells [91].

Many fungi are resistant or develop resistance to flucytosine. Resistant fungi may have a deficiency in one of the enzymes necessary for conversion to the active molecule, may have decreased permeability to the drug, or may synthesize constituents that compete with flucytosine and its metabolites [92]. Flucytosine treatment is not thought to induce resistance but rather selects for resistant strains of *Candida* spp. in a given population, particularly when the compound is used alone. Consequently, when flucytosine is used in the treatment of candidiasis, aspergillosis,

cryptococcosis, or other opportunistic mycosis, it is used only in combination with amphotericin B.

As a low molecular weight, water-soluble compound, absorption of orally administered flucytosine from the gastrointestinal tract is rapid and nearly complete, providing excellent bioavailability [93]. There is negligible protein binding in serum, and the drug has excellent penetration with a volume of distribution that approximates that of total body water [94]. Administration of 150 mg/kg/day results in peak serum concentrations of 50–80 mg/l within 1–2 hours in adults with normal renal function. Cerebrospinal fluid (CSF) concentrations are approximately 74 percent of corresponding serum concentrations, accounting for its usefulness in central nervous system mycoses [20]. However, the compound accumulates in patients with impaired renal function, resulting in potentially toxic serum levels unless the dosage is reduced. The plasma $t_{1/2}$ of flucytosine in adults with normal renal function is 3–5 hours [93]. Dosage adjustments are required in patients with renal insufficiency and those on dialysis [94,95]. As approximately 90 percent of a given dose is excreted unchanged in the urine by glomerular filtration, dosage adjustment of flucytosine is inversely related to creatinine clearance.

Gastrointestinal side effects, such as diarrhea, nausea, and vomiting, are the most common symptomatic side effects associated with flucytosine therapy, occurring in approximately 6 percent of patients [96]. Abnormally elevated hepatic transaminases has also been reported in approximately 5 percent of patients receiving the drug [97]. Dose-dependent bone marrow suppression is the most serious toxicity associated with flucytosine administration [98]. Conversion of flucytosine to 5-fluorouracil by gastrointestinal flora may account for the majority of these toxicities [99,100]. These adverse effects may be controlled by close monitoring of the serum concentrations and adjustment of the dose to maintain peak serum concentrations between 40 and 60 mg/l. Since flucytosine is used in combination with amphotericin B, the conventional dosage of 150 mg/kg/day is not recommended in most patients. Instead, we use 100 mg/kg/day as a starting dose in patients with normal renal function. As the glomerular filtration rate decreases due to amphotericin B, flucytosine dosage is reduced to <100 mg/kg/day in three to four divided doses.

Synergistic or additive effects have been demonstrated in vivo and in vitro with *Candida albicans* and for *Cryptococcus neoformans* [101–103]. These findings are consistent with the clinical observations that the combination of flucytosine and amphotericin B in a prospective, randomized trial cleared CSF more rapidly than amphotericin B alone in the treatment of cryptococcal meningitis in non-human immunodeficiency virus (HIV)—infected patients [104]. This combination has also been shown to be effective against large cryptococcal intracerebral masses (cryptococcomas), eliminating the need for surgical intervention [105]. Larsen et al. [106] recently demonstrated that the combination of amphotericin B plus flucytosine was more effective than fluconazole in primary treatment of cryptococcal meningitis. The combination of flucytosine with amphotericin B is therefore recommended for the treatment of central nervous system (CNS), cryptococcosis or candidiasis, *Candida* endophthalmitis, *Candida* thrombophlebitis of the great veins, renal candidiasis, and hepatosplenic (chronic disseminated candidiasis).

Antifungal azoles

The antifungal azoles are synthetic compounds composed of imidazoles (clotrimazole, miconazole, and ketoconazole) and triazoles (itraconazole and fluconazole). Originally described as inhibiting fungal growth virtually 50 years ago [107], this class of compounds has proven to be a major addition to the antifungal armamentarium. The antifungal azoles demonstrate less toxicity than amphotericin B, have flexibility for oral administration, and have comparable efficacy under many circumstances.

The antifungal azole agents function principally by inhibition of the fungal cytochrome P450 enzyme lanosterol 14 α -demethylase, which is involved in the synthesis of ergosterol [108]. One of the nitrogen atoms of the azole ring is thought to bind to the heme moiety of the fungal cytochrome P450 enzyme lanosterol 14 α -demethylase, thereby interrupting the conversion of lanosterol to ergosterol [108,109]. Antifungal azole compounds also may have a suppressive effect on cytochrome-c oxidative and peroxidative enzymes [110,111].

Antifungal imidazoles

The first two antifungal azoles approved for human mycoses were the imidazoles clotrimazole and miconazole [112,113]. While both compounds have a broad spectrum and potent activity, both agents quickly revealed problems that are relevant to this class of drugs. Clotrimazole and miconazole are relatively insoluble in aqueous solution and are poorly absorbed from the alimentary tract. Clotrimazole also induces its own metabolism after brief courses of oral treatment due to the induction of hepatic microsomal enzymes, which increased metabolism of the drug, thereby destroying its systemic antifungal activity [114]. Consequently, clotrimazole is now only used as a topical agent. The insolubility of miconazole was overcome by dissolving it in a polyethoxylated castor oil that is believed to be responsible for causing the majority of the toxic effects of the drug [115]. These side effects include pruritis, headache, phlebitis, and hepatitis. Rapid intravenous infusion of miconazole has been reported to cause cardiac arrest [116]. While it has become a very successful topical antifungal agent and has been used for systemic antifungal prophylaxis in neutropenic patients [117], intravenous administration of miconazole is now seldom employed. Parenteral usage is currently limited to treatment of invasive infections due to *Pseudallescheria boydii* [25,118].

Ketoconazole was introduced in 1979 as the first successful orally absorbable antifungal azole (figure 2). It provided a broad spectrum of antifungal activity, a relatively long serum half-life, increased water solubility, and lack of significant autoinduction of hepatic degradative enzymes [119]. As ketoconazole is insoluble at neutral pH but is readily solubilized at pH <2, it is dependent upon an acidic intragastric milieu for systemic absorption. Ketoconazole is highly bound to plasma proteins and penetrates poorly into CSF, urine, and saliva [120]. The absorption of orally administered ketoconazole varies greatly from patient to patient [121,122]. A high carbohydrate meal ingested with ketoconazole may decrease total drug absorption, while a high lipid meal may increase it [123]. Bioavailability of the

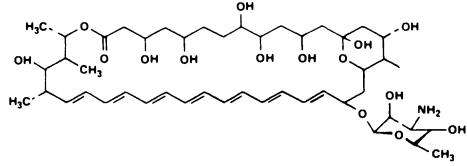

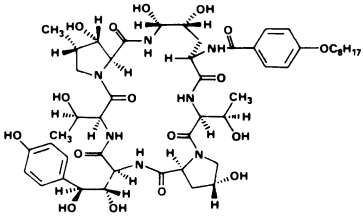
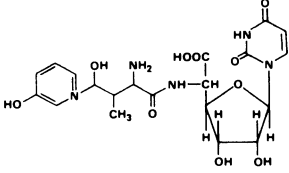
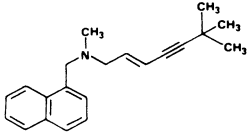
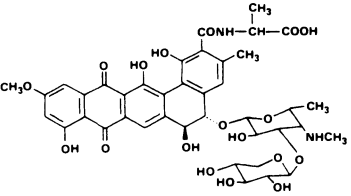
Agent	Class of Compound	Mechanism of Action
	Polyene	Binds to ergosterol, alters membrane permeability causing cation leakage; ? oxidative membrane damage
Amphotericin B		
	Fluorinated Pyrimidine	Disruption of protein synthesis; inhibition of thymidylate synthase
5-Fluorocytosine		
	Echinocandin	Inhibition of 1,3-β-glucan synthetase disrupting fungal cell wall biosynthesis
Cilofungin (LY121019)		
	Nikkomycin	Inhibition of chitin synthase disrupting fungal cell wall biosynthesis
Nikkomycin Z		
	Allylamine	Inhibition of squalene epoxidase
Terbinafine (Sandoz, SF 86-327)		
	Pradimycin	? forms complexes with mannose containing components of fungal membrane
BMY 28567		

Figure 2. Systemically administered antifungal agents: Non-azole compounds.

drug is reduced in patients with gastric achlorhydria [124]. Bioavailability can be improved by concomitant administration of an acidifying agent, such as acidulin, orange juice, or a carbonated beverage. Ketoconazole is extensively metabolized by the liver, primarily by scission of the imidazole and piperazine rings, and then is excreted in the bile as an inactive compound [121,125]. Less than 1 percent of active drug is excreted in the urine. No modification of the dosage is required in patients with renal insufficiency, and clearance is not significantly altered by chronic ambulatory peritoneal dialysis [126].

The most frequent dose-limiting side effects of ketoconazole therapy are nausea and vomiting, which occur in approximately 10 percent of patients receiving 400 mg/day, but increase to >50 percent in patients receiving >800 mg/day [127,128]. Also directly related to dosage of ketoconazole is the occurrence of endocrinopathies, which arise from the cross-reactive inhibition of mammalian cytochrome P450 enzymes. Among these endocrinopathies are antiandrogen effects of gynecomastia, oligospermia, and decreased libido in males, due to inhibition of C17–20 lyase, which is responsible for testosterone synthesis [129]. Less frequently observed is a transient dose-dependent decrease in the corticotropin (ACTH)-cortisol response due to inhibition of cytochrome P450-dependent enzymes involved in adrenal corticosteroid synthesis [130,131].

Hepatotoxicity, which does not appear to be dose dependent, ranges from transient asymptomatic hepatic transaminase elevations to fulminant hepatitis. Approximately 2–8 percent of patients receiving the drug experience some abnormal elevation of serum transaminases [132]. Most cases spontaneously resolve or stabilize during continuation of therapy, or reverse once administration is discontinued. Approximately 1 in 10,000 patients receiving ketoconazole develop progressive hepatitis, which has occasionally been fatal. Ketoconazole-related hepatotoxicity does not appear to be dose dependent.

Several important interactions between ketoconazole and other agents have been described. Ketoconazole prolongs the $t_{1/2}$ of cyclosporin, presumably by inhibition of cytochrome P450 enzymes [133], which may lead to cyclosporin-induced nephrotoxicity. Consequently serum cyclosporin levels are closely monitored and dosages of cyclosporin are adjusted in patients receiving ketoconazole. Ketoconazole's inhibition of the metabolism of antihistamines, such as terfenadine and astemizole, may lead to widening QT intervals and ventricular arrhythmias, including torsades de pointe. The serum concentrations of ketoconazole are decreased with concomitant administration of drugs that induce hepatic microsomal enzymes, such as rifampin [134]. Caution should also be exerted in the coadministration of ketoconazole with coumadin and oral hypoglycemic agents, as the concentrations of these drugs may increase to cause increased prothrombin time and hypoglycemia, respectively.

Plasma levels of ketoconazole are decreased by antacids or histamine H₂-receptor-blocking agents (i.e., cimetidine) due to elevated gastric pH, which impairs absorption of ketoconazole [135]. This erratic bioavailability compromises the role of ketoconazole in neutropenic patients, particularly those with chemotherapy or radiation-induced mucosal disruption. Consequently, ketoconazole has a very limited role in

neutropenic patients and is not recommended for prophylaxis or empirical antifungal therapy [136].

Ketoconazole is active against selected nonmeningeal fungal infections, including paracoccidioidomycosis, blastomycosis, chronic cavitary and disseminated histoplasmosis, and mucosal candidiasis, including chronic mucocutaneous candidiasis [137]. Since ketoconazole penetrates the cerebrospinal fluid poorly, it is not recommended for any fungal infection of the CNS. Thus, ketoconazole is not recommended for the treatment of cryptococcosis [138]. As the endemic mycoses seldom complicate the course of neutropenia, ketoconazole is seldom utilized for this indication in patients with neoplastic diseases. Moreover, itraconazole appears to be safer and at least as effective in the treatment of these infections. In the treatment of mucosal candidiasis in neutropenic patients, fluconazole is more consistently bioavailable than is ketoconazole and the current formulations of itraconazole.

Antifungal triazoles

Substitution of the triazole ring for the imidazole ring confers many structure-function advantages, including (1) greater polarity (improved solubility and reduced protein binding for some compounds), (2) reduced nucleophilicity of the triazole ring (improved resistance to metabolic degradation), (3) increased specificity for fungal enzyme systems, (4) broader antifungal spectrum, and (5) increased potency [139,140]. Itraconazole and fluconazole are the only antifungal triazoles licensed worldwide. Other antifungal triazoles with broader and more potent antifungal activity are currently being studied.

Itraconazole. Itraconazole is a water-insoluble, lipophilic triazole that exhibits potent in vitro and in vivo activity against most human fungal pathogens. The spectrum of itraconazole includes *Candida* spp., *Cryptococcus neoformans*, *Trichosporon* spp., *Aspergillus* spp., dematiaceous molds, and the thermally dimorphic fungi, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Paracoccidioides braziliensis*, and *Sporothrix schenckii* [141]. In comparison to ketoconazole, itraconazole has a broader spectrum of antifungal activity, less toxicity, a longer plasma half-life, and the capacity to penetrate into brain tissue.

Itraconazole is only soluble at low pH, such as in the normal gastric milieu. There is wide intersubject variation in the plasma concentration curves of itraconazole in healthy volunteers [142]. Oral bioavailability is compromised and becomes more erratic in patients receiving intensive cytotoxic chemotherapy causing disruption of gastrointestinal mucosal epithelium [143]. Absorption of itraconazole may be markedly diminished in patients receiving antacid therapy, such as oral antacids or H₂-receptor blocking agents. Mean peak serum concentrations of 0.02 mg/l are attained when a single 100 mg dose is administered during fasting, while peak concentrations of 0.18 mg/l are attained when the drug is administered after feeding, suggesting enhanced absorption with feeding [144]. Bioavailability may be further enhanced by administration of itraconazole with acidulin or a carbonated beverage.

Initial findings indicate that the bioavailability and interpatient variation in absorption of itraconazole is improved by incorporation of the molecule into cyclodextrin. Studies are currently underway to investigate the safety and plasma pharmacokinetics of this novel formulation of itraconazole. These properties should expand the utility of itraconazole to a wider range of patients undergoing intensive cytotoxic chemotherapy.

Itraconazole follows nonlinear plasma pharmacokinetics. Dosage increases between 100, 200, and 400 mg/day produce nonlinear increases in the area under the plasma concentration-time curve, suggesting the possibility of saturable metabolic processes [139]. The drug has a $t_{1/2}$ of 15–20 hours following a single dose and 30–35 hours following multiple dosing [142]. Further reflecting the nonlinear pharmacokinetic properties of itraconazole, twice-daily dosing (i.e., 200 mg twice daily) leads to improved total area under the curve in comparison with once-daily itraconazole (i.e., 400 mg/day). Itraconazole is highly protein bound (>99 percent), with only 0.2 percent available as free drug [145]. Thus, itraconazole concentrations in body fluids equivalent to body water, such as saliva and CSF, are negligible. However, tissue concentrations are two to five times higher than those in plasma, and they persist for longer, explaining the efficacy of the drug despite low plasma concentrations [146].

Itraconazole is extensively metabolized by the liver to hydroxy-itraconazole, which also possesses intrinsic antifungal activity. As the primary route of excretion is the biliary tract, no adjustment of dosage is necessary in patients with renal impairment. Less than 1 percent of the active drug, and approximately 35 percent of the inactive metabolites, are excreted in the urine. Metabolism of the drug is not altered by renal dysfunction, hemodialysis, or continuous peritoneal dialysis, thus precluding modification of dosage [147].

While itraconazole does not induce drug metabolizing enzymes and is a weak inhibitor of microsomal enzymes [145], several drug interactions bear note, particularly in relation to patients with neoplastic diseases. Cyclosporin levels may become elevated with the concomitant administration of itraconazole [148–150]. Cyclosporin concentrations should be monitored closely when these drugs are coadministered. A decrease in itraconazole plasma concentrations has been documented with concurrent administration of rifampin [145], and phenytoin and phenobarbital [151]. Rifampin may further reduce the serum levels of itraconazole. Although the extent of drug interaction may be reduced with itraconazole, caution is still warranted in its coadministration with antihistamines, coumadin, and oral hypoglycemic agents.

Itraconazole is well tolerated with long-term use. Most of the adverse reactions reported are transient and include gastrointestinal disturbances, dizziness, headache, and rarely leukopenia [152]. Itraconazole has a low incidence of hepatic toxicity, with less than 3 percent of patients experiencing transient elevations in serum transaminases [153]. Itraconazole does not appear to have any adverse effect on testicular or adrenal steroidogenesis [146]. A syndrome of hypertension and hypokalemia has been observed in some patients receiving high doses of the itraconazole, particularly at 600 mg/day [154].

Itraconazole is the first orally bioavailable antifungal compound with in vitro and in vivo activity against *Aspergillus* spp. Several studies have demonstrated activity of itraconazole against invasive aspergillosis in immunocompromised patients, including those with neoplastic diseases [155–157]. In a recently reported multicenter study of invasive aspergillosis, itraconazole administered at 400 mg/day following a 4 day loading dose of 600 mg/day demonstrated favorable antifungal activity [158].

Despite these encouraging results, itraconazole is most appropriate in its current formulation for patients with aspergillosis who do not have chemotherapy-associated nausea and vomiting, and who do not have mucositis. Either of these conditions will compromise compliance or oral bioavailability. For neutropenic patients with invasive aspergillosis, high-dose amphotericin B (1.0–1.5 mg/kg/day) remains the drug of choice. Invasive pulmonary aspergillosis in neutropenic patients may rapidly evolve, with ensuing hemorrhagic infarction, hemoptysis, respiratory failure, and disseminated infection. Antifungal therapy in this critical setting must be delivered reliably and in high doses. The unpredictable bioavailability of itraconazole in the profoundly neutropenic host precludes its use as a single agent. While there is considerable interest in combination therapy with amphotericin B and itraconazole, further studies are warranted to establish an understanding of this approach.

The concerns of the bioavailability of itraconazole were illustrated in a recently reported double-blind, placebo-controlled study of the efficacy of itraconazole in the prevention of fungal infections among neutropenic patients with hematological malignancies and intensive chemotherapy [159]. This study was unable to demonstrate a significant effect of itraconazole, underscoring the issue of tissue levels and antifungal activity. A recent study demonstrated in immunocompromised animals that when itraconazole was absorbed to achieve peak plasma concentrations (measured by bioassay) of $>5 \mu\text{g/ml}$, antifungal activity in vivo approximated that of amphotericin B [150]. Levels that were $<5 \mu\text{g/ml}$ were significantly associated with less antifungal activity. Translation of these pharmacodynamic findings to clinical conditions is suggested in the study of itraconazole in patients with prolonged neutropenia, in whom there was a direct relationship between plasma concentrations of drug and antifungal activity [160].

In the treatment of aspergillosis in patients with neoplastic diseases, itraconazole is more appropriate in the setting of patients who have recovered from neutropenia with persistent aspergillosis. If the infection is stable but persistent, then a closely monitored transition from parenteral amphotericin B to oral itraconazole would be more cost effective and beneficial for the patient's quality of life. Bone marrow transplant recipients who develop invasive aspergillosis in the postengraftment period may also be candidates if the infection is initially stabilized and reduced by amphotericin B. Serum concentrations should be monitored in all of these patients in order to ensure adequate bioavailability. Should serum concentrations be inadequate, then an increase of dosage is appropriate.

Itraconazole has been used successfully in the treatment of phaeohyphomycoses according to individual case reports [152,161,162]. An encouraging report from Sharkey and colleagues indicates that itraconazole is beneficial in treatment of

phaeohyphomycosis refractory to other forms of therapy [162], suggesting a primary role for this drug in the initial management of these infections. At doses ranging from 50 to 400 mg/day, itraconazole also has been shown to be effective therapy against paracoccidioidomycosis, blastomycosis, chronic cavitary histoplasmosis, and sporotrichosis [161,163,164]. Wheat and colleagues [165] found that itraconazole is effective for suppressive therapy and primary treatment of histoplasmosis in HIV-infected patients.

Fluconazole. Fluconazole is a water-soluble, meta-difluorophenyl bis-triazole compound that has been shown to be effective against infections due to *Candida* spp., *Cryptococcus neoformans*, and other fungi in patients with neoplastic diseases, HIV infection, and other immunocompromised states. Fluconazole inhibits fungal C-14 demethylase and is significantly less potent in the inhibition of the mammalian cytochrome P450-mediated reactions [166]. In the initial development of fluconazole, there was a disparity between its relatively low activity in vitro and its high in vivo activity. In general, the activity of the azole antifungal drugs can be affected by inoculum size, culture medium, pH, incubation temperature, and duration [167]. Subsequent studies have further clarified the standardized in vitro susceptibility to fluconazole [168]. These methods and those employing a new biochemical defined medium (HR medium) more accurately reflect the minimum inhibitory concentrations (MICs) that would be anticipated from in vivo and clinical data [169].

The low molecular weight and water solubility of fluconazole permit its rapid absorption and high bioavailability [170]. The pharmacokinetics of fluconazole are independent of both the route of administration and formulation [171]. Unlike ketoconazole or itraconazole, oral absorption of fluconazole does not depend upon a low intragastric pH, feeding, fasting, or gastrointestinal disease [172]. Fluconazole has a volume of distribution that approximates that of total body water (apparent volume of distribution of approximately 0.7 l/kg). Unlike ketoconazole and itraconazole, it is only weakly bound to serum proteins (12 percent), and thus most fluconazole circulates as free drug [170]. Mean peak plasma concentrations of 2–4 mg/l are achieved following a single oral or parenteral 100 mg dose [173,174]. Plasma concentrations peak approximately 2 hours after administration and are linearly proportional to the dose [175]. Multiple dosing of fluconazole leads to an increase in peak plasma concentrations to 2.5 times that achieved with single dosing [175]. Steady-state concentrations of fluconazole are generally achieved within 4–7 days during once-daily dosing [175]. Fluconazole exhibits a long $t_{1/2}$, ranging between 27 and 37 hours in adults [173–175]. The substantially shorter mean plasma half-life of 17 hours in febrile neutropenic children warrants that fluconazole be administered more frequently to such patients with life-threatening infections [176]. This shorter half-life in high-risk children also underscores that therapeutic trials conducted in adults cannot be readily extrapolated to children. Instead, separate therapeutic trials are required to accurately ascertain responsiveness in children at a given dosage.

Fluconazole penetrates well into virtually all tissue sites [175,177–179], including

the CSF [180,181]. Several studies have shown that the CSF to serum concentration ratios of fluconazole are between 0.5 and 0.9 [180–182], increasing to between 0.8 and 0.9 in the setting of meningeal disease [183]. Unlike other azole derivatives, fluconazole is relatively stable to metabolic conversion. Renal excretion accounts for more than 90 percent of the dose, with approximately 80 percent recovered in urine as unchanged drug and 11 percent recovered as metabolites [184]. As fluconazole is eliminated primarily by renal excretion, dosage modification is recommended for patients with renal failure. A 50 percent reduction of dosage is recommended in those with a creatinine clearance of 21–50 ml/min, and a 75 percent reduction of dose in those with a creatinine clearance <21 ml/min [125].

Fluconazole has been well tolerated with very few dose-limiting side effects. Nausea, other gastrointestinal symptoms, and elevations in hepatic transaminase have been reported in <5 percent of patients receiving the drug [185]. The incidence of asymptomatic hepatic transaminase elevations attributable to fluconazole may be as high as 12 percent in children with neoplastic diseases [176]. Exfoliative skin reactions (Stevens-Johnson syndrome) have been reported in patients with acquired immunodeficiency syndrome (AIDS), although the exact role of fluconazole in these reactions is unclear [184]. In animal studies, only histopathological changes were observed in the liver: fibroadenomas and mild hepatic steatosis [186]. Fluconazole does not appear to affect the synthesis of steroid hormones.

A minimal number of interactions between fluconazole and other agents have been described. The major interaction reported has been a rise in phenytoin toxicity, requiring monitoring of phenytoin concentrations with fluconazole coadministration [187]. In addition, concentrations of cyclosporin may be increased and the effects of warfarin may be potentiated [188]. Nevertheless, the number of drug interactions reported are substantially fewer than those that have been reported with ketoconazole.

Fluconazole has achieved its most important role in neutropenic patients as an agent for the prevention of invasive candidiasis. The experimental basis for administering fluconazole for prevention of disseminated candidiasis is reviewed elsewhere [189]. In order to investigate the potential use of fluconazole for the prevention and treatment of disseminated candidiasis in granulocytopenic patients, the *in vivo* activity and pharmacokinetics of this agent were investigated in persistently granulocytopenic rabbit models of experimental disseminated candidiasis. These models of disseminated candidiasis in granulocytopenic rabbits reflected critical variables that influenced the outcome in granulocytopenic patients: depth and duration of granulocytopenia (<100/ μ l for 2 weeks), indwelling central silastic venous catheter, broad-spectrum antibiotics, different patterns of disseminated candidiasis (acute, subacute, and chronic), sites of infection, and timing of initiation of antifungal agents. Pharmacokinetic studies in rabbits demonstrated a long plasma half-life and a large volume of distribution, corresponding to high levels of tissue penetration in multiple organ sites.

Fluconazole in these experiments was administered for systemic prophylaxis, early treatment, and delayed treatment. Fluconazole was more effective when used for systemic prophylaxis or early treatment of disseminated candidiasis in comparison with delayed treatment. Moreover, fluconazole was as effective as amphotericin B

plus flucytosine (A+5-FC) in the prevention and early treatment of disseminated candidiasis but was significantly less effective than A+5-FC in delayed treatment of chronic disseminated candidiasis. Dose-response studies demonstrated that the antifungal effect of fluconazole was dose dependent and time dependent, suggesting that more protracted courses of fluconazole would be required for the treatment of chronic disseminated candidiasis.

These experimental findings with fluconazole were predictive of the results obtained in a randomized, double-blind, multicenter trial of fluconazole for the prevention of deeply invasive candidiasis in bone marrow transplant recipients [190]. Fluconazole 400 mg/day Orally or intravenously was initiated on day 1 of marrow-ablative chemotherapy. Among 356 evaluable bone marrow transplant recipients, invasive candidiasis developed in 28 (15.7 percent) of 178 patients who received placebo and in 5 (2.8 percent) of 179 who received fluconazole ($p < 0.001$). Fluconazole in this study also delayed the initiation of amphotericin B from day 17 to day 21 ($p < 0.004$). Infections due to *Candida krusei* were noted in both arms and were not significantly different. Fluconazole was associated with minimal adverse effects in this setting. Another randomized, placebo-controlled trial reported by Slavin and colleagues from the Fred Hutchinson Cancer Center studied fluconazole at 400 mg/day Orally or intravenously in bone marrow transplant recipients [191]. Fluconazole in this study was administered through the duration of granulocytopenia and 100 days after recovery from granulocytopenia. Among the 301 transplant recipients enrolled, most of whom were adult allogeneic recipients, 261 evaluable cases were analyzed. There was a significant reduction in the number of fungal infections (6 of 131 in fluconazole-treated patients vs. 16 of 130 in placebo-treated patients; $p = 0.01$), use of empirical amphotericin B in the fluconazole-treated group, and a decline in mortality.

The beneficial effects of fluconazole in significantly preventing deeply invasive mycoses were not observed in another large randomized trial of fluconazole 400 mg/day versus placebo in adults with acute leukemia [192]. Among 257 evaluable patients, invasive mycoses developed in 10 (7.5 percent) of 133 placebo-treated patients versus 5 (4 percent) of 124 fluconazole-treated patients ($p = 0.3$). The lack of statistical significance in this large clinical trial may be due to a low frequency of proven invasive mycosis and an early usage of empirical amphotericin B. Candidemia and tissue-proven invasive candidiasis was diagnosed infrequently in this population, possibly due to an early and aggressive use of empirical amphotericin B. These findings also suggest that the risk for invasive candidiasis in this population of adults with acute leukemia was less than that of patients undergoing allogeneic bone marrow transplantation in the randomized fluconazole studies. Both multicenter fluconazole studies also reported a striking paucity of invasive aspergillosis in both groups. This effect may have been due to stringent criteria for demonstrating invasive pulmonary aspergillosis. For example, patients with computed tomography (CT) scans consistent with invasive pulmonary aspergillosis and treated as such were not cited as possible or probable infection. Moreover, patients who had completed the study but who were later found at autopsy to have invasive pulmonary aspergillosis were not considered as having this infection during study.

A study by Anaissie and colleagues at the M.D. Anderson Cancer Center compared fluconazole 400 mg/day versus intravenous amphotericin B 0.5 mg/kg/day for the prevention of fungal infections in 55 adults with leukemia [193]. Oropharyngeal candidiasis was prevented in all 45 evaluable cases in both arms. Among those patients receiving amphotericin B, disseminated fungal infections were due to *Candida albicans* in one patient and *Aspergillus* species in two other patients. Among those patients receiving fluconazole, the findings were similar when disseminated fungal infections were due to *Torulopsis glabrata* in one patient and *Aspergillus terreus* in another. Nephrotoxicity in the amphotericin B group required discontinuation of drug in six patients.

While the findings for prevention of invasive candidiasis by fluconazole in bone marrow transplant recipients are encouraging, there are several limitations in antifungal activity. For example, fluconazole at the current dosages of 200–400 mg/day has little or no activity against *Candida krusei*, *Torulopsis glabrata*, *Aspergillus* spp., Zygomycetes, and some hyalohyphomycetes, such as *Fusarium* spp. *Candida krusei* has been reported as a breakthrough infection in patients receiving fluconazole [194–196]. The magnitude of *C. krusei* infection may vary among centers, particularly those institutions that may have intrinsically higher levels of endemic *C. krusei* infections [188]. *Torulopsis glabrata* infections have developed in our center and others in patients receiving fluconazole.

The activity of fluconazole in the prevention of invasive candidiasis in granulocytopenic patients is dose dependent. There appears to be a trend among various studies using 200 mg/day in adults toward more frequent breakthrough fungal infections due to *C. albicans* and *C. tropicalis*, in comparison with those in which 400 mg/day is employed. This dose dependency is also consistent with earlier experimental antifungal studies with fluconazole against disseminated candidiasis in persistently granulocytopenic rabbits, in which a significant dose-response [mg/kg/day vs. colony-forming units (CFU)/g] relationship was observed in the clearance of *Candida* from tissues [189].

The results of a recently reported randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in 206 non-neutropenic adults demonstrated that fluconazole administered at 400 mg/day was equivalent to amphotericin B (0.5–0.5 mg/kg/day) when measured by clearance of fungemia, sequelae, and survival [198]. As non-neutropenic adults with solid tumors were enrolled in this study, these findings have important implications for the treatment of this subpopulation with neoplastic disease.

Cryptococcosis seldom emerges in neutropenic patients as a function of neutropenia per se. Instead, a concomitant defect in cell-mediated immunity is necessary. Such defects in patients with neoplastic diseases may include corticosteroids, fludarabine, lymphoma, or HIV infection. Fluconazole has been demonstrated to be active in suppressive therapy [199,200] and as primary treatment of cryptococcal meningitis in patients with AIDS who are at low risk for treatment failure [201]. Fluconazole may also be useful in the primary treatment of coccidioidal meningitis [202]. However, caution must be exerted in the use of fluconazole in patients with altered mental status, as these patients may further deteriorate.

Fluconazole is active in the treatment of mucosal candidiasis, including oropharyngeal and esophageal candidiasis. There are limited data currently available to support its use in the primary treatment of deeply invasive candidiasis; however, well-designed clinical trials are currently being pursued to investigate fluconazole for such uses. It has also been used for patients with persistent hepatosplenic candidiasis (chronic disseminated candidiasis) or those unable to tolerate amphotericin B [203,204]. The most favorable responses were observed in patients extensively pretreated with amphotericin B, suggesting a beneficial interaction between fluconazole and high concentrations of amphotericin B in hepatic, splenic, and other tissues.

Building upon this approach in the management of hepatosplenic candidiasis, a reasonable strategy is to initiate therapy with amphotericin B plus 5-FC and to complete therapy with high-dose fluconazole (6–10 mg/kg/day) until the disappearance or calcification of lesions. Hepatosplenic candidiasis due to *Candida tropicalis* may be particularly refractory to fluconazole therapy and may be amenable to only long-term amphotericin B. While antifungal therapy of hepatosplenic candidiasis may require 6–12 months, shorter durations of therapy may be achievable with lipid formulations of amphotericin B.

Investigational antifungal azole agents

DO-870, formerly known as ICI 195739, is an orally active bistriazole with broad-spectrum antifungal activity [205]. DO-870 is more freely permeable than ketoconazole and fluconazole, such that organisms that are resistant due to reduced azole uptake are more sensitive to this drug [206]. Pharmacokinetic studies have been limited, but data published thus far look very promising. A single dose of 50 mg/kg in mice produces a peak serum concentration of 17.6 mg/l 12 hours postdose and a $t_{1/2}$ greater than 12 hours. Daily dosing with 50 mg/kg for 21 days gave peak concentrations of 21 mg/l and trough concentrations of 19.5 mg/l with a $t_{1/2}$ greater than 48 hours [207]. Subsequent in vitro and in vivo studies have demonstrated activity of this agent against pathogens relevant to neutropenic cancer patients, including *Candida tropicalis* and *Aspergillus fumigatus* [208,209]. Clinical trials are currently being planned for this promising compound. Other antifungal azoles, including a promising agent manufactured by Pfizer, are currently being investigated in clinical trials; however, little preclinical or clinical data have been reported on these agents at this early stage.

Other antifungal azoles, the most notable of which is SCH39304, have been recently investigated; however, due to toxicity their development has been interrupted. SCH 39304 was an *N*-substituted triazole with broad-spectrum antifungal activity. It was active orally, parenterally, and topically. It exhibited excellent pharmacokinetics, with high levels of penetration into multiple tissues, including the CNS [210–213]. In all animal species tested, plasma concentrations of SCH 39304 were higher than those for fluconazole for a longer period of time [214]. In the setting of disseminated candidiasis in a granulocytopenic rabbit model, daily doses of 2

mg/kg were able to completely clear organisms from choroid, vitreous, and cerebrum, and to reduce CFU/g by $>10^4$ in liver, spleen, lung, and kidney tissue [215]. Combination therapy with a single high dose of amphotericin B and low daily doses of SCH 39304 was effective therapy for murine cryptococcal meningitis [216]. The potent broad-spectrum *in vivo* activity of SCH 39304 against *Candida*, *Aspergillus*, *Cryptococcus*, *Blastomyces*, *Coccidioides*, and dematiaceous molds held exceptional promise as a valuable agent. Anaissie et al. [217] recently reported broad-spectrum and potent antifungal activity of this compound in patients with refractory mycoses. Unfortunately, SCH 39304 has been shown to cause hepatocellular carcinoma in animals. Perhaps analogues of this compound that retain its potent and broad-spectrum antifungal activity, as well as its favorable pharmacokinetic profile, will be developed for treatment of mycoses in patients with neoplastic diseases.

Saperconazole is a water-insoluble, lipophilic fluorinated triazole with a very similar chemical structure to itraconazole, with the two chlorine atoms replaced by fluorine atoms (figure 2). It has a broad spectrum of antifungal activity, including the dimorphic fungi, phaeohyphomycetes, *Cryptococcus* spp., and *Aspergillus* spp. [218–220]. Unfortunately, saperconazole was shown to cause adrenal carcinoma in animals and its development was discontinued.

Investigational non-azole compounds

Echinocandins

The echinocandins are a class of fungicidal cyclic lipopeptide antifungal compounds that inhibit 1,3- β -glucan synthetase *in vitro* and *in vivo* [221]. Echinocandin B, which is produced by some species of *Aspergillus*, has excellent candidacidal activity but is quite toxic, causing hemolysis in particular [222]. However, this natural product provided a basis for the rational development of semisynthetic analogues with similar activity but reduced toxicity.

Cilofungin, which was the first echinocandin compound utilized in patients, is a semisynthetic lipopeptide derived from echinocandin B by the enzymatic removal of its linoleoyl side chain and chemical replacement with a 4-*N*-octyloxybenzoyl group [222,223]. (figure 1). The primary mechanism of action is the disruption of fungal cell wall biosynthesis by noncompetitive inhibition of 1,3- β -glucan synthetase [224]. The inhibition is specific with little or no effect on chitin, mannan, DNA, RNA, or protein synthesis [225]. Cilofungin has a narrow spectrum of antifungal activity limited to *Candida* species, specifically *C. albicans* and *C. tropicalis* [226,227]. However, echinocandins also have *in vivo* activity against *Pneumocystis carinii* [228]. High doses of cilofungin were also active against aspergillosis *in vivo* [158].

Cilofungin is very lipophilic and is not absorbed by the gut. Therefore, it can only be administered intravenously and is rapidly distributed. It is excreted almost exclusively in bile, with less than 2 percent of the dose being recovered in the urine

[229]. The drug has a short plasma $t_{1/2}$ of 1–2 hours, with a small area under the plasma concentration-time curve [230]. However, cilofungin administered by high-dose continuous or intermittent infusion results in nonlinear saturation plasma pharmacokinetics, which are associated with unexpectedly sustained, high plasma concentrations and significantly improved antifungal activity [231]. Unfortunately, cilofungin has been withdrawn from clinical trials because the carrier for the drug, polyethylene glycol, may cause metabolic acidosis in impaired renal function. However, the nonlinear pharmacokinetics characteristic of cilofungin emphasize the need to carefully determine the optimal dosing necessary to achieve effective therapy with future echinocandin derivatives. Other echinocandins are currently being developed that may permit the use of safer vehicles and broader spectrum antifungal derivatives [232–234].

Polyoxins and nikkomycins

Polyoxins and nikkomycins are nucleoside peptide antibiotics that are produced by soil strains of streptomyces [235]. The polyoxins, first described in the 1960s, were isolated from *Streptomyces cacaoi* var. *asoensis*, and the nikkomycins were characterized in the late 1970s as metabolites from *S. tendae* [236,237]. The polyoxins and nikkomycins are very specific inhibitors of chitin synthase, mimicking its substrate uridine diphosphate-*N*-acetylglucosamine [238]. The enzyme is an integral membrane protein, acquiring substrate from the cytosol. Therefore, these drugs require transport into the fungal cell in order to be effective [239]. This results in a wide range of susceptibility in intact fungi, although the isolated enzyme is uniformly sensitive. The nikkomycins, especially nikkomycin Z, have been shown to be effective against the highly chitinous, dimorphic fungi [240]. However, limited pharmacokinetic studies in mice suggest the drug has a very short $t_{1/2}$ (10–15 min). Therefore, more extensive pharmacokinetic and toxicological studies are necessary before the usefulness of this drug can be accurately determined. There have been many polyoxin derivatives produced in an effort to improve their antifungal potential [241,242]. Unfortunately, none have proven exceptionally useful thus far, and many investigators are now focusing on novel peptide delivery systems.

Allylamines

The allylamine derivatives are a class of agents derived from heterocyclic spiro-naphthalenones [243]. Their spectrum of antifungal activity includes *Aspergillus* spp., *Candida* spp., and *Sporothrix schenckii* [244]. However, their use has been directed more towards dermatophytic infections thus far. They function by inhibiting squalene epoxidase, a key enzyme in sterol biosynthesis [245]. Squalene epoxidase is also involved in mammalian cholesterol biosynthesis but is considerably less sensitive to the allylamines than the fungal enzyme [246]. Toxicity studies are very promising thus far. Since the allylamines do not inhibit cytochrome P450, they do not alter steroidal hormone levels, as observed with the azole derivatives [247].

Terbinafine (SF 86327) is considered the most active of the allylamine derivatives currently produced. Terbinafine is used worldwide as an oral agent for the treatment of onychomycosis and other dermatophyte infections. Terbinafine's in vitro activity is most striking against the dermatophytes, with good in vitro activity against *Aspergillus fumigatus*, *Sporothrix schenckii*, and other dimorphic fungi [248]. Unfortunately, there is little in vivo efficacy of oral terbinafine in animal models of aspergillosis, histoplasmosis, cryptococcosis, and coccidioidomycosis. This lack of efficacy is related to tissue distribution, where the lipophilic terbinafine accumulates on epidermis and subcutaneous fat tissue, to plasma protein binding (all plasma fractions including albumin and high, low, and very low density lipoproteins), and to rapid drug metabolism [249], all of which impair distribution into visceral tissue.

Pradimicins and benanomicins

The pradimicins and benanomicins are sterol-like molecules with amino acid-containing side chains that form calcium-linked complexes with mannose-containing components of the fungal cell membrane [250]. Pradimicin A (BMY 28567) is produced by a strain of *Actinomadura hibisca* [251], and the benanomicins are produced by an unidentified actinomycete [252]. They are fungicidal against a wide variety of fungi, including isolates resistant to other antifungal agents. Pradimicin A is not toxic to cultured mammalian cells at concentrations 100 times higher than the antifungal MICs (0.8–12.5 mg/l) [253]. The benanomicins also appear to have low toxicity. Of additional interest is the ability of pradimicin A to inhibit influenza virus replication and its possible anti-HIV effects at the stage of viral adsorption and cell-to-cell infection [254].

Recombinant human cytokines and immune reconstitution

Administration of the recombinant human cytokines, such as granulocyte-colony-stimulating factor (G-CSF), granulocyte-macrophage-colony-stimulating factor (GM-CSF), and macrophage-colony-stimulating factor (M-CSF) may decrease the duration of neutropenia (G-CSF, GM-CSF); increase the microbicidal function of neutrophils, monocytes, and macrophages (G-CSF, GM-CSF, M-CSF); and possibly improve mucosal integrity (G-CSF, GM-CSF) following cytotoxic chemotherapy under experimental and clinical conditions [255,256]. Shortening the duration of neutropenia by the use of recombinant human cytokines may permit more intensive cytotoxic chemotherapy. The impact of these cytokines on invasive fungal infections cannot be readily determined from the clinical trials performed thus far due to the relatively small numbers of patients studied. Clearly, decreasing the duration of granulocytopenia should decrease the frequency of invasive fungal infections. For example, autologous bone marrow transplantation with intensive cytotoxic chemotherapy is being conducted in some centers as an outpatient procedure as the result of recombinant human cytokines and administration of peripheral blood stem cells.

Nevertheless, some patients with profound persistent granulocytopenia, such as those with acute nonlymphocytic leukemia or those undergoing allogeneic bone marrow transplantation, may have only a modest shortening of their duration of granulocytopenia, thereby still carrying a high risk for invasive fungal infections. Patients also undergoing repeated cycles of intensive cytotoxic therapy may become colonized with *Candida* species during the course of repeated cycles, resulting in the potential for invasive candidiasis despite an abbreviated course of granulocytopenia. Nevertheless, cytokines such as G-CSF and GM-CSF appear to have ameliorated one of the important risk factors for the development of invasive fungal infections.

Whether cytokines are effective in the treatment of proven fungal infections in cancer patients is not known. Recent studies with GM-CSF suggest that this recombinant cytokine may be active as adjunctive therapy in the management of invasive fungal infections in patients with cancer [257]. A phase I clinical trial of recombinant human macrophage–colony-stimulating factor (M-CSF) in patients with invasive fungal infections demonstrated that M-CSF was well tolerated but did produce a transient dose-related thrombocytopenia [258]. The study design did not permit the evaluation of the potential antifungal properties of M-CSF versus optimal antifungal therapy alone. A randomized placebo-controlled clinical trial is being planned to delineate the potential role of M-CSF in the prevention of invasive fungal infections in neutropenic hosts.

Newer recombinant cytokines, such as interleukin (IL)-1, IL-3, IL-6, stem cell factor, and hematopoietic dipentapeptides, may result in improved recovery from marrow aplasia, lead to increased microbicidal function, and reduce the risk of invasive mycoses. Transfusion of elutriated monocytes, or of neutrophils from donors treated with G-CSF, may be important therapeutic or preventive adjuncts that merit further study. Such immune reconstitution with transfused effector cells would also provide a larger cell population for activation by cytokines in neutropenic patients.

Future directions

Antifungal chemotherapy has evolved to the stage where new agents from different classes of compounds, with different mechanisms of action, are being synthesized and extensively studied. Ideally, new antifungal agents should possess the following characteristics: potent broad-spectrum antifungal activity, no toxicity, flexibility of oral or parenteral administration, and favorable pharmacokinetics. In addition to antifungal chemotherapy, augmentation of host defense mechanisms will emerge as an important adjunct to antifungal therapy in neutropenic patients with neoplastic diseases. A functional immune system is the greatest defense against opportunistic fungi. Thus, biological response modifiers such as interferons, interleukins, and colony-stimulating factors may prove to be important adjuncts to antifungal chemotherapy.

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7 Herpesvirus infections in immunocompromised patients

Robert Snoeck and Erik De Clercq

Among infections of cancer patients, the relative importance of viral infections has increased in the last decade. More aggressive and prolonged immunosuppression, together with improved supportive care, have led to an increased survival of cancer patients. Meanwhile, a parallel increase in opportunistic infections, mainly viral infections, has been noted in such patients. Over the last few years, a better understanding of the physiopathology of these viral infections has enabled us to optimize both prophylaxis and treatment. At the same time, both molecular biology and monoclonal antibody technology have helped to improve diagnostic procedures, leading to more rapid and more accurate diagnosis.

Herpesviruses, particularly herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), and Epstein-Barr virus (EBV), are detected more frequently in immunocompromised hosts than in immunologically intact individuals. Other viruses, such as adenoviruses, papovaviruses (polyoma- and papillomaviruses), enteroviruses, and paramyxoviruses, have also been recognized as factors that contribute to morbidity in immunocompromised patients.

Herpes simplex virus

Descriptions of infections thought to be due to HSV, particularly the spread of cutaneous lesions, date to ancient Greek times and the writing of Hippocrates. Scholars of Greek civilization defined the word *herpes* to mean creep or crawl, in reference to the spreading nature of the visual skin lesions. Despite suggestions made on a clinical basis at the beginning of the century, it was not until 1968 that well-defined antigenic and biologic differences were demonstrated between herpes simplex type 1 (HSV-1) and herpes simplex type 2 (HSV-2) by Nahmias and Dowdle [1]. They showed that HSV-1 was more frequently associated with nongenital infection, while HSV-2 was associated with genital infection. The other major steps that have contributed to a better understanding of the natural history of herpes simplex infections and their treatment include: (1) the utilization of viral antigens to understand clinical epidemiology and to improve diagnosis; (2) the use of restriction endonuclease analysis as an epidemiologic tool; and (3) the determination of

successful antiviral therapy for HSV encephalitis, genital HSV infections, and mucocutaneous HSV infections of the immunocompromised host.

Clinical presentation

In nonimmunocompromised patients, HSV is known to be responsible for both primary and recurrent mucocutaneous infections, including orolabial and genital infections as well as keratoconjunctivitis. Herpes simplex virus is the most commonly identified cause of sporadic encephalitis. The virus may spread to the brain during primary or possibly recurrent infections, but vesicles are not usually present on the skin or mucosa [2]. Herpes simplex virus infections in immunocompromised patients are characterized by severe, chronic, and often extensive involvement of mucous membranes. Herpes simplex virus infections of the lip, mouth, skin, perianal area, or genital region may be more severe in immunocompromised patients than in normal subjects. The lesions tend to be more invasive, slower to heal, and associated with prolonged viral shedding. The study of natural history infection in immunocompromised patients (mainly renal transplant patients) has shown that HSV is often reactivated at multiple sites. There is mostly no evidence of systemic HSV disease [3]. While rarely occurring in immunocompetent patients [4], HSV hepatitis has been noted more frequently in immunocompromised patients. Herpes simplex hepatitis has been observed in recipients of solid organ transplants (two thirds were liver transplants). The hepatitis developed at a median of 18 days after transplantation. Eight of the 12 patients died and the clinical manifestations associated with mortality were hypertension, disseminated intravascular coagulation, metabolic acidosis, gastrointestinal bleeding, and bacteremia [5].

In a series of 46 patients with hematologic malignancies, viral cultures from saliva revealed an association between the presence of HSV in saliva and oral ulcers, especially those located on the alveolar process [6]. Recently, some data suggest that HSV isolation from lower respiratory secretions is associated with a more severe presentation and a worse outcome in immunocompetent patients than in immunocompromised patients [7]. While described in the initial reports on AIDS patients as one of the major opportunistic infections [8], HSV is found only in patients already infected with other opportunistic pathogens. The incidence of EBV and human CMV (HCMV) infections is much higher than for HSV [9]. In a large series of acquired immunodeficiency syndrome (AIDS) patients, a sharp rise was demonstrated in the incidence of oral HSV ulcerations in patients with low CD4 cell counts, with 60 percent of all ulcerations being HSV positive, suggesting that an appropriate anti-HSV treatment should be installed in such patients at the onset of these ulcerations [10].

The virus grows well on different cell lines, and the diagnosis can be made within 24–48 hours by the appearance of characteristic cytopathic changes. Diagnosis on biopsy specimens can be based on the presence of the characteristic multinucleated giant cells and intranuclear inclusions. Polymerase chain reaction (PCR) techniques can be applied on cerebrospinal fluid (CSF) specimens in the diagnosis of HSV encephalitis.

Treatment of HSV infections

The treatment of HSV infections is based on the use of intravenous acyclovir (ACV). Those immunocompromised patients who received ACV had a shorter duration of viral shedding and more rapid healing of lesions than patients receiving placebo [11,12]. Oral ACV therapy and, to a lesser extent, topical application of ACV have been shown to have quite a significant effect on viral shedding, pain, and healing of mucocutaneous lesions [3,13].

Intravenous or oral administration of ACV given prophylactically in severely immunocompromised patients reduces the incidence of symptomatic HSV infections from about 70 percent to 5–20 percent [14,15]. In solid organ transplantation, ACV prophylaxis has dramatically reduced the incidence of HSV hepatitis [5]. A sequential regimen of intravenous followed by oral ACV for 3–6 months can virtually eliminate symptomatic HSV infections in transplant recipients [16]. Cessation of ACV administration resulted in recurrence rates similar to those seen in placebo recipients. ACV requires phosphorylation by the virus-encoded deoxycytidine/thymidine kinase (TK) to express its antiviral action. This leads to the formation of ACV monophosphate (ACV-MP), and after further phosphorylation to the triphosphate by cellular enzymes the drug acts as a competitive inhibitor/alternate substrate of the viral DNA polymerase [17].

HSV drug resistance

Resistance to ACV is readily obtained *in vitro* by serial passages of HSV in the presence of the drug [18]. Only rarely has drug-resistant virus been isolated from normal, immunocompetent patients receiving ACV for HSV infections [19]. Furthermore, the recovery of ACV-resistant HSV clinical isolates from these patients has not been associated with the progression of clinical disease, and patients from whom isolates were obtained who were ACV resistant *in vitro* were found to respond well to continued ACV therapy [20,21].

However, the situation in the immunocompromised host is quite different, and ACV-resistant HSV strains have often been recovered from organ transplant recipients [22,23], patients with hematological malignancies [24], and those suffering from AIDS [23,25,26]. Infections with ACV-resistant viruses can result in progressive subcutaneous lesions, becoming a source of severe pain, disfigurement, and bacterial superinfection.

There are at least three mechanisms by which HSV can acquire resistance to ACV: reduction or loss in the TK activity, alteration of substrate specificity of the viral TK, and reduction of substrate affinity of the viral DNA polymerase [27]. Most of the HSV ACV-resistant strains that have been isolated from patients apparently belong to the first category, that is, they are TK deficient (TK⁻) [28,29].

Alternative antiviral agents for the treatment of TK⁻ ACV-resistant strains are those agents that do not require activation by the viral TK. The pyrophosphate analogue, foscarnet (PFA), is an inhibitor of HSV DNA polymerase that does not require phosphorylation for antiviral activity [30]. Foscarnet has become a useful

alternative for the treatment of TK⁻ ACV-resistant strains. However, it may be ineffective in the treatment of infections with ACV-resistant virus of the altered DNA polymerase variety. Some reports have documented alterations in the DNA polymerase of clinical HSV isolates that confer resistance to both ACV and PFA [31,32].

(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) was shown to be a potent antiherpesvirus compound, including HCMV, EBV, VZV, HSV, and those viruses that are deficient for their TK. Two immunocompromised patients were treated by local applications of HPMPC 1 percent, in a cream, once daily for 3 consecutive days per week, for mucocutaneous herpesvirus infections resistant to ACV and/or PFA. Patients were cured, and when they relapsed it appeared that the recurrence was due to the initial HSV wild strains, which had established a latency in the sensory ganglia. This work supports the potential usefulness of alternate therapy (ACV/HPMPC) for the treatment of mucocutaneous HSV infections in immunocompromised patients [33].

Varicella-zoster virus

Varicella-zoster virus is responsible for a primary disease (varicella or chickenpox) as well as recurrent disease (zoster or shingles) following reactivation of the virus at the level of one or more dermatomes.

Clinical presentation

The rash of varicella is the most typical feature of the disease, and the course of illness is generally benign. Varicella pneumonia is the most common serious complication in adults. It is rarely seen in children. Mortality from VZV pneumonia ranges from 10 percent to 40 percent [34,35], and fatal cases are invariably associated with widespread hematogenous dissemination. The severity of VZV infections in cancer patients, particularly those suffering from hematopoietic or reticuloendothelial malignancies undergoing cytotoxic and/or radiation therapy, is now well demonstrated [36,37].

Varicella-zoster virus is common in bone marrow transplant (BMT) patients. The median time of occurrence is 4–5 months after transplantation, with almost all the cases occurring in the first year. An overall mortality rate of 4–10 percent has been observed among patients not receiving antiviral treatment, death being the result of progressive dissemination with pneumonia. The mortality rate is nearly 30 percent in patients presenting with disseminated rash [38,39]. In adults with autologous BMT for Hodgkin's disease, a prior history of zoster is often associated with the development of herpes zoster in the first 150 days after transplantation [40].

Varicella-zoster virus infections in patients infected with the human immunodeficiency virus (HIV) may be more prolonged or severe, and their clinical presentation is often unusual. Multidermatomal involvement and hyperkeratotic skin lesions seem to occur specifically in patients with AIDS. Coalescence of single

lesions, hemorrhagic bullae, extensive ulceration with epidermal necrosis, and black eschars have also been observed. Isolation of virus from these lesions has proved difficult [41,42]. Central nervous system (CNS) diseases attributed to VZV in immunocompromised patients could appear without recent skin rash [42–45].

Prophylaxis of VZV infections

Prophylaxis of VZV infections is essentially reserved to patients at risk of contracting severe forms of varicella: patients with leukemia, Hodgkin's disease, or other diseases of the lymphoreticular system; cancer patients treated with immunosuppressive drugs; and BMT patients, irrespective of their own or donor serological VZV status.

Passive immunization is based on the use of human immunoglobulin preparations with high titers of antibody against VZV. Specific VZV immune globulins should be given preferably not later than 36 hours after contact with either varicella or herpes zoster. Nevertheless, most of the studies concluded that specific immune globulins do not effectively prevent VZV infection. Even in patients at risk in whom the rationale for administering specific immune globulins was not so much to prevent infection as to attenuate the severity of the disease, no clear-cut data could be obtained [46,47].

A live-attenuated vaccine has been obtained starting from the reference strain Oka [48]. The vaccine is highly protective in healthy children, and those not fully protected acquire at least partial immunity [49]. Seroconversion after one dose of the vaccine occurs in about 95 percent of healthy children, and persistence of antibodies has been observed in >90 percent of them for at least 2 years [49,50]. The more pronounced the antibody response after VZV vaccination, the more likely an individual is to have complete protection in subsequent years. The antibody titers measured 6 weeks after vaccination could be used as a surrogate marker for protection against a subsequent infection by the natural route [51]. Most breakthrough infections seem to occur in the first years after vaccination. It has been recently demonstrated that there is no transmission of the live-attenuated vaccine strains to immunocompromised children after immunization of their siblings [52].

The varicella vaccine is highly protective in leukemic children, although a minority of children only achieve partial immunity. The seroconversion rate was >90 percent following a two-dose vaccination regimen [53]. The efficacy of the vaccine in leukemic children who seroconvert was similar to that in healthy children. In leukemic children, the incidence of adverse effects in the first 6 weeks after immunization was significantly higher than in healthy children. About 1 month after vaccination, 50 percent of the children developed rash and fever, and some of them were treated with oral or intravenous ACV. It was possible to isolate the viral vaccine strain from the skin lesions [54]. After vaccination, leukemic patients acquired long-term immunity. In addition, the attack rate of clinical varicella among vaccinees who had again become seronegative and who had household exposures was only 30 percent compared with the 80–90 percent that could be expected in varicella-susceptible patients [55].

Leukemic children do have a higher incidence of zoster than a healthy matched population. Therefore, vaccinated leukemic children were followed closely for zoster and compared with leukemic children who had had natural varicella. From this surveillance study it appeared that the incidence of zoster was significantly lower in vaccinees than in leukemics with a history of natural varicella [49,56]. The lower incidence of zoster in the vaccinees could be explained by the fact that the vaccine strain is attenuated. Most likely, the virus may have no access to the sensory ganglia if the skin is not infected [57]. This was confirmed by follow-up studies of leukemic children, in whom zoster developed far more frequently in those who had rash after immunization than in those without rash [58].

Varicella-zoster virus must be cultured fresh on human fibroblasts. Distinct cytopathic effects usually appear after 3–10 days. Monoclonal antibodies are useful to confirm the diagnosis and for direct staining on vesicle fluid.

Treatment of VZV infections

Several experimental antiviral drugs have been tried because of the complications of varicella in the immunocompromised host. Cytosine arabinoside (araC) and iododeoxyuridine (IDU) have proven too toxic for systemic use in patients with VZV infections [59]. Acyclovir [60], in addition to alpha-interferon and vidarabine (araA), has proved efficacious in the treatment of varicella and herpes zoster.

The first drug shown to be successful in the chemotherapy of varicella in immunocompromised hosts was araA. In a study in which araA at 10 mg/kg/day was compared with placebo, patients receiving the drug ceased to form new lesions and defervesced more rapidly than the patients receiving placebo. The incidence of life-threatening complications was significantly lower in the treated groups than in the placebo group [61]. When ACV was used in a similar study, therapy had no effect on cutaneous healing or fever. However, administration of ACV did counteract the development of pneumonitis [62]. Improvement of the outcome of varicella in immunocompromised children treated with ACV was confirmed in another study [63]. Acyclovir given orally at 800 mg five times daily for 7 days proved to be efficacious in 25 immunocompromised children with varicella. In only two patients did oral ACV have to be changed to intravenous ACV. All children recovered from their VZV infection [64].

Acyclovir was first demonstrated to be active against zoster in a placebo-controlled trial [65], in which it reduced the frequency of cutaneous dissemination and visceral complications. In those studies in which ACV and araA were compared for their efficacy in the treatment of zoster in immunocompromised patients [66, 67], ACV proved clearly advantageous over araA in terms of cutaneous healing or disease progression, and also those patients receiving ACV were discharged more promptly from the hospital [67].

Among the nucleoside analogues that have been pursued in the clinic for the treatment of VZV infections, the (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) and 1- β -D-arabinofuranosyl (*E*)-5-(2-bromovinyl)uracil (BVaraU) are the most potent inhibitors of in vitro VZV replication that have ever been described [68]. A few

clinical trials have been conducted in patients with severe varicella or zoster. BVDU given orally to patients with underlying malignancy and severe herpes zoster did stop the progression of the disease within the day after beginning the treatment [69]. Similar results were obtained in children with cancer [70], as well as in severely immunosuppressed adults [71,72] and in immunocompetent adults with herpes zoster [73,74]. As a rule, all patients recovered rapidly from their VZV infection, and in no case did the treatment have to be prolonged for more than 5 days. BVaraU was found clinically efficacious in both immunocompetent [75] and immunocompromised patients [76].

Varicella-zoster virus drug resistance

Recently, several case reports appeared on the emergence of ACV-resistant VZV strains in AIDS patients following long-term ACV therapy [45,77–80]. Mutations at the level of the VZV thymidine kinase are responsible for the development of VZV resistance to these drugs that depend on the viral enzyme for their phosphorylation [45,81,82]. There is only little evidence for resistance due to mutations located at the level of the VZV DNA polymerase, although suggestive evidence for such alterations stems from the increased IC_{50} of the virus for foscarnet [80]. Five cases of ACV-resistant VZV infections treated with foscarnet have been reported [83] in which the clinical responses were not predicted by the *in vitro* drug susceptibility; healing was observed despite resistance to PFA and clinical failure was observed despite susceptibility to PFA. As already mentioned for HSV, HPMPC is a new alternative for the treatment of VZV infection resistant to ACV in immunocompromised patients, particularly AIDS patients [45].

Human cytomegalovirus

Human cytomegalovirus is the single most important infectious agent affecting organ transplant recipients, with evidence of HCMV infection in two thirds of these individuals. The prevalence, timing, and clinical effects of HCMV in organ transplant recipients are remarkably similar whether the transplant organ is a kidney, a liver, a heart, or such organ combinations as heart-lung and pancreas-kidney [84,85].

Human cytomegalovirus is reactivated following exogenous immunosuppressive therapy and allograft rejection [86]. In patients undergoing allogeneic BMT, among all the viral pathogens, HCMV causes the greatest mortality and morbidity, and has been most common infectious cause of death. Human cytomegalovirus infection also occurs after syngeneic or autologous BMT, but is less severe in these situations [87,88]. Approximately 50 percent of all allogeneic transplant recipients develop HCMV infection [87,89,90].

The major risk factors for HCMV infections after allogeneic BMT are HCMV infection in the marrow recipient before transplantation (seropositivity), frequent blood transfusions from HCMV-seropositive donors, graft-versus-host disease (GvHD) in the recipient, and HCMV infection in the bone marrow donor

(seropositivity). The incidence of HCMV infection and of HCMV pneumonia is higher in patients seropositive for HCMV before transplantation than in those who are seronegative. Even when an external source of infection could not be excluded, it was shown that the pneumonia in seropositive patients was caused by a HCMV strain genetically identical to the HCMV detected in their blood before transplantation. In HCMV-seronegative BMT recipients, primary HCMV infection usually is acquired from blood products infected with latent virus.

HCMV contributes directly or indirectly to morbidity and mortality in AIDS patients. There is an extremely high prevalence of HCMV infections in most HIV-infected populations [91,92]. Rates of seropositivity for HCMV in healthy American homosexual men are usually above 90 percent. In homosexual men with AIDS, seropositivity for HCMV approaches 100 percent. Excretion of HCMV is increasing with HIV-induced immune dysfunction, and HCMV is easily isolated from urine, throat, and blood, while recovery of virus in the semen is exceedingly common, with isolation rates of up to 40 percent in homosexual men [93].

Clinical presentation

Very often, the target organ of HCMV infection is the organ that is transplanted. For example, more hepatitis occurs in liver transplant recipients and more pneumonitis occurs in lung transplant patients when compared with other transplant patients [86,94,95]. The interstitial pneumonitis is associated with significant morbidity and mortality in BMT patients. Human cytomegalovirus interstitial pneumonitis in the immunocompromised host may be difficult to distinguish from pneumonitis caused by gram-negative bacteria, *Aspergillus*, *Nocardia*, *Legionella*, and *Pneumocystis carinii* or a combination of any of these. Interstitial pneumonitis occurs in 20–30 percent of the allogeneic BMT recipients. Human cytomegalovirus is associated with almost 50 percent of the cases [12,87,90,96,97]. The overall mortality from interstitial pneumonitis is high (60–80 percent) and is somewhat greater in patients with HCMV interstitial pneumonitis (70–90 percent).

The risk factors associated with the development of interstitial pneumonitis are allogeneic BMT, acute GvHD, prior HCMV exposure of the donor and recipient, occurrence of active HCMV infection in lungs and blood, conditioning regimen with total body irradiation (TBI), and to a lesser extent age and disease status [96,98]. Although virus is detected, it is often present in quantitatively low amounts, relative to the degree of pulmonary infiltrates that are visible on the chest radiograph. This suggests that there are probably host immune processes that contribute to the disease itself. HCMV-interstitial pneumonitis typically occurs between 3 and 12 weeks after transplantation and has a median time of onset of 7 weeks after transplantation [12]. Most cases of interstitial pneumonitis that occur before 9 weeks or after 12 weeks are either idiopathic or caused by organisms other than HCMV [99]. The onset of symptoms may be rapid, with fulminant respiratory failure developing over 2–30 days in association with the formation of bilateral diffuse interstitial infiltrates. Many cases have a more benign course, characterized by prolonged fever for one or more weeks, followed by the development of a

nonproductive cough, dyspnea, and lower lobe infiltrates, which progress to more diffuse infiltrates. In a review of pulmonary complications in patients undergoing autologous BMT, the spectrum of infection was similar to that of reported following allogeneic BMT, but HCMV interstitial pneumonitis was not as frequent a problem in the autologous transplant groups [100].

Sequelae of HCMV interstitial pneumonitis infection may be serious, as demonstrated in a series of lung allograft recipients. The roles of chronic rejection and both fungal and bacterial infections were significantly higher in patients with HCMV biopsy-proven pneumonitis [101]. Isolation of HCMV from pulmonary secretions or lung tissues and pneumonia is common in patients with AIDS, but a true pathogenic role of the virus in the progression of the disease has not been established [102].

Open-lung biopsy and bronchoalveolar lavage associated with the use of monoclonal antibodies and/or DNA hybridization have greatly improved the diagnosis of HCMV interstitial pneumonitis.

Clinically significant hepatitis is usually not a serious problem after transplantation. There are, however, some reports of hepatitis after renal transplantation, and it is a definite problem after liver transplantation. Biochemical evidence of hepatitis due to HCMV is frequently seen in liver transplant recipients with HCMV infections. The most important diagnosis to exclude is transplant rejection, since the therapy for HCMV hepatitis is aimed at reducing immunosuppression, while for rejection it has to be potentiated. In the last 10 years, liver biopsies have been increasingly used for the diagnosis of liver dysfunction after transplantation [95,103–105]. Histological evidence of HCMV hepatitis is seen in one third to one half of patients with AIDS who have evidence of HCMV infection in other organs [102].

Gastrointestinal hemorrhage caused by ulcerations in the gastrointestinal tract mucosa, in which cells bearing the typical HCMV inclusions can be easily recognized, has been shown to be an important manifestation of HCMV infection in transplant patients. Human cytomegalovirus-associated gastrointestinal lesions can appear in the absence of other manifestations of HCMV disease [106,107]. A recent report [108] pointed to the importance of HCMV infection of the upper gastrointestinal tract in patients with heart transplantation. Among 53 patients with persistent gastrointestinal symptoms, 16 (30.2 percent) had positive biopsies for HCMV in cell culture, most of them being taken from the gastric mucosa. In AIDS patients, consistent clinical syndromes of colitis, gastritis, and esophagitis have been described along with histological evidence of severe HCMV vasculitis in these organs [109].

The major late manifestation of HCMV infection in transplant patients is chorioretinitis. Infection first becomes apparent more than 6 months after transplantation. Most of the patients present with complaints of blurred vision, scotoma, and decreased visual acuity. Symptoms may be restricted to one eye on presentation, but progression to bilateral involvement is the rule. A similar course of events is seen in AIDS patients [102]. Human cytomegalovirus retinitis has been observed in 15–46 percent of AIDS patients in the United States [110], but it has not been seen in AIDS patients in Africa [111]. Human cytomegalovirus retinitis is usually the result of disseminated HCMV infection and severe immunosuppression. The

differential diagnosis of retinal lesions in AIDS includes cotton-wool spots (present in 50 percent of AIDS patients), retinal hemorrhages, Roth spots, choroid granulomas, retinal periphlebitis, and central nervous toxoplasmosis [112].

Central nervous system disease is a rare complication of HCMV infection in transplant patients [96]. Encephalitis with histologic changes characteristic of HCMV has been described. As with HCMV interstitial pneumonitis, coinfection with other opportunistic pathogens is commonly present, so that a distinct encephalitis syndrome attributable to HCMV is difficult to define.

Prophylaxis of HCMV infections

The development of live attenuated vaccine against HCMV is still controversial. The main objections to such a vaccine are the following:

- Primary infection may not be the main cause of mortality or morbidity due to HCMV. Reactivation or reinfection in immunosuppressed patients may be more important.
- Like the natural virus, a live vaccine strain may persist in the recipient, and it may be reactivated at unpredictable times.
- There are no clear markers of attenuation either in cell culture or in animals (there is no animal model available).
- There are numerous strains of HCMV, and they may differ in antigenic composition.

Nevertheless, the development of a vaccine against HCMV has been pursued, particularly for two clinical situations in which high mortality and morbidity have been described: pregnant women with an immature fetus [113] and exogenous infection of the immunocompromised patients.

A live attenuated vaccine has been developed by serial passages of the Towne strain in cell culture in order to obtain a high-passage strain that replicates well in cell culture. At the 125th passage, pools of virus were made for human trials [114].

- The Towne live attenuated vaccine strain produces a cellular and humoral immune response without viral excretion or latency [115].
- The Towne vaccine partially protects seronegative renal transplant recipients from severe HCMV disease but does not prevent them from getting infected [116].
- In healthy subjects, the live vaccine is also protective [117].

Since there was some concern about the use of live herpesvirus vaccines because of their theoretical potential to be oncogenic, other approaches have been designed. Actually, a recombinant vaccine based on the HCMV gB protein has been considered. Whether gB is the best HCMV protein for a vaccine is still under discussion, although only a limited number of distinct gB variants among clinical strains have been found [118].

Several clinical trials have been conducted with hyperimmunoglobulin, hyperimmune plasma, and high doses of nonspecific immunoglobulins in the prophylaxis of HCMV disease in bone marrow and renal transplant recipients. In BMT patients, a reduction was demonstrated in the rate of HCMV pneumonia and a reduction in

symptomatic HCMV-associated disease was also noted, yet no differences in overall rates of HCMV infections were seen. A significant reduction in GvHD was demonstrated in the group receiving immunoglobulin prophylaxis [119]. In other studies, a significant reduction was observed in the rate of HCMV infections in those patients who received, in addition to hyperimmunoglobulins, screened HCMV blood products [120].

Antiviral drugs have also been used in the prevention of HCMV disease in BMT patients. Despite the discouraging results of ACV therapy in the treatment of established HCMV disease, the drug has been administered prophylactically, with the intention of providing systemic levels of ACV before viral replication begins or accelerates, less drug being supposed to be required to prevent HCMV replication than to suppress it.

In a randomized study, ACV was able to reduce the rates of HCMV pneumonia, invasive HCMV disease, mortality during the first 100 days after transplantation, and virus shedding compared with controls [121]. Similar results were reported for kidney and liver transplant patients.

Recently, the use of ganciclovir in the prophylaxis of HCMV disease was suggested, and several studies have been conducted to clarify the potential of this compound for this indication. In recipients of allogeneic BMT, neither interstitial pneumonitis nor other signs of HCMV disease were noted when ganciclovir was given prophylactically [122]. Similar observations were made by others [123], giving ganciclovir prior to transplantation and as soon as hematologic parameters recovered until day 70. In a number of pulmonary allograft recipients, ganciclovir given for 3 weeks after transplantation and followed for 2 months by oral ACV appeared to have considerable potential for the prevention of HCMV infections, as compared with a previous study in which patients received only ACV prophylaxis [101].

Prophylaxis with ganciclovir for HCMV infections in transplant patients must be regarded as early or preemptive therapy. Patients have to be examined after transplantation for the presence of virus in bronchoalveolar lavage (BAL) or buffy coats before they show any signs of disease. If the samples are positive, treatment is initiated. Bone marrow transplant patients with a positive BAL on day 35 post-transplant are randomized to receive either ganciclovir (5 mg/kg once daily for 2 weeks and then five times per week until day 120) or placebo. Under these conditions, ganciclovir proved effective in preventing HCMV infections [124]. In a similar study in 73 BMT patients excreting HCMV, ganciclovir was compared with placebo; ganciclovir was found to reduce the incidence of HCMV disease and to increase the survival rate [125].

The diagnosis of HCMV infection can be made in cell culture (human fibroblasts), in which it leads to a typical cytopathic effect (CPE). Nevertheless, the time required for a viral CPE to develop is often 2–3 weeks. The recent advance in molecular biology has permitted the development of rapid assays based on the detection of immediate early antigens by specific monoclonal antibody. An answer can be given within 24 hours. Also polymerase chain reaction (PCR) techniques are being elaborated for early diagnosis of HCMV infections.

Treatment of HCMV infections

In the early days of HCMV therapy, several anticancer drugs with uncertain antiviral activity were tested to treat HCMV diseases. Drugs such as idoxuridine or cytosine arabinoside were used in small groups of patients with poor results, discouraging their further use in controlled trials [126]. Vidarabine that was shown to have activity against herpesviruses in vitro, including HCMV [127], was subjected to a few uncontrolled studies without much benefit but was associated with significant gastrointestinal, hematological, and neurological adverse effects [126]. Although HCMV strains are relatively insensitive to ACV in vitro [128], a randomized, placebo-controlled double-blind trial of ACV therapy in immunocompromised patients was conducted [129]. Renal allograft recipients receiving ACV defervesced and showed clinical improvement sooner than did patients receiving placebo. Although HCMV was recovered from the throat and urine of patients treated with ACV throughout the study, viremia ceased after the first day of drug administration. Allograft BMT recipients treated with ACV alone or in combination with interferon did not show improvement of their HCMV pneumonitis [130].

Among the drugs shown to be active against HCMV both in vivo and in vitro, two have been licensed for clinical use: ganciclovir and foscarnet. Ganciclovir is currently the reference drug for the treatment of HCMV diseases and has been subject of many clinical evaluations. As expected from preliminary studies in vitro on normal human hematopoietic progenitor cells [131], and more recently on granulocyte-macrophage progenitor cells [132], the main adverse effect shown by ganciclovir is neutropenia. In vivo, neutropenia may be both dose related or idiosyncratic. Recipients of allogeneic BMT appear to be more susceptible to ganciclovir-associated neutropenia than other immunosuppressed patients [133]. Other adverse effects of ganciclovir therapy include hepatocellular dysfunction, thrombocytopenia, infusion site reaction, and gastrointestinal and CNS abnormalities [134]. All these adverse reactions are usually reversible with discontinuation of the drug.

Like ganciclovir, PFA is now widely used for the treatment of HCMV infection in immunocompromised patients, particularly in those patients in whom HCMV strains resistant to ganciclovir have been isolated. The major adverse effect of PFA is renal dysfunction [135,136]. Other adverse effects include phlebitis at the infusion site, gastrointestinal disturbance, decrease in hemoglobin concentrations, and electrolyte abnormalities (i.e., hypocalcemia and hyperphosphatemia) that may be responsible for the arrhythmias and seizures observed in the context of acute overdose or excessively rapid infusion of PFA.

In HCMV retinitis, ganciclovir given at doses of 3–15 mg/kg stabilizes or improves retinitis and vision in 75–85 percent of AIDS patients [133,137]. A randomized prospective trial has shown that progression of retinitis occurred sooner in patients not given maintenance therapy [138]. Relapse or progression of retinitis during maintenance therapy ultimately occurs in many cases but may respond to reinduction and higher maintenance doses [139,140]. The use of granulocyte-macrophage–colony-stimulating factor (GM-CSF) in combination with ganciclovir has been reported in patients with AIDS and HCMV retinitis. Ganciclovir resistance

did not develop in any patient, and progression of retinitis was prevented in most patients [141]. The concomitant administration of HCMV immunoglobulins and ganciclovir in AIDS patients with HCMV retinitis did not appear to give additional benefit [142]. HCMV retinitis has also been treated successfully with ganciclovir in patients who were immunologically compromised as a result of solid organ or bone marrow transplantation [133]. Unlike patients with AIDS, these patients often do not require maintenance ganciclovir therapy to control disease progression as the recovery of their immune system helps to prevent further active infection.

Another treatment modality with ganciclovir that has potential utility is intravitreal administration. Advantages include the absence of systemic toxicity, the absence of a need for intravenous access, and the ability to administer zidovudine simultaneously. Disadvantages include lack of treatment of systemic infections and local complications such as retinal detachment, vitreal bleeding, or endophthalmitis. In patients treated with intravitreal ganciclovir, vision improved or remained stable after induction therapy. Relapses occurred while on maintenance in about 20 percent of eyes, but in general there was a response to repeated induction [143,144].

In uncontrolled trials, PFA has been shown to be an effective agent for the treatment of HCMV retinitis, with an initial response rate of nearly 90 percent [145]. As with ganciclovir, subsequent maintenance therapy is necessary since most patients relapse within 1 month after completion of PFA induction therapy [146].

Data from AIDS Clinical Trial Group (ACTG) program suggest that intravenous PFA maintenance therapy at 60, 90, or 120 mg/kg/day in AIDS patients with HCMV retinitis, who successfully completed PFA induction therapy is associated with a median time of retinitis progression of 90, 95, and >122 days, respectively [147]. A study comparing ganciclovir with PFA in the treatment of sight-threatening HCMV retinitis has recently been reported [140]. The two drugs were about equally effective in the treatment of HCMV retinitis. It was noted that patients treated with PFA had a 4 month longer survival than those receiving ganciclovir.

Although ganciclovir monotherapy may prevent the production of HCMV virions, it does not appear to prevent the production of viral proteins, which continue to be expressed at the cell surface. Thus, some patients with HCMV interstitial pneumonitis may appear to respond to ganciclovir therapy, becoming HCMV culture-negative, but nevertheless develop interstitial pneumonitis as a result of immune-mediated damage directed against infected cells. Meanwhile, ganciclovir monotherapy in immunocompromised patients with severe HCMV interstitial pneumonitis has shown consistently good clinical responses in solid organ recipients, as recently confirmed in a group of heart-lung transplant recipients [148]. However, responses have been variable in BMT recipients.

Relapses of HCMV disease are relatively uncommon in solid organ transplant recipients, particularly in those receiving a prolonged course of induction therapy, probably as the result of the relatively rapid recovery of their immune function. Monotherapy with ganciclovir in BMT patients has been reported to be more effective when given early in infection, as was demonstrated also in renal transplant recipients [149–151]. Nevertheless, results obtained with ganciclovir monotherapy for HCMV interstitial pneumonitis in BMT patients were generally disappointing

[133,152,153]. Ganciclovir appears to be well tolerated by children, and results obtained in pediatric patients are similar to those obtained in adults. Combination of ganciclovir and immunoglobulins for the treatment of HCMV interstitial pneumonitis in BMT patients has considerably improved the outcome: Almost 60 percent of the BMT patients treated for HCMV interstitial pneumonitis with anti-HCMV-Ig plus ganciclovir survived [154,155]. Extensive reviews of the ganciclovir studies for HCMV interstitial pneumonitis have appeared elsewhere [96,126,156–158]. In AIDS patients, therapy with ganciclovir for HCMV interstitial pneumonitis, unlike therapy for HCMV retinitis, may be stopped once the interstitial pneumonitis has resolved [102]. Foscarnet has been administered to immunocompromised patients in limited uncontrolled studies in which clear clinical improvement was shown [159,160].

Gastrointestinal HCMV disease responds well to ganciclovir, regardless of the underlying course of immunosuppression. Although many patients with AIDS do not have a complete response to ganciclovir therapy, HCMV disease progression is usually arrested [133]. Patients not receiving ganciclovir usually have persistent infection [134].

Unlike patients with AIDS, transplant recipients generally do not require maintenance ganciclovir therapy to prevent clinical relapse of HCMV gastrointestinal or hepatic infections. Ganciclovir has been successfully used in combination with HCMV-Ig in liver transplant recipients with HCMV hepatitis [161,162].

A relatively large number of investigations have been reported using ganciclovir in varying dosages in a few patients with confirmed or suspected CNS HCMV infection. While improvement was reported in a few patients, others failed to respond and some worsened during ganciclovir administration [157,163]. HPMPC is now under clinical investigation for systemic administration in immunocompromised patients with HCMV infections. It appears from the preliminary studies that HPMPC given at 3 mg/kg/week or 5 mg/kg/qiw reduced HCMV excretion in urine and semen significantly [164,165].

HCMV drug resistance

Severely immunocompromised patients, notably people with AIDS but also transplant patients, often require long-term suppressive ganciclovir therapy for the management of HCMV infections. Based on currently available data from clinical trials with ganciclovir, 10–15 percent of patients with HCMV retinitis who receive long-term ganciclovir therapy develop ganciclovir-resistant strains of HCMV.

Human cytomegalovirus is not known to encode or express a specific TK, like that of HSV, responsible for the conversion of either ACV or ganciclovir to their monophosphate forms. Recently, a virus-induced protein kinase, encoded by the UL-97 ORF (open reading frame), was shown to account for the phosphorylation of ganciclovir [166,167]. Compared with the wild type, the ganciclovir-resistant mutant exhibited both a 10-fold increase in the 50 percent virus-inhibitory dose of ganciclovir and a 10-fold decrease in the amount of phosphorylated ganciclovir [168]. Thus, the resistance of HCMV to ganciclovir has mainly been associated

with impaired phosphorylation of the drug [168,169]. This particular mutant remains susceptible to foscarnet [168,170]. Recently, Sullivan et al. [171] described a ganciclovir-resistant mutant derived from the reference strain AD-169 that contains two mutations responsible for the virus drug resistance, one of which is located at the UL-97 gene and results in decreased ganciclovir phosphorylation. The second mutation was mapped in a 4.9 kb DNA fragment containing the DNA polymerase gene, which conferred resistance to ganciclovir without impairing phosphorylation.

An HCMV isolate obtained from a BMT patient appeared to be resistant to both ganciclovir and foscarnet [172]. This could be explained by a single or double mutation affecting the viral DNA polymerase or two mutations located in the UL-97 and DNA polymerase genes, respectively.

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8 New and unusual infections in neutropenic patients

Stephen H. Zinner

Medical practice lives with change. New advancements often bring unanticipated problems and new challenges. Thirty years ago the approach to fever in a granulocytopenic patient with acute leukemia was individualized, expectant, and based on microbiological documentation of the invading bacterial pathogen, with attribution of fever itself in large part to the underlying disease. The landmark paper of Schimpff et al. in 1971 [1] introduced the concept of empirical therapy with early administration of antibiotics directed against the most likely bacterial pathogens. This approach resulted in improved outcome from infectious episodes, and it has become the standard of therapy.

Empirical therapy was relatively simple two decades ago when the most likely infecting organisms were quite predictable: *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. In fact, gram-negative rods were then responsible for over two thirds of the bacteremic infections in febrile neutropenic patients. However, over the course of these past 20 years, a dramatic and significant shift has occurred in the relative frequency of isolation of gram-negative and gram-positive pathogens (figure 1).

Using data from the International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC), figure 1 plots the relative frequency of gram-negative and gram-positive organisms as single causative pathogens isolated from bacteremic episodes in febrile granulocytopenic patients with cancer. Clearly, gram-negative bacteria have declined and gram-positive organisms have increased in their pathogenetic role in this patient population.

The last decade has also witnessed the emergence of the acquired immunodeficiency syndrome (AIDS), with its ever expanding list of invading pathogens. As neutropenia is the most frequently encountered immunocompromised state in clinical medicine, this paper will review the changing array of infections in neutropenic and other immunocompromised patients with cancer and will highlight some of the more unusual infections. As will be seen, as patients are increasingly immunocompromised, and as antibiotic-susceptible organisms are facily eradicated, then we will continue to see the increasing pathogenic significance of organisms previously thought to be commensal or 'nonpathogenic.' In this context, no organism can be safely dismissed as a contaminant, and physicians must increase their

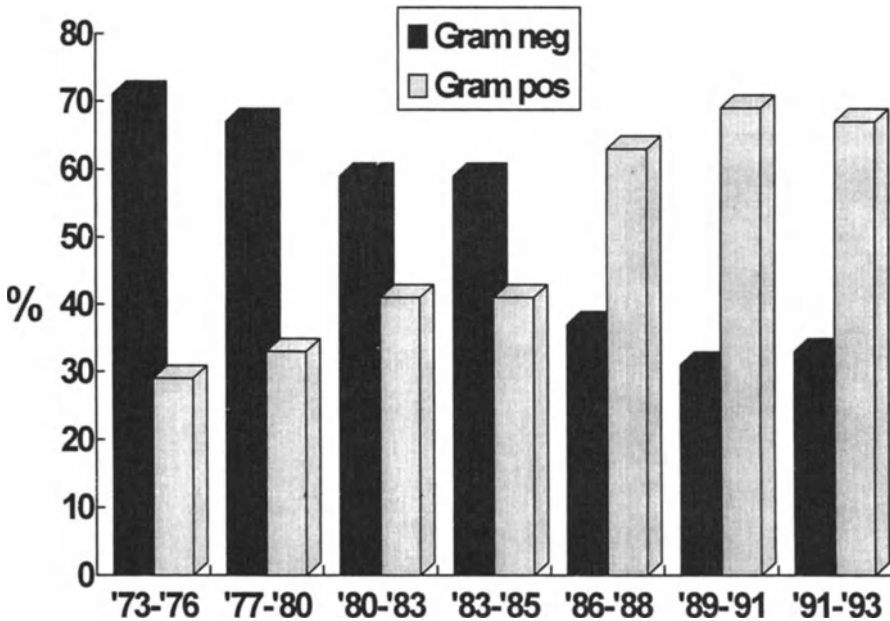


Figure 1. Relative frequency of isolation of gram-positive and gram-negative bacteria as single blood-stream isolates. (Data from the EORTC International Antimicrobial Therapy Cooperative Group.)

awareness of microbes whose names they had never encountered, even a decade earlier.

Reasons for change

Several reasons have been postulated to explain the shift in bacterial infections in neutropenic patients. First, with the increasing intensity of anticancer chemotherapy regimens, oral and upper gastrointestinal tract mucositis has become more significant, and this forms a ready site for entry of gram-positive coccal flora. Second, long dwelling intravascular catheters, such as the Hickman, Broviak, or Portacath devices, have become increasingly commonplace and routine, and these provide ready bloodstream access of gram-positive skin flora. Third, introduction of the fluoroquinolone antibiotics as prophylactic agents in neutropenic patients has impacted dramatically on the frequency of gram-negative rod bacteremia without a major effect on gram-positive infections [2]. Other pressures from widespread use of broad-spectrum antibiotics have been implicated but are more difficult to prove. Recently, data from the M.D. Anderson Cancer Center have suggested that the increasing use of H₂-antagonists in hospitalized cancer patients is related to the increase in viridans streptococcal bacteremia [3].

New gram-positive pathogens

Although not strictly 'new' organisms, recent studies have highlighted the emergence of alpha-hemolytic or 'viridans' streptococci as important pathogens in the neutropenic patient. In fact, a recent IATCG trial reported that streptococcal species were responsible for 57 of 129 (44 percent) single-organism bacteremic episodes and of these 44 (77 percent) were due to viridans group streptococci [4]. Viridans streptococci such as *Streptococcus mitis* have been associated with sepsis and the adult respiratory distress syndrome (ARDS) in leukemic patients [3,5–8]. *Leuconostoc* species had been regarded as a commensal or nonpathogen, but Handwerger and colleagues [9] reported intravenous catheter-associated bacteremias caused by this vancomycin-resistant, fastidious, slow-growing gram-positive coccus, which may be confused microbiologically with viridans streptococci, enterococci, or lactobacilli. This organism is also resistant to teichoplanin but is susceptible to aminoglycosides and clindamycin, with variable susceptibility to penicillins and first-generation cephalosporins.

Corynebacterium jeikeium are nonsporulating, small gram-positive diphtheroids that form gray-white, nonhemolytic smooth colonies in 5 percent CO₂. A characteristic metallic sheen may be useful to suspect these organisms, which also are catalase positive. J-K corynebacteria, as these organisms are also known, colonize the skin, axilla, and rectum and cause intravenous catheter-associated bacteremia in neutropenic patients, especially in those who have received third-generation cephalosporins. These organisms have caused endocarditis, peritonitis, prosthetic joint infections, etc. [10–12].

Rhodococcus equi (formerly *Corynebacterium equi*) is a pleomorphic nonmotile, nonhemolytic, gram-positive rod that is acid fast when grown on Lowenstein-Jensen media. It causes suppurative pneumonitis, abscesses, with pleural effusion and empyema in severely immunocompromised patients, including patients with AIDS [13]. Although bacteremia is relatively rare, it can occur. *Rhodococcus equi* is resistant to penicillin and first-generation cephalosporins but susceptible to macrolides, chloramphenicol, vancomycin, clindamycin, aminoglycosides, rifampin, and sulfonamides.

Stomatococcus mucilaginosus (formerly known as *Neisseria mucosa* or *Staphylococcus salivarius*) was thought to be nonpathogenic or commensal. However, this slime-producing, nonhemolytic, catalase-variable, oxidase-negative organism has been reported recently to cause catheter-associated bacteremia in severely immunocompromised patients, especially following bone marrow transplantation [14,15]. This organism is a prominent member of the oral flora and may be associated with dental caries. It forms adherent, mucoid gray colonies but does not grow on 5 percent NaCl media. *Stomatococcus mucilaginosus* is usually susceptible to vancomycin, erythromycin, penicillin (not all), rifampin, and fusidic acid. However, clinical infections in immunocompromised patients may respond slowly and might recur following therapy.

Another gram-positive organism, *Bacillus cereus*, has been reported responsible for a relatively typical scenario in severely neutropenic and immunocompromised

patients. *Bacillus cereus* may be associated with a vesicle or pustule on the digit or a limb that progresses to an eschar-coated draining wound. Although bacteremia is not common, patients may develop necrotizing fasciitis, pneumonitis, and meningitis, and may appear quite septic. This organism is resistant to penicillin, cephalosporins, and trimethoprim/sulfamethoxazole but is usually susceptible to vancomycin and also to clindamycin, erythromycin, aminoglycosides, and chloramphenicol [16].

Other gram-positive bacteria that might be troublesome for neutropenic patients include *Enterococcus* species (especially those resistant to vancomycin and aminoglycosides), *Lactobacillus rhamnosus*, *Corynebacterium striatum*, *Clostridium septicum*, and *Cl. tertium*.

New gram-negative pathogens

Although bacteremia due to gram-negative bacilli is decreasing in neutropenic patients, primarily attributed to increasing use of fluoroquinolone prophylaxis, these organisms are still responsible for infections in this patient population. Some of the newly recognized organisms are notable for their antimicrobial resistance and others for their epidemiology or novel clinical presentation.

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia*, *Pseudomonas maltophilia*) is particularly problematic because of its resistance to many antibiotics. It is resistant to imipenem, beta-lactam antibiotics, and the aminoglycosides! Some strains may be susceptible to trimethoprim-sulfamethoxazole (which is probably the first-line drug of choice) and variably to some fluoroquinolones. This organism is found with increasing prevalence in neutropenic patients as a nosocomial pathogen, especially in hospitals where imipenem use is high [17].

Aeromonas putrefaciens, an oxidase positive, non-glucose-fermenting gram-negative rod, is associated with spoiled meats and tainted butter. It has been isolated as a cause of cutaneous ulcers, cellulitis, and occasionally bacteremia in neutropenic patients. This organism is susceptible to second- and third-generation cephalosporins, ureidopenicillins, imipenem, aminoglycosides, and the fluoroquinolones [18].

A recent report showed that *Vibrio parahaemolyticus*, an organism usually associated with sea water, caused a paronychia with subsequent fever, hypotension, and hemolytic anemia in a patient with acute myelocytic leukemia who lacerated her finger while preparing fresh squid in her kitchen [19]. This organism is susceptible to trimethoprim/sulfamethoxazole, ureidopenicillins, fluoroquinolones, imipenem, ceftazidime, chloramphenicol, and tetracyclines.

Capnocytophaga species (formerly DF-1 and DF-2) are members of the normal oral, vaginal, and gastrointestinal flora. These capnophilic, facultatively anaerobic gram-negative rods grow on blood agar and are catalase, oxidase, and indole negative, but they do ferment glucose, sucrose, maltose, lactose, and mannose. They have been reported to cause bacteremia in patients with severe oral and mucosal pathology following bone marrow transplantation [20]. Although resistant to aminoglycosides and trimethoprim, these organisms are susceptible to clindamycin

and penicillins, with variable susceptibility to cephalosporins, imipenem, chloramphenicol, tetracyclines, and the fluoroquinolones. A related species, *Dysgonic Fermenter-3*, has been reported as a cause of bacteremia in a leukemic patient receiving broad-spectrum antibiotics [21]. This organism was susceptible to chloramphenicol and trimethoprim/sulfamethoxazole.

Other gram-negative bacteria recently associated with infections in neutropenic patients include: *Pseudomonas cepacia*, a biofilm producer susceptible to ceftazidime, piperacillin, and cotrimoxazole but resistant to imipenem, tobramycin, and ticarcillin, and associated with intravenous catheter infections [22]; *Achromobacter xylosoxidans*, a cause of bacteremia associated with mucositis, a gastrointestinal focus, and possibly intravenous catheters that respond to trimethoprim/sulfamethoxazole but not usually to aminoglycosides, cephalosporins, and quinolones [23]; *Ochrobactrum anthropi* (CDC group Vd), a non-lactose-fermenting, oxidase-positive, gram-negative rod that caused persistent bacteremia in a child with cancer despite therapy with vancomycin and ceftazidime but that responded to cotrimoxazole plus amikacin [24]; and *Agrobacterium radiobacter*, an aerobic, catalase- and oxidase-positive plant pathogen resistant to tobramycin but sensitive to ticarcillin, cefoxitin, ceftriaxone, cefotaxime, and gentamicin, and that caused catheter-related bacteremia, peritonitis, and urinary infection in three reported patients [25].

Methylobacterium extorquens used to be known by many other species names: *Pseudomonas mesophilica*, *Ps. methanolica*, *Protaminobacter rubra*, *Vibrio extorquens*, and *Mycoplana rubra*. It is a gram-negative, aerobic oxidase and catalase-positive motile rod that does not ferment glucose. It has caused three reported cases of catheter-associated bacteremia in leukemic patients, but these were not believed to be life threatening. Treatment with aminoglycosides and possibly with cotrimoxazole or ciprofloxacin has been recommended [26].

Anaerobic organisms in neutropenic patients

Classically, infections with anaerobic organisms such as *Bacteroides fragilis* and other species were not found frequently in granulocytopenic patients unless they had destructive gastrointestinal malignancies. Recently, infections caused by some 'new' gram-negative and gram-positive anaerobes have been reported. A beta-lactamase-producing strain of *Fusobacterium nucleatum* was isolated from a leukemic patient with ulcerative pharyngitis and nodular pulmonary infiltrates suggestive of septic emboli [27]. Clindamycin plus metronidazole was effective clinically. *Leptotrichia buccalis*, an anaerobic gram-negative rod found normally in the oral cavity, was reported to cause several cases of bacteremia in patients with leukemia and advanced stage malignancies who also had severe oral and gastrointestinal mucosal inflammation and ulceration [28]. This organism is resistant to aminoglycosides, vancomycin, fluoroquinolones, and the new macrolides, but is susceptible to penicillins, cephalosporins, clindamycin, metronidazole, and tetracycline.

Clostridium septicum is an anaerobic gram-positive rod known to cause necrotizing enterocolitis. Recently, a non-toxin-producing, presumably 'nonpathogenic'

related strain, *Clostridium tertium*, has been reported to cause bacteremia in granulocytopenic patients. This organism produces a milder illness than *Cl. septicum* and was isolated from seven patients in Finland, most with perirectal cellulitis or another presumed gastrointestinal tract source. Antibiotic therapy with a third-generation cephalosporin and an aminoglycoside was successful in most cases [29].

Fungal infections in neutropenic patients

Physicians who care for patients with cancer expect to see infections due to *Candida* spp. and *Aspergillus* spp., especially after long courses of antibiotics in profoundly neutropenic patients. Similarly, cryptococcal meningitis was not unknown in patients with lymphocytic malignancies or with lymphomas under treatment with corticosteroids. However, with increasing use of intensive chemotherapy regimens and with widespread use of new triazole and imidazole antifungal drugs, a broader spectrum of fungal infections is emerging. Many fungal infections in patients with cancer are associated with long-dwelling intravascular catheters, and these have been reviewed recently [30].

Anaissie and colleagues have recently reviewed fungal infections in patients with cancer [31] and reported that fungemia, sinus infections, and skin and soft tissue infections caused by dermatophytes and 'low-virulence' plant fungi were increasing in frequency in patients with cancer. For example, *Trichosporon beigeli*, the agent of white piedra, was isolated as a causal organism in pneumonia, nodular purpuric skin lesions, hepatitis, glomerulonephritis, endophthalmitis, and even endocarditis with fungal emboli. This organism may be resistant to amphotericin B. The therapy for fungal infections is addressed in two other chapters in this book.

Infections due to *Fusarium* spp. may be suspected clinically by the presence of painful, necrotic, and nodular skin lesions that begin as tender erythematous papules. Disseminated infections are seen and these organisms are resistant to the imidazoles and triazoles [32,33]. *Rhodotorula rubra* and other species were isolated from 23 patients with intravenous catheters at Sloan Kettering, with a good response to catheter removal and amphotericin B [34].

Dematiaceous soil fungi, such as *Exophiala jeanselmei*, *E. pisciphila*, *E. spinifera*, and *Scedosporium inflatum*, have also caused infections in neutropenic patients [35,36]. In neutropenic patients the flask-shaped *S. inflatum* has caused fungemia associated with intravascular devices, retinal lesions, esophagitis, and hepatosplenic infections. These organisms resist amphotericin and fluconazole in vitro [36].

The Zygomycetes (*Absidia*, *Rhizopus*, and *Cunninghamella* spp.) also are reported with increasing frequency from neutropenic and other immunocompromised patients. *Alternaria* have been associated with minimally symptomatic sinusitis, which responded to aggressive surgical debridement plus amphotericin B [37]. *Rhizomucor pusillus* and *Cunninghamella* spp. may cause invasive pulmonary disease with hemorrhagic alveolitis [38].

Other fungi recently reported to cause infections in cancer patients include *Pseudallescheria boydii*, *Torulopsis pintolopesi*, *Geotrichum candidum*, *Saccharomyces cerevisiae*, *Drechslera* sp., *Exserohilum rostratum*, *Phialophora parasitica*,

Acromonium sp., *Malassezia furfur*, *Pichia farinosa*, and *Hansenula anomala*, among others. Most of these fungi are isolated as vascular catheter-associated fungemia in neutropenic patients.

Mycobacterial infections

As the AIDS epidemic continues its ravaging course, tuberculosis is again on the rampage and drug resistance among *Mycobacterium tuberculosis* is also increasing. In addition, neutropenic patients may be infected with so-called atypical mycobacteria, such as *Mycobacterium chelonae*, *M. fortuitum*, etc.

In a recent report, the *Mycobacterium fortuitum* complex (which used to include *M. chelonae*) was isolated from 15 patients at the M.D. Anderson Cancer Center [39]. Most of these infections were associated with intravenous catheters, but patients presented with cellulitis, skin nodules, and abscesses. Catheter removal or surgical excision of the catheter tunnel plus treatment with either amikacin plus cefoxitin, trimethoprim/sulfamethoxazole, doxycycline, or erythromycin was associated with clinical recovery.

Mycobacterium chelonae also is a rapidly growing species that resembles *Nocardia* on Gram stain because of its beaded-rod appearance. Three patients with prolonged neutropenia at the Royal Free Hospital in London presented with disseminated infection but responded to antibiotics as their granulocyte counts improved [40].

Viral infections

Oncologists have been familiar with disseminated infection due to Varicella-zoster and herpes simplex viruses, especially in patients with lymphomas and chronic lymphocytic leukemia. These viruses may cause meningoencephalitis or visceral involvement. The introduction of prophylactic and therapeutic acyclovir, ganciclovir, and foscarnet has had a favorable impact on these conditions, and they will not be considered further in this review.

Other emerging pathogens in neutropenic patients

Bartonella (Rochalimaea)

The application of molecular biological techniques to diagnostic microbiology is certain to enhance the identification of organisms responsible for many diseases. Among the first examples of this advance is the association of *Bartonella* (formerly, *Rochalimaea*) species with a variety of illnesses. *Bartonella quintana*, a Rickettsial-like pathogen, was initially associated with bacillary angiomatosis and peliosis hepatis in patients infected with the human immunodeficiency virus [41]. This organism

has been renamed *Bartonella henselae* [42]. This organism also has been isolated from febrile, bacteremic patients with cancer, including neutropenic patients [42,43].

Bartonella henselae can be isolated using the red blood cell lysis-centrifugation method, and it grows in 4 days on several media, including charcoal-yeast extract, and blood or chocolate agars. *Bartonella* species are susceptible to macrolides, tetracycline, and many antituberculous drugs. The organisms can be recognized in tissue biopsy specimens using the Warthin-Starry stain. A related organism, *Afipia felis*, is probably the etiologic agent of cat scratch disease. As the clinical spectrum of infections caused by *Bartonella* and related organisms is expanding, clinicians can expect to see more patients with these infections [44].

Toxoplasmosis

Infections caused by *Toxoplasma gondii* are frequent in patients with the acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV) infection, in whom toxoplasmic encephalitis is most common. Patients with Hodgkin's disease, non-Hodgkin's lymphoma, leukemias, and a variety of solid tumors are subject to develop toxoplasmosis with more protean manifestations [45]. These patients may manifest fever, lymphadenopathy, hepatosplenomegaly, pneumonitis, retinochoroiditis, myocarditis, and rash, in addition to central nervous system signs and symptoms [45].

The diagnosis of toxoplasmosis in the patient with cancer depends on serological evidence, biopsy to identify organisms in tissue, and/or cell culture or mouse inoculation to isolate the organism. New antibody detection methods and polymerase chain reaction techniques are being developed. Treatment modalities include pyrimethamine and sulfonamides, or clindamycin with pyrimethamine; experimental studies with the new macrolide/azalide drugs and atovaquone are in progress.

Pneumocystis carinii

Like toxoplasmosis, pneumonia due to *Pneumocystis carinii* is very common in patients with AIDS (although prophylactic therapy has reduced its incidence). However, prior to the AIDS epidemic infectious disease clinicians were familiar with this infection in unprophylaxed patients with lymphocytic malignancies, Hodgkin's disease, rhabdomyosarcoma, severe combined immunodeficiency syndrome, and in those undergoing bone marrow or organ transplantation [46]. Patients with cancer have a similar illness to those with AIDS, except that cancer patients have a shorter prodrome of a brief illness, with fever, dry cough, and dyspnea, which may rapidly progress to respiratory distress. Today, *Pneumocystis carinii* pneumonia presents less commonly in patients with malignancies than in those with HIV infection in the absence of prophylaxis. Corticosteroid use is a major risk factor in cancer patients [47]. Extrapulmonary manifestations are not common in either patient group.

As the organism load appears to be much greater in patients with HIV infection than in those with malignancies, biopsy or direct sampling of bronchial secretions

was often necessary in patients with cancer. However, recent series have suggested that induced sputum as well as bronchoalveolar lavage are useful in identifying pneumocysts [48]. Polymerase chain reaction amplification techniques are under development to increase the diagnostic yield. Physicians have been familiar for a long time with other parasitic diseases, such as strongyloidiasis, in the immunocompromised host. These will not be further reviewed here.

Treatment for 2 weeks with trimethoprim/sulfamethoxazole and pentamidine is effective. Experience with other regimens used in patients with AIDS has not been adequate to recommend them in patients with malignant underlying diseases.

Microsporidia

Microsporidia are pathogens relatively recently associated with cancer and immunosuppressing conditions or treatments. The AIDS epidemic has brought to the forefront infections caused by *Encephalitozoon*, *Nosema*, and enterocytozoon species and cryptosporidial diarrhea as well. In one report of 20 patients with hematologic malignancies, *Cryptosporidium parvum* was associated with severe intestinal disease, moderate diarrhea, acalculous cholecystitis (similar to patients with HIV infection), and even pneumonia. Resolution occurred spontaneously but relapse was common [49]. Although no effective therapy is available for cryptosporidiosis, the new azalide/macrolide drugs reduce coccidial load in experimental animal infections.

Algae

As a prime example of infection with organisms previously thought to be non-infectious for humans, recent reports have indicated that the unicellular algae *Prototheca wickerhamii* and other *Prototheca* species may cause algemia and localized granulomatous infections in immunocompromised as well as some immunocompetent patients. Ulcerative skin lesions have been described in a patient with systemic lupus erythematosus [50] and an ulcerating soft tissue pharyngeal mass in a chronically endotracheally intubated patient [51]. *Prototheca wickerhamii* also has been isolated from a case of peritonitis associated with chronic ambulatory peritoneal dialysis [52] and from the blood of an immunocompromised child with Hodgkin's disease and a Hickman catheter [53]. Treatment with amphotericin B or imidazole or triazole antifungal agents has met with some success.

Summary

Infections in immunocompromised patients with cancer are common and the primary risk factor is neutropenia, usually induced by chemotherapeutic agents. The spectrum of bacterial infection is shifting from gram-negative to gram-positive. The array of fungal infections in cancer patients is expanding to include organisms previously unknown as invasive human pathogens. New species are being defined

to explain extant pathologies, and free living algae are now emerging as pathogens in immunocompromised patients. Physicians must remain alert to these emerging pathogens and to the need to evaluate optimal treatments for the usual and unusual infections in neutropenic and other compromised patients with cancer and allied diseases.

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9 Pneumonia in cancer patients

Estella Whimbey, James Goodrich and Gerald P. Bodey

Pneumonia is one of the most common and life-threatening infections occurring among patients with cancer [1–3]. Among neutropenic patients hospitalized at the M.D. Anderson Cancer Center (MDACC) between 1978 and 1985, pneumonia accounted for one quarter of the 1329 febrile episodes caused by documented infections [4]. A pathogen was identified in only 34 percent of these pneumonias, and the overall response rate was only 45 percent.

Several distinctive features make the diagnosis and management of these pneumonias a formidable challenge. Most striking is the broad spectrum of causative microorganisms, ranging from pathogens that routinely invade nonimmunocompromised persons (such as pneumococcus, *Mycobacterium tuberculosis*, and influenza virus) to opportunistic microorganisms that thrive on impaired host defenses (such as *Nocardia*, atypical mycobacteria, *Aspergillus*, *Pneumocystis carinii*, and cytomegalovirus). Any evaluation of pneumonia in the cancer patient must take into consideration the specific deficits in host defense mechanisms inherent in the underlying disease as well as induced by its therapy (illustrated by the cellular immune deficiency associated with Hodgkin's disease as well as with corticosteroid, cyclosporine, and fludarabine therapy). Specific defects predispose to specific types of infections (Table 1). Frequently, multiple facets of the host defense system are impaired simultaneously or become successively impaired at different stages in the underlying disease and its therapy. For example, among allogeneic bone marrow transplant (BMT) recipients, the pre-engraftment period is characterized by infections associated with neutropenia, while the post-engraftment period is characterized by infections associated with cellular immune deficiency. Among patients with acute myelocytic leukemia, the likelihood of developing a fungal pneumonia is less during the initial remission-induction therapy than during subsequent cycles of chemotherapy for relapse of disease. Similarly early stages of multiple myeloma are characterized by infections with encapsulated organisms such as pneumococcus, whereas later stages are characterized by infections related to chemotherapy-induced granulocytopenia, such as gram-negative bacilli and fungi.

These impairments in host defense related to the neoplasm and its therapy must be weighed along with the usual myriad of clinical clues, including age; underlying cardiopulmonary, metabolic, and collagen vascular diseases; risk factors for human immunodeficiency virus (HIV) infection; parenteral drug abuse; prior antibiotic or

Table 1. Host defects predisposing to specific types of pneumonia in cancer patients

Host defect	Underlying disease predisposing factors	Microorganisms
Neutropenia	Acute leukemia Aplastic anemia Chemotherapy Radiation	Gram-negative bacilli <i>Escherichi coli</i> <i>Klebsiella pneumoniae</i> <i>Pseudomonas aeruginosa</i> , other spp. <i>Xanthomonas maltophilia</i> <i>Serratia marcescens</i> Gram-positive cocci <i>Staphyococcus aureus</i> Coagulase-negative <i>Staphylococcus</i> Alpha-hemolytic <i>Streptococcus</i> Fungi Yeast <i>Candida</i> <i>Torulopsis</i> <i>Trichosporon</i> Filamentous <i>Aspergillus</i> <i>Fusarium</i> Agents of mucormycoses
Humoral immune dysfunction	Multiple myeloma CLL	<i>Pneumococcus</i> , <i>Haemophilus</i>
Splenectomy		<i>Pneumococcus</i> , <i>Haemophilus</i>
Cellular immune dysfunction	Leukemia (ALL) Lymphoma (Hogkin's) Organ transplant Corticosteroids Cyclosporine Fludarabine	Bacteria <i>Legionella</i> <i>Nocardia</i> <i>Mycobacterium</i> Fungi <i>Cryptococcus neoformans</i> <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i> Herpesviruses CMV, VZV, HSV, HHV-6 Parasites <i>Pneumocytis carinii</i> <i>Toxoplasma gondii</i> Helminth <i>Strongyloides stercoralis</i>
Damage to anatomical barriers		
Mucositis, loss of ciliary function	Chemotherapy	Organisms colonizing near the site of damage or obstruction
Loss of gag reflex	Head and neck tumors Analgesics	
Local obstruction	Lung tumors Lymphadenopathy	
Catheters	Endotracheal, nasogastric	
Catheters	Intravascular	<i>Staphylococcus</i> , <i>Candida</i> , gram-negative bacilli
Defects being defined	Organ transplant Leukemia	Community respiratory viruses Influenza, RSV Parainfluenza, adenovirus

immunosuppressive therapy; recent surgery, trauma, or anesthesia; time of year; preceding upper respiratory tract illness; evidence of latent fungal or mycobacterial infection; travel; pets; hospital, community, household, and occupational exposures; epidemic or sporadic occurrence of the infection; and primary or secondary occurrence of the pneumonia in the setting of hematogenous dissemination.

Also to be considered are the many noninfectious causes of fever and pulmonary infiltrates. These include neoplastic disease, drug toxicity, hemorrhage, leukoagglutinin reactions, radiation pneumonitis, pulmonary edema, pulmonary emboli, and the acute respiratory distress syndrome. Frequently, several infectious and noninfectious pulmonary processes are present concurrently, or the initial pneumonia becomes complicated by a nosocomial superinfection or a noninfectious process such as pulmonary hemorrhage.

The diagnosis of pneumonia in the immunocompromised patient is often further confounded by an impaired inflammatory response [5]. Classical signs and symptoms of pneumonia may be lacking, particularly in patients with neutropenia in whom fever may be the only presenting symptom. Physical examination may be relatively unrevealing, sputum production may be absent or minimal, and the chest radiograph may be clear at the onset of pneumonia. These features were highlighted in a study of 50 consecutive autopsied patients with acute leukemia: 60 percent of 31 major pulmonary infections were not recognized clinically, and 30 percent of the patients had normal chest radiographs initially [6].

Further obscuring the diagnosis in many cases is the inability to obtain a tissue diagnosis because of the risk of hemorrhage with thrombocytopenia. Even when optimal specimens are available, cultures are frequently unrevealing because of the widespread use of prophylactic and empirical antibiotics.

Coupled with the diagnostic complexity is the need to administer appropriate therapy promptly to achieve a favorable outcome. This is particularly true in patients with neutropenia or splenectomy in whom the risk of fulminant fatal infection is great. This requires a thorough knowledge of the wide spectrum of potential pathogens and the clinical settings in which they occur. These will be reviewed, with focus on those pathogens that show a propensity to cause pneumonia more frequently and/or more severely in the cancer patient.

Bacteria

Bacteria are the most common cause of pneumonia in cancer patients. While the causative bacteria may be the same as in immunocompetent patients, the majority of these pneumonias are caused by bacteria which thrive on specific defects in host defense.

Neutropenia

Bacterial pneumonia in the neutropenic patient is characterized by a high incidence of infections due to enteric aerobic gram-negative rods [7,8]. During the 1960s and

1970s, the predominating pathogens were *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [9–14]. The last decade, however, has been characterized by a much broader and changing spectrum of infecting organisms, with an increased frequency of less common species of gram-negative bacilli, such as *Xanthomonas maltophilia*, other non-aeruginosa *Pseudomonas* spp., *Enterobacter* spp., and *Citrobacter* spp. [15–20] and a resurgence of gram-positive aerobic cocci, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and alpha-hemolytic streptococci [21,22]. There has also been an alarming increase in the frequency of resistant pathogens, including methicillin as well as vancomycin-resistant, gram-positive bacteria and beta-lactam, as well as multidrug-resistant, gram-negative bacilli. These changes in the epidemiology of infection in cancer patients are thought to reflect the more immunosuppressive chemotherapeutic regimens, causing more severe and prolonged neutropenia and more severe mucositis; the increased use of long-term indwelling intravascular catheters; the widespread use of prophylactic and empirical antibiotic therapy; and the use of chemotherapeutic agents such as interleukin-2 (which has been associated with a propensity for gram-positive infections such as staphylococci).

Bacterial pneumonia in the neutropenic patient is characterized by a high incidence of bacteremia and shock, and a high mortality. The frequency and severity of infection correlate inversely with the patient's absolute neutrophil count, with both becoming most pronounced at counts below 100/ μ l [23]. The outcome depends largely on whether the neutrophil count increases during therapy and on the extent of pulmonary damage when the appropriate therapy is begun.

In most cases of bacterial pneumonia in the neutropenic patient, the infecting pathogen is not identified and empiric antibiotic therapy needs to be initiated promptly to avoid a fatal outcome. The difficulty in establishing the diagnosis stems from several factors: (1) the clinical picture is seldom diagnostic of a particular organism, (2) former distinctions between community and hospital-acquired infections have become obsolete in the setting of increasing outpatient management of the cancer patient, (3) patients are seldom able to produce sputum because of a poor inflammatory response, (4) invasive diagnostic procedures are frequently prohibited by severe thrombocytopenia, and (5) patients are frequently already receiving prophylactic or empirical therapeutic antibiotics when the specimen is obtained.

Occasionally clinical clues are present that are suggestive of specific pathogens. The presence of cutaneous ecthyma gangrenosum, though not pathognomonic, is highly suggestive of infection due to *P. aeruginosa*. However, this finding is only present in approximately 2 percent of such patients [12]. The radiographic appearance of a necrotizing pneumonia may suggest infection due to *P. aeruginosa*, *K. pneumoniae*, or *S. aureus*. The occurrence of a shock syndrome characterized by hypotension, rash, desquamation, and the adult respiratory distress syndrome in a profoundly neutropenic bone marrow transplant recipient or a patient with leukemia may suggest infection due to alpha-hemolytic streptococci [22].

Because of the high risk of a rapid progression to pulmonary insufficiency and death, empiric therapy must be initiated at the onset of fever or respiratory symptoms. The diversity of organisms causing infection in recent years and the availability of

many truly broad-spectrum antimicrobial agents has made it increasingly difficult to recommend a single regimen as the best empirical therapy [24–35]. The optimal regimen will vary considerably because of institutional variability in the predominant organisms as well as the antimicrobial susceptibility patterns. In general, the initial empiric antibiotic regimen should provide bactericidal broad-spectrum coverage that encompasses the classic aerobic gram-negative bacilli, particularly *P. aeruginosa* (despite the declining frequency of its isolation). The choice of antibiotics should be further guided by the clinical setting and the recent experience of a particular hospital.

Since pneumonia is one of the most life-threatening infections, combination therapy is preferable because it provides a broader initial empirical coverage and offers the potential for synergistic activity against the infecting organism [36,37]. Various antibiotic combinations have been tried, including an extended spectrum beta-lactam antibiotic and either another beta-lactam antibiotic, a carbapenam, an aminoglycoside, a quinolone, or trimethoprim-sulfamethaxazole. These various antibiotic combinations have resulted in a similar overall response rate. In some cases, monotherapy with an extended spectrum penicillin or cephalosporin, or with a carbapenam, may be a safe alternative [38]. Monotherapy with an aminoglycoside, however, is not effective, even for infections caused by susceptible gram-negative bacilli [39,40]. The question of whether a specific antibiotic for gram-positive infections such as vancomycin is routinely needed in the initial empiric antibiotic regimen is highly controversial [41,42]. In some clinical settings in which gram-positive infections are not a serious problem, it may be safe to cautiously withhold such therapy until the pathogen has been identified. Unfortunately, the overall response rate of pneumonia has been suboptimal (approximately 45 percent), regardless of the regimen chosen, and is consistently poorer than the response rate with bacteremia (approximately 70 percent) [4].

Humoral immune dysfunction and splenectomy

Patients with immunoglobulin dysfunction (exemplified by multiple myeloma and chronic lymphocytic leukemia) and patients who have undergone splenectomy have an increased frequency of overwhelming pneumonia and bacteremia due to encapsulated pyogenic bacteria, such as *Streptococcus pneumoniae* and *Hemophilus influenzae*. Because resistant strains of these encapsulated organisms have emerged over the past decade, the choice of antibiotics should be guided by susceptibility testing.

Cellular immune dysfunction

Patients with cellular immune dysfunction have an increased susceptibility to intracellular bacteria, such as *Legionella*, *Nocardia*, and mycobacteria.

Legionella. Legionellosis occurs with increased frequency and severity among patients with cell-mediated immune deficiency [43–48]. The organism resides in water reservoirs and is transmitted via aerosols to the lung. The usual presenting

syndrome is pneumonia. Although multisystem abnormalities are prominent, invasion of extrapulmonary organs is unusual. The incidence varies greatly in different regions and hospitals, depending on water contamination, the susceptibility of the population, the intensity of the exposure, and the ability of the laboratory to identify these organisms, which require special processing. *Legionella pneumophila* and *L. micdadei* are responsible for approximately 90 percent and 6 percent of the cases, respectively, in immunocompromised patients. Cases occur in sporadic, endemic, and epidemic forms. Nosocomial outbreaks have been well described among immunocompromised patients, with an overall mortality of 50–60 percent. The organism can be identified by direct fluorescent antibody staining or culture of respiratory secretions or lung tissue, or by radioimmunoassay for urinary antigen. The therapy of choice has been erythromycin, usually for at least 3 weeks to prevent relapses. Rifampin is added in more severe cases. Alternative therapies include trimethoprim/sulfamethoxazole and ciprofloxacin.

Nocardiosis. Patients with cellular immune deficiency are also at increased risk for severe pneumonia and disseminated disease due to *Nocardia*, primarily *N. asteroides* [49–54]. The organism is widely distributed in soil and, except for primary cutaneous infection, enters the body through the respiratory tract. The pulmonary infection may be acute or chronic, resembling tuberculous or fungal pneumonia. The chest radiograph classically reveals single or multiple nodules-abscesses, but may also reveal consolidation or a diffuse micronodular or miliary pattern. Hematogenous dissemination is common and most frequently involves the central nervous system (typically, brain abscesses) and the skin and subcutaneous tissue. The presence of cutaneous and central nervous system abnormalities with pneumonia suggests nocardiosis. Although usually fatal without therapy in the immunocompromised patient, the response to early therapy is favorable. The drug of choice is trimethoprim/sulfamethoxazole [55,56], which is continued for months after apparent cure because of the tendency to relapse and metastatic disease. Alternative therapies include other sulfonamides, minocycline, and imipenem [57].

Mycobacteriosis. Tuberculous and atypical mycobacteria are assuming an increasingly important role in cancer patients [58–67]. This is in part because of the growing epidemic of multidrug-resistant tuberculosis [68] and the growing population of severely compromised patients with prolonged, profound cellular immune deficiency (exemplified by marrow transplant recipients). These infections are discussed in detail in another chapter.

Anatomic impairments

Several anatomic defects may predispose the cancer patient to bacterial pneumonias, including loss of ciliary function and gag reflex, oral and tracheobronchial mucositis, local obstruction by tumors or lymph nodes, tracheoesophageal fistulas, and long-term indwelling intravascular, endotracheal, and nasogastric catheters. The types of infections to be anticipated are listed in Table 1.

Fungal pneumonias

Fungal pneumonias are much less common than bacterial pneumonias and occur primarily in patients with severely compromised host defenses. While most pneumonias are primary and can serve as the site of origin for subsequent dissemination, a few, such as *Candida* pneumonia, almost always are a consequence of hematogenous dissemination. The most common fungal pneumonias are caused by *Candida* spp. and *Aspergillus* spp. Other less common pneumonias are caused by *Cryptococcus* spp., *Trichosporon* spp., *Fusarium* spp., and rarely other molds and *Pseudallescheria* spp.

Candidiasis

Pulmonary involvement in disseminated candidiasis appears to be related to the patients' underlying disease and to whether fungemia is detected. Myerwitz et al. found pulmonary involvement in 80 percent of patients with acute leukemia but in 50 percent of other patients [68]. Maksymiuk found pulmonary involvement in 50 percent of patients with fungemia compared with 95 percent of patients without fungemia [69]. The probable explanation for this observation is that patients with fungemia often have catheter-related infection that is not associated with tissue invasion, while patients with disseminated candidiasis often have extensive tissue invasion yet never have positive blood cultures. Pulmonary infection of hematogenous origin is characterized by random macroscopic nodular lesions throughout both lungs with small subpleural nodules. The typical lesion is a hemorrhagic nodule consisting of necrotic lung and proliferating organisms associated with minimal acute inflammation.

Many patients with hematogenously disseminated pulmonary infection do not have any specific pulmonary symptoms. The most common symptoms are fever and tachypnea. Symptomatic hypoxemia may develop in some patients as the infection progresses. The abnormalities on chest radiography are nonspecific and consist of multiple, rounded parenchymal densities of varying sizes with ill-defined borders. As the infection progresses there may be coalescence of these lesions, resulting in a diffuse pneumonitis.

Primary *Candida* pneumonia is an uncommon infection in cancer patients. In an autopsy review of 351 cases of pulmonary candidiasis during a 20 year period, only 31 cases represented primary pulmonary infection [70]. Primary pneumonia may result from aspiration of infected oropharyngeal secretions. Some patients have associated thrush, esophagitis, or laryngitis. Whereas prolonged severe neutropenia is a common predisposing factor for hematogenous pneumonia, only about 30 percent of patients with primary pneumonia have severe neutropenia [70]. Some of these patients may develop tracheobronchitis or lung abscesses. There are no specific symptoms of primary *Candida* pneumonia. In addition to fever, patients may have chest pain, cough, dyspnea, and sputum production. Primary pneumonia may be limited to a single lobe on the chest radiograph or may be characterized by diffuse bilateral infiltrates.

The diagnosis of *Candida* pneumonia is difficult to establish since the isolation of *Candida* spp. from the sputum of a patient with pneumonia does not establish the diagnosis. The oropharynx of many patients receiving broad-spectrum antibiotics is colonized by *Candida* spp. Indeed, *Candida* spp. have been isolated from 55–75 percent of sputum specimens collected from hospitalized patients. The only reliable method for diagnosing this infection is by obtaining a tissue biopsy. Unfortunately, many patients are not appropriate candidates for this invasive procedure. A recent study suggests that if large numbers of yeasts and hyphae are detected in all fields of a cytological specimen, it is highly likely that the patient has *Candida* pneumonia [71].

Amphotericin B has been used most frequently for serious *Candida* infections. Anecdotal reports suggest that the combination of amphotericin B plus flucytosine is more effective. Recent randomized studies indicate that fluconazole is as effective as amphotericin B for serious *Candida* infections, but there is little experience with any of these agents for the treatment of primary *Candida* pneumonia [72].

Cryptococcosis

Since *Cryptococcus neoformans* is an intracellular pathogen, patients with impaired cellular immunity, such as occurs in Hodgkin's disease and other lymphomas, are most susceptible to this infection [73]. *Cryptococcus neoformans* is a respiratory pathogen; hence, infection usually begins in the lung. Most immunocompromised patients with cryptococcosis present with disseminated infection, at which time the pulmonary infection has usually resolved. The most common manifestation of disseminated infection is meningitis. Some patients present with cryptococcal pneumonia. There are no characteristic signs and symptoms of this form of infection. If the pneumonia is associated with disseminated infection, the patient may have skin lesions that are nonspecific and may present as acne, plaques, nodules, or ulcerations. Some patients may have associated lymphadenitis or pleuritis. Although the infection may appear to be relatively innocuous, it can be extremely fulminant and progress to completely involve both lungs within a week from presentation. Cryptococcal pneumonia may appear as miliary, nodular, or cavitory lesions on chest radiographs. The diagnosis is usually not difficult to make because the organism usually can be cultured from bronchoalveolar fluid. It can also be isolated from blood culture specimens of patients with disseminated infection. Amphotericin B, flucytosine, fluconazole, and itraconazole are effective against this yeast.

Aspergillosis

Aspergillus spp. are respiratory pathogens and about 70 percent of infections involve the lung. About 30 percent of pulmonary infections disseminate to other organs. Both the neutrophil and the macrophage are important host defenses against *Aspergillus* infections. The macrophage ingests and kills *Aspergillus* spores. The sporocidal activity of macrophages is impaired by adrenal corticosteroids; hence,

patients receiving high-dose or prolonged therapy with these agents are susceptible to infection. The neutrophil is the primary defense against mycelia, and infection is especially prevalent in neutropenic patients. *Aspergillus* spp. have a propensity for invading blood vessel walls, causing thrombosis and infarction. Extensive tissue invasion with destruction is common.

About 30 percent of patients with pulmonary aspergillosis (and other mold pulmonary infections) present with the characteristic signs and symptoms of acute pulmonary infarction with the sudden onset of fever, hemoptysis, and pleuritic chest pain. Physical examination reveals a prominent pleural friction rub. However, many patients have nonspecific signs and symptoms. Indeed, some may have only fever at the onset of their infection and have no abnormalities on chest roentgenogram. Abnormalities on chest roentgenogram do appear within a few days after the onset of fever so that prolonged fever of unknown origin is unlikely to be due to aspergillosis. Since blood vessel involvement is a prominent feature of this infection, early or late exsanguinating pulmonary hemorrhage is a threat to these patients.

The earliest manifestation of *Aspergillus* infection on chest radiographic examination is a single or multiple nodular infiltrates [74]. Computed tomography may reveal lesions that are not detected on conventional roentgenograms. As the disease progresses a variety of patterns of involvement may occur. In some patients, a wedge-shaped infiltrate suggestive of pulmonary infarction may be observed. Others may develop lobar pneumonia or bilateral diffuse pneumonitis. Those patients whose infection is controlled will usually have residual necrotic lesions that cavitate. Frequently, residual *Aspergillus* organisms may form fungus balls within these cavities.

The diagnosis of pulmonary aspergillosis is difficult to establish because the organism is cultured infrequently from sputum specimens or broncho-alveolar lavage fluid. For many years it was taught that *Aspergillus* spp. are common laboratory contaminants, and their isolation from respiratory secretions should be ignored. Yu et al. have clearly demonstrated that the isolation of *Aspergillus* spp. from susceptible patients usually indicates the presence of infection [75].

Few patients recover from aspergillosis unless their underlying deficiency in host defenses resolves. Many of them are left with residual foci that can cause subsequent complications. One risk is late exsanguinating hemorrhage from a residual cavity. Patients requiring further myelosuppressive or immunosuppressive therapy are at risk of recrudescence of their infection. Hence, for those patients whose lesions do not improve rapidly with antifungal therapy, surgical excision should be considered. Computed tomography of both lungs should be performed to be certain there are no additional lesions that are not apparent on routine chest roentgenograms. When surgical excision is not possible, therapy should be continued for prolonged periods. Patients with acute leukemia who are to receive subsequent courses of myelosuppressive chemotherapy should be given amphotericin B during the first several courses, while they are neutropenic [76]. Amphotericin B is only minimally effective, and few patients with persistent neutropenia survive their infection despite therapy with this antifungal agent. While itraconazole has activity

against *Aspergillus* spp., its role as therapy for these infections in cancer patients has not been adequately defined.

Fusariosis

Fusarium spp. are respiratory pathogens and cause pulmonary infection similar to aspergillosis [77]. These organisms also have a propensity for invading blood vessels, causing thrombosis and infarction. They can be confused with *Aspergillus* spp. on histopathological examination. Occasionally, the two infections can occur concomitantly in the same patient. There are several important differences between infections caused by these two molds. *Fusarium* infection disseminates widely in about 75 percent of cases, whereas *Aspergillus* infection disseminates in about 30 percent. *Fusarium* spp. are usually isolated from blood cultures of patients with disseminated infection, whereas *Aspergillus* spp. are rarely isolated from blood cultures. Widespread skin lesions are common in disseminated fusariosis but are uncommon in disseminated aspergillosis. No currently available antifungal agent has activity against *Fusarium* spp., and recovery from infection has only occurred in patients whose predisposing deficiencies in host defenses have resolved.

Other fungal pneumonias

Occasional pulmonary infections in cancer patients have been caused by other yeasts and mold. *Trichosporon* spp. can cause a primary pneumonia, or pulmonary involvement may occur in association with disseminated infection [78]. This yeast infection occurs primarily in patients with severe neutropenia. The organism usually can be isolated from blood culture specimens of patients with disseminated infection. The organism is more likely to be susceptible to therapy with azoles such as fluconazole than with amphotericin B. Pseudallescheriasis is a rare cause of pulmonary infection in cancer patients. The preferred treatment for this infection is an azole, since amphotericin B is not reliably effective. Rarely other fungi, such as *Bipolaris* spp. and *Curvularia* spp., may cause pulmonary infection in neutropenic patients, but sinus infection is more likely.

Viral pneumonia

Viral pneumonia is an important cause of morbidity and mortality in the immunocompromised host. Traditionally, the herpesviruses have been the most recognized pathogens, but there is mounting evidence that community respiratory viruses are also a frequent cause of severe pneumonia in these patients [79–81]. Viral infection is different in the immunocompromised host than in the non-immunocompromised host. Infections that would typically cause trivial illness frequently develop into severe, life-threatening disease in the immunocompromised host. Similarly, in many situations involving organ transplantation, a temporal

relationship exists between the onset of overt viral disease and the time after transplantation.

Herpesviruses

Cytomegalovirus. Cytomegalovirus (CMV) is one of the most important virus infections of the immunocompromised host, causing a variety of diseases, including encephalitis, gastrointestinal disease, retinitis, and hepatitis. The most important complication of CMV infection is pneumonia. The radiographic presentation is usually interstitial infiltrates, but nodular or localized patterns may occur. The clinical presentation may range from a chronic nonproductive cough accompanied by changes in the chest roentgenogram to a fulminant pneumonia with fever, shortness of breath, tachypnea, and rapidly developing infiltrates. The laboratory findings include hypoxia and leukopenia. The differential diagnosis depends on the host, the level of immunosuppression, underlying disease, time after transplant, and treatment regimen. It includes other viral diseases, pulmonary edema, pulmonary hemorrhage, drug toxicity, *Pneumocystis carinii* pneumonia, and atypical presentations of fungal and mycobacterial disease.

Cytomegalovirus interstitial pneumonia has been described in a wide variety of patients, including those with AIDS, organ transplantation, and leukemia. The most extensively studied patient population is marrow transplantation. Cytomegalovirus has been found to cause interstitial pneumonia in 16.7 percent of patients undergoing allogeneic marrow transplant [79]. In keeping with the temporal distribution of disease, CMV pneumonia occurs with the highest frequency between day 30 and day 100 after transplantation.

The mortality from CMV pneumonia has been as high as 85 percent prior to the introduction of ganciclovir and immunoglobulin. Because of this high mortality rate, there has been a substantial effort to prevent CMV pneumonia in transplant patients. In renal transplant patients, acyclovir has been used successfully to prevent CMV pneumonia, especially in patients who are CMV seronegative and who receive a CMV-seropositive transplant [82]. In marrow transplant patients, ganciclovir has been shown to prevent CMV infection and disease in patients who are CMV seropositive prior to transplant [83,84] or who have evidence of active CMV replication by surveillance cultures after marrow infusion [85,86].

Treatment of CMV pneumonia has involved the combination of high-dose ganciclovir and intravenous immunoglobulin. This combination has reduced the mortality of CMV pneumonia from 85 percent to between 35 percent and 55 percent, depending on the marrow transplant center [87,88]. This treatment has been extrapolated to other patient populations with some success, but whether it is necessary to include immunoglobulin with ganciclovir when treating renal transplant or other immunocompromised patients with CMV pneumonia remains to be determined. It should be noted that at the time of the introduction of the combination of ganciclovir and immunoglobulin for the treatment of CMV pneumonia, the method of diagnosis changed from open lung biopsy to bronchoalveolar lavage (BAL). One hypothesis to account for the difference in survival is that BAL has

enabled the clinician to diagnose a population of patients who have less advanced pulmonary disease than patients who underwent open lung biopsy. This would result in a bias toward a population of patients whose survival may have been better because of the detection of milder disease.

Until recently, fatal CMV pneumonia was a rare disease among cancer patients who had not received a transplant. Among 9549 adult nontransplanted cancer patients who underwent autopsy at MDACC between 1964 and 1990, only 16 (0.17 percent) patients were diagnosed with CMV pneumonia (89). Whether the incidence of CMV pneumonia is increasing in this patient population in the setting of more immunosuppressive chemotherapeutic regimens is currently being investigated.

Herpes simplex virus. The most common presentation of herpes simplex virus (HSV) in the immunocompromised host is mucocutaneous disease [90,91]. Herpes simplex virus pneumonia is an uncommon disease and may involve both HSV type I and II. The most common clinical presentation of pneumonia is dyspnea and cough. The chest roentgenogram may have a focal, multifocal, or diffuse interstitial pattern. The pathogenesis may involve contiguous infection of the esophagus and tracheobronchial tree, with extensions to the lung or hematogenous dissemination from another organ. The diagnosis of HSV pneumonia is suggested by the recovery of virus or the demonstration of viral antigens in lung parenchyma. Because of the potential for oropharyngeal contamination, the recovery of virus from BAL fluid can only suggest the diagnosis. In addition, infection with other opportunistic pathogens may complicate HSV pneumonia [90]. Acyclovir remains the drug of choice, although controlled trials are not available and would be difficult to accomplish due to the infrequency of pneumonia.

Varicella-Zoster virus. Varicella-Zoster virus may cause pneumonia either by primary infection or by reactivation and dissemination of a latent infection. Populations at risk for varicella include children with malignancies, marrow transplant recipients, and patients with Hodgkin's disease [92–95]. With primary infection, pneumonitis may occur 2–5 days after the onset of rash and may present with a nonproductive cough, fever, and interstitial changes on chest roentgenogram. The pathogenesis of reactivation of varicella is similar, except that hematogenous dissemination may occur 5–7 days after the initial dermatomal rash. Besides the lung, both the liver and central nervous system may be affected, either during primary infection or during reactivation with dissemination. The prompt institution of parenteral acyclovir at the dermatomal stage will prevent clinically important dissemination.

Human herpes virus-6. Recently, a new herpesvirus has been described, called *human herpesvirus-6* (HHV-6) [96–98]. The virus was first isolated from patients with lymphoblastoid disease and has been shown to cause exanthem subitum in children. Recent work has suggested that this virus may be responsible for interstitial pneumonia as well as marrow suppression and fatal encephalitis in marrow

transplant patients. More work is needed to define the pathogenic role of HHV-6 in immunocompromised patients.

Community respiratory viruses

Besides the herpesviruses, community respiratory viruses, such as influenza virus, respiratory syncytial virus (RSV), parainfluenza virus, and adenovirus, may cause severe, life-threatening pneumonia in the immunocompromised host. Nosocomial acquisition of these infections is common. Two studies conducted a decade apart at the Fred Hutchinson Cancer Center highlight the growing knowledge of the importance of these viruses [79,80]. The first study reviewed 85 episodes of nonbacterial interstitial pneumonia occurring among 525 allogeneic marrow transplant patients from 1969 to 1979. The causes were CMV (40 percent), HSV and VZV (7 percent), pneumocystosis (PCP) (16 percent), 'idiopathic' (29 percent), and 'clinically diagnosed' (15 percent). Other than one case of adenovirus pneumonia, no pneumonias were recognized to be caused by a community respiratory virus. The second study specifically looked at community respiratory virus infections among 78 patients admitted for allogeneic marrow transplant from January to April, 1987. Nineteen percent of patients were diagnosed with a respiratory virus, including parainfluenza virus (eight patients), adenovirus (five patients), and influenza A virus and RSV (one patient each). These two studies suggested that community respiratory viruses are a part of the group of previously classified 'idiopathic' and 'clinically diagnosed' interstitial pneumonias and will go undetected unless specifically sought.

Influenza virus. Although influenza virus is a well-recognized cause of pneumonia in the general population, there have been few studies of influenza in patients with cancer [99–102]. In general, there are three types of pneumonia associated with influenza infection: viral, mixed viral-bacterial, and bacterial, which is by far the most common. At MDACC, we prospectively followed all adult leukemia and marrow transplant patients hospitalized during the 1991–1992 influenza season [101,102]. Twenty-five percent of the marrow transplant patients and 10 percent of the leukemia patients who had an acute respiratory illness had culture-proven influenza A infection. Over two thirds of these infections were complicated by pneumonia. Approximately 80 percent of the pneumonias responded to antibacterial antibiotics, suggesting that these were bacterial superinfections. However, 20 percent of the pneumonias were viral in origin and were fatal. Whether amantadine and/or ribavirin is of benefit in the therapy of influenza virus pneumonia needs to be defined. Annual influenza vaccination is recommended for patients, families, and hospital staff, though its efficacy in severely immunocompromised patients is questionable [103].

Respiratory syncytial virus. Respiratory syncytial virus (RSV) is the most frequent cause of lower respiratory tract infection in young children. Similar to influenza, infections tend to occur annually on a seasonal basis. Though immunity is

incomplete and repeated infections are common throughout life, RSV infections in the nonimmunocompromised adult are typically limited to the upper respiratory tract infection. Among adult bone marrow transplant (BMT) recipients, however, RSV may cause severe and life-threatening pneumonias [104–107]. Devastating outbreaks of RSV disease have been reported from two marrow transplant centers [106,107]. The illness typically begins with signs and symptoms of an upper respiratory tract infection, such as nasal and sinus congestion, rhinorrhea, pharyngitis, otitis media, and cough, which then may progress to tracheobronchitis and pneumonia. Risk factors for pneumonia include marrow aplasia, recent marrow transplant (<50 days), and chronic immunosuppressive therapy for graft-versus-host disease.

The response to therapy with ribavirin alone has been dismal. In a study involving 18 adult BMT recipients with radiographic and clinical pneumonia, the overall mortality was 70 percent among 13 patients treated with aerosolized ribavirin alone and 100 percent among 5 untreated patients [106]. A recent study conducted at MDACC suggests that combination therapy with aerosolized ribavirin (18 hours/day) and intravenous immunoglobulin (500 mg/kg every other day) may be efficacious if initiated at an early stage of pneumonia [107]. Thus, the mortality was approximately 25 percent among BMT recipients treated at an early stage of pulmonary involvement, compared with 100 percent among patients treated after the onset of respiratory failure and among untreated patients. Because prolonged aerosolized ribavirin therapy is associated with considerable psychological and physical discomfort to the patient and poses the risk of environmental contamination with a potentially teratogenic drug, alternative therapies are being investigated, including high-dose, short duration aerosolized ribavirin and intravenous ribavirin [108]. The role of RSV in the etiology of pneumonia in nontransplanted immunocompromised patients is only beginning to be defined. A recent study suggests that during community outbreaks, RSV is also a frequent cause of life-threatening pneumonia among adult patients with leukemia [109]. Because of the significant incidence of nosocomial transmission of RSV and the substantial morbidity and mortality associated with these pneumonias, intensive efforts should be employed to prevent infection, including strict hospital infection control measures.

Parainfluenza virus. Parainfluenza virus is the second most common cause of lower respiratory tract disease in young children. Unlike RSV and influenza, parainfluenza virus infections occur year round. While nonimmunocompromised adults rarely develop more than a self-limited upper respiratory tract infection, severely immunocompromised patients, such as marrow transplant recipients, may develop life-threatening pneumonias. Similar to RSV, these pneumonias are characteristically preceded by signs and symptoms of an upper respiratory tract infection. In two large retrospective studies involving BMT recipients, the incidence of parainfluenza virus infection has been approximately 3 percent [110,111]. Over 60 percent of these infections have been complicated by pneumonia, which has been associated with an overall mortality of 30–50 percent. However, the precise contribution of parainfluenza virus to death has been difficult to define because of the

frequent presence of other opportunistic pulmonary pathogens. The role of parainfluenza virus in nontransplanted immunocompromised patients needs to be studied. Similar to RSV, parainfluenza virus has been found to be susceptible to ribavirin in vitro; however, little is known about its efficacy in vivo. Rapid diagnostic tests are needed, as are available for RSV, since culture results frequently only become available after the illness has resolved or the patient has expired.

Adenovirus. Among immunocompromised patients, adenovirus may cause a wide range of respiratory illnesses, ranging from self-limited upper respiratory tract infections to fatal pneumonia [112,113]. These infections may be acquired exogenously or endogenously by reactivation of latent infection. Pneumonia in the severely immunocompromised patient, such as the marrow transplant patient, typically occurs as part of fatal, disseminated disease involving the gastrointestinal, hepatobiliary, and genitourinary tract. There is no known therapy, though anecdotal reports suggest that ribavirin may be of benefit.

Other opportunistic pulmonary infections

Other organisms causing pneumonia with increased frequency and/or severity in cancer patients include the parasites, *Pneumocystis carinii* and *Toxoplasma gondii*, and the helminth, *Strongyloides stercoralis*.

Pneumocystosis

Similar to patients with AIDS, cancer patients with impaired cellular immunity are at risk for PCP, particularly patients with acute lymphocytic leukemia receiving intense maintenance therapy, transplant recipients, and patients receiving prolonged corticosteroids [114–119]. An unusually high incidence has also been reported among patients with brain tumors whose steroids are being tapered [120,121]. The incidence is directly related to the type and intensity of prolonged immunosuppression. Pneumonia usually represents reactivation of latent infection; however, person-to-person airborne transmission has also been suggested by outbreaks occurring in families, orphanages, and hospitals [122]. An increased incidence is being reported among cancer patients [123,124], but it is not clear whether this is due to increased exogenous exposure or more immunosuppressive therapy. Similar to patients with AIDS, symptoms may be subtle lasting from weeks to months; however, a fulminant course is more typical [125]. The overall mortality is 30–50 percent.

The typical presenting symptoms are fever, dyspnea, exercise intolerance, and a nonproductive cough. Often, there are few findings on lung exam in spite of extensive radiographic infiltrates. The lung exam and chest roentgenogram may both initially be unrevealing in spite of significant respiratory compromise. Diagnosis is made by histopathologic demonstration of the organism. Induced sputum may occasionally reveal the organisms and avoid the need for bronchoscopy [126]. Intermittent prophylaxis with trimethoprim/sulfamethoxazole is effective in reducing

the incidence in high-risk patients [127]. Other preventive and treatment options are similar to those for patients with AIDS [128].

Toxoplasmosis

In contrast to its high incidence in AIDS, clinically severe toxoplasmosis has infrequently been reported in cancer patients [129–136]. These patients have usually had an underlying hematologic malignancy or have been transplant recipients. The common denominator appears to be cellular immune dysfunction. The disease usually results from reactivation of a latent infection, though it may be acquired exogenously. The most common clinical syndromes are encephalitis, myocarditis, and pneumonitis. The clinical and radiologic features of pneumonitis are nonspecific, and the diagnosis may be obscured by copathogens, notably CMV. Pneumonitis typically occurs as part of disseminated disease and should be suspected in the setting of neurological and/or myocardial dysfunction. The disease readily responds to therapy, yet is often lethal if untreated. The diagnosis can be made by visualizing the organisms in BAL fluid or lung tissue, or by isolating the organism by mouse inoculation or cell culture. Therapy consists of the combination of sulfadiazine and pyrimethamine, or of clindamycin and pyrimethamine.

Strongyloides stercoralis is an intestinal nematode that is endemic in many regions. Because it has an autoinfection cycle, chronic asymptomatic gastrointestinal infection may persist for decades. Cancer patients with cellular immunodeficiency may develop an overwhelming hyperinfection syndrome, characterized by hemorrhagic pulmonary consolidations, severe gastrointestinal symptomatology, and persisting polymicrobial bacteremia and/or meningitis, due to adherence of the gut bacteria to the migrating larvae. Diagnosis depends on demonstrating the larvae in feces, duodenal fluid, respiratory secretions, cerebrospinal fluid, and tissue [137,138]. Because of the high mortality (>80 percent), asymptomatic carriers should be treated with thiabendazole prior to immunosuppression. Therapy of the hyperinfection syndrome includes systemic antibiotics for the complicating bacteremia and meningitis, as well as thiabendazole.

Diagnosis

The diagnosis of pneumonia in the cancer patient may be overlooked, and the causative organism is often difficult to determine. Fever is the usual hallmark of severe infection, but patients receiving adrenal corticosteroid therapy often remain afebrile despite extensive infection. This is especially true with fungal infections. Neutropenic patients may have extensive pneumonia yet have a normal physical examination.

The value of sputum smears and culture for identifying the infecting organism has been questioned in recent years. Doctors often delegate the responsibility for collecting sputum specimens to other persons. Frequently, this results in a poorly collected specimen (saliva) or one that is collected after antibiotic therapy has been

initiated. The extent of oropharyngeal contamination of a sputum specimen can be estimated by the number of squamous epithelial cells and leukocytes present. Generally, a specimen is considered to be useful if it contains less than 10 epithelial cells and greater than 25 leukocytes per low-power field ($\times 100$); however, a severely neutropenic patient may not be able to mount such an inflammatory response.

Several other factors affect the utility of sputum smears and cultures in cancer patients. Patients with postobstructive pneumonia and severely neutropenic patients often cannot produce adequate specimens. Some organisms may be overlooked because they require special stains or cultural media (i.e., *Legionella* spp., *Nocardia* spp.). Some organisms that are part of the normal respiratory flora and that are considered to be nonpathogenic in normal hosts, such as alpha-hemolytic streptococci, can cause severe infection in neutropenic patients. Lastly, some organisms cannot be cultured readily and diagnosis depends upon other techniques, such as serological titers or biopsy. Attempts to improve sputum collection have included methods such as induced sputum collection or transtracheal aspiration. The latter technique has been generally abandoned and may be hazardous in thrombocytopenic patients. Several blood cultures should be collected as part of the initial workup. These cultures may yield a diagnosis when sputum cultures fail to do so. Bacteremia is most likely to be present in neutropenic patients.

Several invasive techniques have been developed to improve diagnostic capabilities. The most widely utilized procedure is bronchoscopy with transbronchial biopsy, protected brush collection, or BAL [139]. Bronchoscopy with BAL can be performed safely, even in severely thrombocytopenic patients. The value of protected brush specimens is enhanced if quantitative cultures are performed. The diagnostic yield of these procedures varies considerably, depending upon the patient population, the diversity of diagnostic possibilities, and the expertise of the physician. For example, the diagnostic yield with BAL is much greater in HIV-infected patients than in neutropenic patients. The most invasive procedures, percutaneous needle aspiration or biopsy and open lung biopsy, are the most effective for diagnosis but also are associated with the greatest risks [140,141]. Serious complications occur following 8–40 percent of open lung biopsies. These invasive procedures should not be done in patients with platelet counts less than 50,000/mm. Furthermore, even open lung biopsies provide a diagnosis in less than 40 percent of neutropenic patients. Invasive procedures are more likely to be useful in patients with diseases such as lymphoma, in which there is a greater diversity of potential pathogens and less invasive procedures are less likely to provide a diagnosis.

In summary, if simple procedures fail to provide a diagnosis in neutropenic patients and the patient is not responding to therapy, bronchoscopy with BAL should be considered. In patients with defects in other aspects of cellular immunity or in bone marrow transplant recipients who have recovered their neutrophil count, bronchoscopy with BAL should be performed expeditiously and open lung biopsy should be considered if a diagnosis is not established. In all patients who are immunocompromised, appropriate diagnostic procedures should be performed expeditiously because pneumonia that is not treated appropriately can progress rapidly to pulmonary insufficiency and death.

Approach to the cancer patient with pneumonitis

Pneumonitis is the most difficult infection to manage in the cancer patient for several reasons. A successful therapeutic outcome frequently depends upon correction of the predisposing factor, such as bronchial obstruction or neutropenia, which may not be possible. A careful history and physical examination often is of little help in determining the cause of pneumonitis, as in the case of neutropenic patients, who may only have fever.

Nevertheless, in some patients there may be important clues that may not indicate the precise pathogen, but at least limit the possibilities to a few pathogens or suggest the appropriate tests to make the correct diagnosis. The most important information to be obtained from the history is the predisposing factor responsible for the patient's infection. Mechanical factors secondary to the tumor may be present, such as aspiration, tracheoesophageal fistula, or bronchial obstruction. Certain diseases are associated with specific defects in host defenses predisposing the patient to certain pathogens. Thus, a neutropenic patient is susceptible to infection caused by enteric aerobic gram-negative bacilli, *Candida* spp., and molds, whereas a patient who has impaired cellular immunity is susceptible to infections caused by intracellular pathogens such as mycobacteria, *Cryptococcus neoformans*, and *Toxoplasma gondii*. Adrenal corticosteroids interfere with macrophage function; hence, patients receiving these agents at high doses or for extended periods of time are susceptible to mold infections such as aspergillosis [142]. Pneumocystosis classically occurs as the dose of corticosteroids is gradually being reduced after high-dose therapy. Patients with humoral immune dysfunction and splenectomized patients are susceptible to overwhelming infections by encapsulated organisms such as *Streptococcus pneumoniae*.

The place of residence and travel history may be of importance. Fungii such as *Coccidioides immitis* and *Histoplasma capsulatum* and helminths such as *Strongyloides stercoralis* are endemic in some areas of the world and are a threat to patients with impaired cellular immunity. Multiple drug-resistant tuberculosis is also endemic in some areas and poses a special threat to some cancer patients.

Some patients present with signs and symptoms that are most often associated with certain pathogens. For example, the sudden onset of symptoms suggestive of acute pulmonary infarction occur in 30 percent of patients with pulmonary aspergillosis and also occur in other mold infections of the lung [143]. Fever and a chronic, nonproductive cough may be the earliest signs of PCP. The pneumonitis caused by CMV or *Pneumocystis carinii* may cause profound dyspnea and cyanosis after minimal exertion. Patients with progressive dyspnea associated with minimal or no fever are most likely to have pneumonitis secondary to a chemotherapeutic agent such as mitomycin C or busulfan, or lymphangitic spread of their malignancy.

Often the chest roentgenogram examination indicates only the presence of pneumonitis without providing any clues to the cause. Indeed, severely neutropenic patients may have extensive pneumonitis without developing any radiographic abnormalities at the time of initial presentation. Nevertheless, some patients present with abnormalities that are suggestive of specific infections. Abscess formation is

suggestive of anaerobic, gram-negative bacillary or *Nocardia* infection. The appearance of a single or several nodular lesions is suggestive of aspergillosis or other mold infection. Some patients with these infections develop wedge-shaped infiltrates suggestive of pulmonary infarctions. Hematogenously disseminated pneumonitis is suggestive of *Staphylococcus* or *Candida* pneumonia [144]. A bilateral butterflylike infiltrate has been classically associated with PCP, though other types of infiltrates have been described. Associated mediastinal or hilar lymphadenopathy is suggestive of histoplasmosis, tuberculosis, or disseminated malignancy. Some pulmonary infections are a manifestation of disseminated disease, and the cause may be suggested by the extrapulmonary symptoms. Concomitant symptoms of CNS involvement can occur in toxoplasmosis, nocardiosis, tuberculosis, histoplasmosis, and candidiasis. Skin lesions may be found in disseminated candidiasis, aspergillosis, or fusariosis. Ecthyma gangrenosa is usually caused by *Pseudomonas aeruginosa*, but occasionally is due to other infections. Myocarditis or hepatitis may be associated with pneumonitis due to CMV or toxoplasmosis. Retinal lesions may be found in patients with *Candida* or CMV infection.

Once a careful history, physical, and chest roentgenogram examination have been completed, it should be possible to focus on the appropriate diagnostic procedures, such as collection of sputum and blood culture specimens. The microbiological laboratory should be notified if special stains and culture techniques are necessary. Since infection can progress rapidly in patients who have severely compromised host defenses, diagnostic tests should be performed expeditiously. Antibacterial (and occasionally antifungal) therapy should be initiated immediately in neutropenic patients. Early consideration should be given to invasive procedures, such as bronchoscopy or open lung biopsy. The relative value of these diagnostic procedures has been discussed earlier.

Some severely immunocompromised cancer patients present with extensive, bilateral pneumonitis with significant pulmonary compromise. Many of these patients have multiple anatomic and immune deficiencies, and the diagnostic possibilities are vast. Often there are no clues to the causative organism, and it is apparent that if effective therapy is not instituted promptly, the patient will die. There is no entirely satisfactory regimen for these patients. The following type of approach is recommended. A broad-spectrum beta-lactam that provides antipseudomonal coverage should be utilized. An aminoglycoside can be included for synergistic potential, and perhaps for broader coverage, but there is little evidence that these agents enhance efficacy, and they can increase the potential for nephrotoxicity. High-dose trimethoprim/sulfamethoxazole should be given to provide coverage against *Pneumocystis carinii*, *Legionella*, and some other bacterial pathogens. Amphotericin B should be used as the antifungal agent, since it provides the broadest spectrum of activity. Foscarnet is probably the best antiviral agent to use empirically, since it provides the broadest spectrum of activity against the herpesviruses, although ganciclovir may be used. Depending on the individual clinical situation, other agents may be included initially, or may be added 24–36 hours later if the patient is not improving, such as vancomycin, ribavirin, antituberculosis medications, or an azolide. High doses of adrenal corticosteroids may be life saving in occasional

patients. Obviously, such broad-spectrum regimens should be modified as soon as the diagnosis is established.

In conclusion, there is no generic cancer patient with pneumonia. Successful management of these patients requires a complex assessment of the many interdigitating clinical clues of each individual case. Aggressive, empirical, broad-spectrum antimicrobial therapy is often necessary because of the difficulty in obtaining a timely diagnosis and the need to treat these pneumonias early for a favorable outcome.

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10 Intravascular device-related infections in cancer patients

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The successful management of oncology patients entails the safe use of intravascular catheters. Central venous catheters (CVC), particularly long-term silastic catheters, are commonly used in cancer patients to administer chemotherapy, antibiotics, blood products, and parenteral nutrition. Infection is one of the leading complications of these devices, and catheter-related septicemias represent the most frequent life-threatening complication of intravascular catheters [1–7]. The rate of septicemias associated with noncuffed CVC has ranged from 4 percent to 14 percent [8]. For long-term cuffed silastic catheters, a range of 8–43 percent has been reported [5]. More than 5 million CVCs are inserted in the United States annually [9]. Of those, about 0.5 million are cuffed silastic catheters [10]. Assuming a conservative average septicemia rate of only 8 percent, one would expect at least 400,000 CVC-related septicemias per year.

In addition to the patient morbidity and mortality that occurs with such infections, it has been clearly shown that catheter-related infections prolong hospitalization and lead to excess cost. Maki et al. estimated the cost of treating one episode of catheter-related septicemia to be \$6000 (1988 dollars), including an extension of the period of hospitalization by at least 7 days [11]. Based on these figures, the annual economic burden resulting from the infectious complications of CVC in the United States is at least 2.4 billion dollars. The majority of CVC infections are reversible and preventable if one is well aware of the risks and preventive factors, and knows how to appropriately diagnose and treat these infections.

Definitions

The terms *catheter-related infections* and *catheter-associated infections* have been used by different investigators interchangeably. Unfortunately, these terms were often used to mean different things, which has led to confusion and difficulty in comparing the results of clinical studies. Standard, well-accepted definitions of the terms do not exist. Therefore, a clear understanding of the most accepted definitions is important for an intelligent interpretation of the literature. Catheter-related infections can be divided into two main entities: local catheter infections and systemic catheter-related septicemias.

Local catheter infection

Any of the following conditions can be considered a local catheter infection:

An exit or insertion site infection. Purulence around the catheter insertion site in the absence of a bloodstream infection represents a local exit or insertion site infection. Catheter or port-site inflammation, consisting of erythema, warmth, tenderness, and swelling, are suggestive but not specific for an infection. Inflammation could represent a sterile mechanical condition, particularly for the peripherally inserted central catheters (PICC). A quantitative skin or subcutaneous catheter segment culture may help in distinguishing a sterile inflammation from an exit tunnel infection. The erythema usually begins at least 1 cm from the catheter insertion site and tracks up the catheter tract.

Tunnel infection. This condition is characterized by a spreading cellulitis around the subcutaneous tunnel tract of tunneled long-term catheters, such as Hickman/Broviac catheters [1].

Significant catheter colonization. Maki et al. have demonstrated a strong correlation between the isolation of ≥ 15 colony forming units (CFU) of an organism from a catheter segment and catheter site inflammation [12]. Because of this relationship, the term *local infection* has often been used as the equivalent of ≥ 15 CFUs isolated from a catheter segment using the roll-plate culture technique [13,14]. Other investigators have used the term *colonization* to describe this entity, in contradistinction to *contamination* when < 15 CFUs are isolated. In all cases a positive semiquantitative culture of a catheter tip should not be used as the equivalent of catheter-related bacteremia or fungemia in the absence of positive blood cultures.

Systemic catheter-related septicemia

This term has often been used as a diagnosis of exclusion to describe a bloodstream infection caused by a skin organism in a patient with a vascular catheter who has clinical manifestations of sepsis and no apparent source for the septicemia (such as pneumonia or a wound or urinary tract infection) except the catheter [15,16]. This diagnosis of exclusion is better termed *primary nosocomial bloodstream infection* (as defined by the Centers for Disease Control) or *probable catheter-related septicemia* [17]. Definite catheter-related septicemia is a primary bloodstream infection with clinical or quantitative microbiologic evidence that implicates the catheter as a definite source of the bloodstream infection (Table 1).

The clinical evidence implicating the catheter as a source could be either of the following: (1) an exit or tunnel infection with the same organisms (same species and antibiogram) isolated from the insertion site discharge and the bloodstream; (2) a resolution of the clinical sepsis (fever and chills) within 48 hours of catheter removal while the patient is on no active antibiotics or after an unsuccessful trial of active antibiotics for at least 72 hours.

The quantitative microbiologic evidence that is necessary to implicate the catheter as the source of the primary nosocomial bacteremia includes either quantitative catheter cultures or quantitative blood cultures.

Table 1. Evidence implicating the catheter as the source of sepsis

Clinical evidence

Pus at the insertion site/tunnel inflammation

or

Clinical sepsis refractory to antibiotics that resolves after catheter removal

Microbiologic evidence

Positive quantitative catheter culture with same organism cultured from blood

or

Differential quantitative blood cultures: 10:1 ratio of organisms isolated from blood drawn through CVC versus peripheral vein

Quantitative catheter cultures. In this method, the same organism is isolated from the catheter and the bloodstream. The positivity level depends on the quantitative culture technique used [18]. The roll-plate semiquantitative culture technique is the simplest and most commonly used method. Several studies have demonstrated the usefulness of the roll-plate technique in diagnosing CVC-related septicemia [18–20]. Its limitation is that it cultures only the external surface of the catheter [21]. After prolonged placement and excessive use of the catheter hub, intraluminal colonization of the long-term CVC becomes equal to or greater than that of the external surface. This is why other quantitative catheter culture techniques might be useful [21]. The flush technique first described by Cleri et al. quantitates the number of colonies that could be flushed from the internal surface of a catheter [22]. Sonication, vortex, and centrifuge techniques can isolate organisms from the internal and external surfaces of catheters. These techniques yield large number of colonies and are highly sensitive in diagnosing catheter-related septicemia [23–25]. In three clinical studies, we tested the sonication technique alone and in comparison with the roll-plate technique and found it to be highly diagnostic [25–27].

However, the limitation of all quantitative catheter culture techniques is that the diagnosis is always retrospective. The clinician has to remove or exchange the catheter to culture the colonies. A recent study of 359 CVCs removed at the M.D. Anderson Cancer Center demonstrated that of the 91 CVCs removed because of suspected catheter-related sepsis, only 8 (8.8 percent) had such a diagnosis and only 17 (18.7 percent) were colonized [28]. All catheters were cultured by the roll-plate and sonication technique. Because of the high rate of unnecessary and wasteful catheter removal, interest has developed in in-situ cultures, such as the quantitative brush catheter culture and quantitative blood cultures [29].

Quantitative blood cultures. In this method, simultaneous quantitative blood cultures are drawn through the catheter and peripheral vein without catheter removal or exchange [30]. When the number of organisms obtained through the CVC is severalfold greater than that quantitated from a peripheral blood culture, catheter-related sepsis is diagnosed. In the absence of peripheral blood cultures, a positive quantitative (or nonquantitative) blood culture obtained through the catheter is not on its own sufficient evidence to establish the diagnosis of catheter-related bacteremia

or fungemia. Several investigators have used simultaneous quantitative blood cultures and found that a positive differential of 10:1 colony count from the CVC compared with the peripheral vein is indicative of catheter-related septicemia [31–35]. Few other studies have reported a discrepancy between positive semiquantitative catheter cultures and differential quantitative blood cultures [20,36]. The discrepancy could be partly explained by the fact that quantitative blood cultures drawn through the CVC retrieve organisms from the internal surface of catheters, while the semiquantitative roll-plate technique cultures only the external surface.

Staining of catheters using a Gram stain or acridine orange stain has been proposed as a rapid method for the diagnosis of catheter-related infections. Cooper and Hopkins found the Gram stain method to be highly diagnostic but reported the need for at least 15 minutes of microscopic scanning of the catheter surface [37]. Zuffery et al. used the direct acridine stain and reported a high sensitivity, specificity, and predictive values (all ≥ 84 percent) [38]. Other studies have reported a low-positive predictive value (44–48 percent) for the two staining methods [39,40]. Labor intensive and of possible low positive predictive value, these staining methods are considered experimental at this point. Other quantitative techniques, such as the quantitative insertion skin culture, have been proposed [35,41,42]. These cultures are of high-negative predictive value if catheter exit-site inflammation is absent [35].

Pathogenesis

There are four potential sources for catheter colonization and catheter-related sepsis: the skin insertion site, the hub, hematogenous seeding of the catheter, and infusate contamination. The skin insertion site and the catheter hub are by far the two most important sources. For short-term catheters (including short-term CVC and arterial catheters), there is a strong correlation between high insertion skin colonization, external catheter colonization, and catheter-related sepsis [23]. It is suggested that bacteria (coagulase-negative staphylococci and *Staphylococcus aureus*) migrate from the exit site along the intercutaneous tract and the external surface of the catheter, causing a high colonization of the distal vascular segment (tip) and ultimately resulting in catheter-related bacteremia [9]. Maki has shown that the skin is the most common source for short-term catheter colonization and infection [43]. This is why factors that decrease the colonization of the insertion site (such as topical antibiotics and disinfectants [44–46]) and those that interrupt the intercutaneous migration of organisms (such as the silver cuff or Dacron sheath cuff [13]) decrease the risk of acquiring catheter-related infections. On the other hand, factors that tend to increase the multiplication of organisms at the insertion site, such as an occlusive transparent plastic dressing [47], and that lead to site contamination (for example, heavily contaminated disinfectants [48,49]) increase the risk of developing catheter-related infections.

The catheter hub is another source for the colonization of the catheter lumen. Organisms can be introduced into the hub from the hands of medical personnel.

From this contaminated hub, the organisms migrate along the internal surface of the catheter, where they create a bloodstream infection. Sitges-Serra and coworkers from Spain highlighted the hub as the most common source for catheter-related septicemia [50–52], while Maki and coworkers found the hub to be the second most common source of catheter-related infections [43]. This discrepancy could be related to the fact that Maki and coworkers studied short-term catheters with a mean in-place duration of 7.2–9.1 days, whereas the Sitges-Serra group studied longer term CVCs with a mean duration of 23.4–26.5 days. More recently, Salzman and coworkers demonstrated that 54 percent of Broviac and other silicone catheter-related sepsis were hub related [53]. The mean duration of placement for these catheters was 24 days.

At the University of Texas M.D. Anderson Cancer Center, we used quantitative scanning and transmission electron microscopy to study the degree of biofilm formation and ultrastructural colonization on the internal and external surfaces of the CVC. For CVCs with a relatively short term (mean, 15 days) of use, both surfaces were colonized to an equal extent [54]. This finding was further confirmed in a longer study involving 359 indwelling CVCs at the M.D. Anderson Cancer Center. For silicone catheters that remained in place for <10 days, the extent of colonization and biofilm formation on the internal and external surfaces were comparable (using semiquantitative scanning electron microscopy). For long-term CVCs, the degree of colonization and biofilm formation on the internal surface was at least twice that of the external surface [27]. It is therefore possible that prolonged use of the CVC hub in catheters that remain in place for long periods (>30 days) would result in a high degree of internal surface colonization that would exceed the external surface colonization originating from the insertion skin site.

Hematogenous seeding of the CVC from a distant focus (such as pneumonia, and gastrointestinal and urinary tract infections) has been suggested [55,56]. Its contribution to catheter colonization and sepsis is minimal and rarely demonstrated. Electron microscopy studies of CVCs removed from patients with non-CVC-related bacteremia failed to reveal any seeding of the CVC with organisms compatible with the preceding bacteremia [54].

Several epidemics of infusion-related bacteremia have been related to contaminated infusate [57–59]. Unlike other catheter-related septicemias in which the staphylococci and *Candida* species are the most common organisms, infusion-related sepsis from contaminated infusate is often caused by gram-negative bacilli, such as *Enterobacter*, *Pseudomonas*, *Citrobacter*, and *Serratia* species. Parenteral nutrition solutions and lipid emulsion can promote the growth of many bacteria and fungi [60–62], such as *Candida parapsilosis* and *Malassezia furfur*. Although many epidemics of nosocomial bacteremia have been caused by contaminated infusate, the contribution of such a source to endemic nosocomial primary bacteremia is very low [43].

Adherence of the bacteria to the catheter surface depends on the interaction of three factors: the host factor, the microbial factors, and the catheter material. The host reacts to the catheter as a foreign medical device by forming a thrombin sleeve around it [63,64]. This layer of the host biofilm is rich in fibrin and fibronectin, two

Table 2. Organisms causing catheter-related infections

Common organisms	Other commonly reported organisms
Coagulase-negative staphylococcus	<i>Bacillus</i> species
<i>Staphylococcus aureus</i>	<i>Corynebacterium</i> JK
<i>Candida</i>	<i>Acinetobacter</i> species
	<i>Pseudomonas</i> species
	<i>Xanthomonas maltophilia</i>

substances that are tightly adhered to by *S. aureus* and *Candida* species [66,67]. Both *S. aureus* and *Candida albicans* are coagulase-producing organisms that promote the process of thrombogenesis to their benefit by adhering tightly to the fibronectin and fibrin layer of the biofilm. Coagulase-negative staphylococci adhere to fibronectin but not to fibrin [66].

The microbial factors consist of the fibrous glycocalyx substance. Microbial organisms, particularly slime-producing coagulase-negative staphylococci, enhance their adherence by producing a fibrous glycocalyx material, also known as extra-cellular slime, which constitutes the microbial substance of the biofilm [68–71]. The biofilm layer made of microbial and host substances is conducive not only to the adherence of the organisms, but also to their maintenance, because it acts as a barrier that protects embedded organisms from antibiotics, phagocytic neutrophils, macrophages, and antibodies [72–75]. The third factor that plays a role in the adherence process is the catheter material. Several investigators have shown, for example, that *S. aureus* and *Candida* species adhere better to polyvinylchloride catheters than to Teflon catheters [76,77].

Microbiology

Several prospective studies using quantitative catheter cultures have shown that the three most common types of organisms causing catheter-related infections are coagulase-negative staphylococci, *S. aureus*, and *Candida* species (Table 2) [18–28]. *Candida albicans* followed by *C. parapsilosis* account for most of the *Candida* species causing catheter-related infections. Coagulase-negative staphylococci and *S. aureus* are introduced from the skin insertion site and hands of medical personnel contaminating the hub, while half of the *Candida* species are thought to seed hematogenously from the gastrointestinal tract and to adhere to the fibrin and fibronectin on the surface of the catheter [9,21]. *Corynebacterium*, especially JK strains, and *Bacillus* species can cause catheter-related infections, and they are usually introduced from the skin or hub. Gram-negative bacilli acquired from the hospital environment, such as *Acinetobacter* species, *Pseudomonas* species, and *Xanthomonas maltophilia*, have also been reported to cause catheter-related sepsis [78,79]. Enteric organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, and enterococci rarely cause catheter-related infections.

Table 3. Risk and protective factors associated with catheter-related infection

Risk factors	Protective factors
Prolonged catheterization	Infusion therapy team
Frequent manipulations	Topical disinfectants and antibiotics
Occlusive plastic dressings	Silver-impregnated cuff
Contaminated skin solutions	Coating catheters with antimicrobials
Improper aseptic techniques ^a	Maximal sterile barrier precautions ^b
Catheter material	
Location of catheter	

^a Improper aseptic techniques during insertion or maintenance.

^b Maximal sterile barrier precautions during insertion.

Prevention

The prevention of any nosocomial infection involves a cost-effective, concentrated effort by health care workers to minimize the risk factors and maximize the protective factors. Several factors have been associated with an increased risk of catheter-related infections (Table 3). Prolonged catheterization is one of the major risk factors of infection for short-term venous and arterial catheters. Several other studies have shown a strong relationship between prolonged catheterization and arterial or CVC-related infections [80–85].

Catheter material may be an important factor in promoting thrombogenesis and adherence of organisms. Linder and colleagues have demonstrated that flexible silicone and polyurethane catheters are less thrombogenic than polyvinylchloride catheters [86]. Other investigators have shown that staphylococci and fungi are prone to adhere better to polyvinylchloride surfaces than to Teflon [76,77].

Several nonrandomized and most retrospective studies have suggested that triple-lumen CVCs were associated with a higher risk of infection than are single-lumen CVCs [87–92]. However, other recent prospective randomized trials have failed to demonstrate any significant difference in infection rates [93–95]. The location of the catheter could affect susceptibility. For example, a higher infection rate has been reported for CVCs than for arterial or short peripheral catheters. Hampton and Sherertz reviewed 30 prospective clinical studies involving pulmonary artery, peripheral arterial, short peripheral venous, and central venous catheters [21]. They evaluated the risk of infection per day of catheterization. This risk was 1.3 percent per day for peripheral plastic venous catheters, 1.9 percent for peripheral arterial catheters, and 3.3 percent for central venous catheters. Some have suggested that internal jugular CVCs are more likely to become infected than are subclavian catheters [83]. However, this issue remains controversial, as others have presented data to the contrary [96].

Another risk factor is the direct application of occlusive transparent plastic dressings to the CVC insertion site. Conly and coworkers have shown that this type of dressing leads to a warm, moist insertion site with a high microbial burden, thereby increasing the risk of catheter colonization and septicemia [47]. This finding

has been supported by several other investigations [97,98]. Recently, Hoffman et al. conducted a meta-analysis on all randomized controlled trials that compared transparent polyurethane film and gauze dressings used on central and peripheral venous catheters on hospitalized patients [99]. Risks for catheter tip infections for patients with either central or peripheral venous catheters were increased with the use of occlusive transparent polyurethane film compared with gauze dressings.

It is important to realize that the largest prospective randomized studies reviewed by Hoffman failed to show a significant difference in catheter-related septicemia. In addition, the results of this review might not be applicable to the new nonocclusive transparent dressings. Other risk factors include frequent manipulations of catheters [20,21] (as with Swan-Ganz catheters), using contaminated antiseptic skin solutions on the insertion site [48,49], using improper insertion and maintenance techniques [100,101], such as the violation of aseptic techniques by inexperienced inserters or staff, and using cutdowns for the insertion of catheters [102].

Several protective and preventive methods have been suggested to guard against infection. To avoid improper insertion and maintenance by inexperienced health care workers, several centers have established an expert infusion therapy team for the insertion and maintenance of catheters. Several studies have shown that such a team can decrease the infection rate five- to eightfold [100,104]. In addition, the team can be cost effective in centers with high rates of catheter-related infections or with a large volume of immunosuppressed patients. At the M.D. Anderson Cancer Center, for example, the infection rate and durability of nontunneled, noncuffed, silastic CVCs (infection rate, 0.13/100 catheter days; mean in-place duration, 109 days) was comparable with that of the Hickman tunneled CVC [28]. We attribute this low rate partly to the availability of an expert infusion therapy team.

Another preventive method consists of lowering the microbial burden at the skin insertion site. Povidone-iodine ointment applied to the insertion site has not been shown to significantly decrease the rate of catheter-related infections [45]. However, topical antibiotics (such as polymyxin-neomycin-bacitracin) have significantly decreased the total risk of acquiring catheter infections, though at the expense of the higher risk of acquiring fungal (*Candida*) colonization and infection [44,45]. In a three-arm trial, Maki and coworkers compared the effectiveness of 70 percent alcohol with 10 percent povidone iodine and with 2 percent chlorhexidine gluconate. The rate of catheter-related bacteremia was almost fourfold lower in the chlorhexidine arm than in the other two arms [46].

Several studies have shown that the attachable silver-impregnated cuff can reduce the incidence of catheter-related infections among critically ill patients with short-term CVCs (mean in-place duration, 5.6–9.1 days) [13,14]. The silver cuff failed to protect against infections in the longer term CVCs (mean in-place duration, 20 days) [105] or in the long-term tunneled Hickman catheters [106].

Schwartz et al. have used a solution made of heparin and vancomycin to flush tunneled CVCs and compared its efficacy with that of heparin alone [107]. Daily flushing with heparin/vancomycin decreased the frequency of catheter-related bacteremia attributed to luminal colonization and caused by gram-positive organisms

susceptible to vancomycin. It is unknown whether heparin/vancomycin flushing will make any difference in the overall rate of catheter-related infections.

Investigators have recently studied the protective effect of coating catheters with antibiotics or antiseptics. Kamal and colleagues demonstrated the protective efficacy of bonding CVCs with cefazolin using a cationic bonding surfactant [108] (tridodecyl methylammonium chloride). Maki and colleagues coated CVCs with silver sulfadiazine and chlorhexidine. Coated CVCs were twofold less likely to become colonized and were at least fourfold less likely to produce bacteremia [109] (4.7 percent vs. 1.0 percent, $p = 0.02$).

Using maximal sterile barriers during the insertion of a CVC may help minimize catheter-related infections. A maximal sterile barrier involves wearing sterile gloves, a mask, a gown, and a cap, and using a large drape; the normal procedure is to wear gloves and use a small drape. McCormick and Maki have shown that using maximal sterile barriers led to a fourfold decrease in the rate of pulmonary artery catheter-related bacteremia and a significant decrease in the colonization of the introducer [110]. At the M.D. Anderson Cancer Center we recently conducted a randomized prospective controlled trial comparing maximal sterile barrier precautions during insertion versus control (gloves and small drape). The catheter-related sepsis rate was 6.3 times higher in the control group compared with maximal sterile barrier ($p = 0.3$). Most (67 percent) of the catheter infections in the control group occurred during the first week postinsertion, whereas all of the catheter infections in the sterile barrier group occurred more than 2 months following insertion ($p < 0.01$). Cost-benefit analysis of these data showed that the use of such precautions is highly cost effective [111].

The role of CVC exchange over a guidewire as a preventive or therapeutic procedure is a controversial issue. Several uncontrolled trials that failed to perform quantitative cultures suggested the routine exchange of CVCs as a practice that would reduce the risk of CVC-related infections [112,113]. However, Pettigrew and coworkers showed that organisms colonizing a CVC could be transferred to the new CVC exchanged over a guidewire [114]. Using semiquantitative catheter cultures, Eyer et al. showed that crosscontamination of the external surface occurred in only 25 percent [115]. Two recent prospective clinical trials randomized patients to either exchanging the CVC every 3 days over a wire or changing the CVC only when clinically indicated. These studies failed to show any preventive benefit from regularly scheduled exchanges [6,116]. On the contrary, the study by Cobb et al. showed that exchanging a CVC routinely over guidewires will increase the risk of bloodstream infection [116]. In a sheep model, Olson and coworkers showed that the exchange of the CVC over a guidewire carried with it a high risk of reinfesting the new CVC and of showering the lung with small septic emboli [117].

Preliminary data suggest that prophylaxis with a fibrinolytic agent, urokinase, rather than heparin, may be more effective in preventing catheter occlusion and infection in patients with ports (118). This approach needs to be further explored. Other practices have also failed to show any preventive potential. Using in-line filters, which can reduce the rate of phlebitis, does not decrease the frequency of catheter infections [119,120]. Changing the insertion site dressing and the infusate

Table 4. Management of uncomplicated catheter-related septicemia

Organism	Immediate catheter removal	Antimicrobial proposed	Duration of therapy (days)
Coagulase-negative staphylococci	Yes	Vancomycin	5–7
<i>Staphylococcus aureus</i>	Yes	Antistaphylococcal penicillins or cephalosporins or vancomycin	>10
<i>Candida</i>	Unknown	Amphotericin B or fluconazole	7–10
Gram-positive bacilli	Yes	Vancomycin	7
Gram-negative bacilli	Yes	Aminoglycosides, quinolones, third-generation cephalosporins, imipenem, or monobactams	7
<i>Mycobacterium fortuitum</i> complex	Yes	Amikacin and ceftoxitin	7

tubing every 24 hours is no more protective than changing them every 72 hours [121,122].

Management

The treatment and catheter management of catheter-related infections is dependent on at least four variables: (1) extent of the infection: whether the infection is local (exit-site or tunnel infection) or systemic (uncomplicated septicemia or septic thrombosis); (2) microorganisms causing the infection (*S. epidermidis*, *S. aureus*, *C. albicans*, or gram-negative bacilli); (3) type of catheter (surgically implantable or percutaneous nontunneled CVC); and (4) underlying condition of the catheterized host (critical or immunosuppressed patient; low platelet count or coagulopathy). Prudent decisions related to the duration and type of antimicrobial therapy, as well as whether the catheter should be removed, need to be made after individualizing every case in light of these four variables, especially the causative organism (Table 4).

Local infections

Exit-site infections are the least serious infectious complications related to the catheter. Benezra and coworkers showed that such infections (except for those caused by *Pseudomonas* species) could be treated by antibiotics and local care without removal of the tunneled catheter [78]. Short-term percutaneous CVC with exit infection should be removed if the patient is febrile or septic and is failing to respond to intravenous antibiotics. Tunnel infections are often serious and are best managed by removing the CVC and administration of intravenous antibiotics [78]. Tunnel infection caused by *Mycobacterium fortuitum* or *Mycobacterium chelonae*

may require surgical excision of the infected tunnel after catheter removal and the initiation of antibiotics [123].

Systemic infections

Catheter-related septicemia with or without a local infection (exit or tunnel infection) should be classified into two categories: uncomplicated versus complicated septicemia associated with either septic thrombosis (septic thrombophlebitis) or deep-seated infections. Most catheter-related septicemias are uncomplicated bloodstream infections that respond well to intravenous antibiotic therapy and, if necessary, catheter removal. Should the septicemia persist for more than 48 hours after catheter removal and antibiotic initiation, then a complicated intravascular focus should be considered, such as endocarditis or septic thrombosis [124]. Under this circumstance an echocardiogram and distal arm venogram are warranted. Septic thrombosis of the central vein or infective endocarditis should be treated for at least 4 weeks with parenteral antibiotics. The issue of catheter removal is dependent on some of the variables discussed earlier, particularly the identity of the organisms causing the septicemia. Therefore, the management of catheter-related septicemias will be studied in light of the most common causative microbial pathogens (Table 4).

Coagulase-negative staphylococci. More than one positive blood culture belonging to the same species (such as *S. epidermidis*) are required to ascertain the diagnosis of a true bacteremia and to rule out a skin contamination [17]. Since most (50–80 percent) of the coagulase-negative staphylococci are resistant to the antistaphylococcal penicillins (e.g., oxacillin), intravenous vancomycin is the treatment of choice. The optimal duration of therapy is not yet defined. However, if the patient responds within 48–72 hours, a treatment course consisting of 5–7 days should be adequate [21]. Catheter removal used to be considered essential [125–127]. However, recent data show that patients with catheter-related, coagulase-negative staphylococcal bacteremia could be treated successfully without removing the catheter [8,15,16]. In a recent study done at M.D. Anderson we have shown that the acute morbidity and mortality is not influenced by catheter removal. However, if the CVC is not removed, there is a 20 percent chance that the bacteremia would recur compared with only 3 percent risk of recurrence if the CVC is removed ($p < 0.05$) [128]. Therefore, this low but significant risk of relapse should enter into the risk-benefit equation of whether the CVC should be removed. Although the immediate removal of a surgically implantable CVC that is associated with coagulase-negative bacteremia might not be possible in a cancer patient with thrombocytopenia, the CVC should not be left in place any longer than is necessary, particularly following such a bacteremia.

Staphylococcus aureus. Serious infectious complications have been reported in association with catheter-related *S. aureus* bacteremia. The frequency of such complications ranged from 19 percent to 31 percent in the general medical patient

population [129–135] and from 33 percent to 46 percent in cancer and other high-risk patients [136–140]. These infectious complications consisted of septic thrombosis, fatal sepsis, and deep-seated infections (e.g., endocarditis, osteomyelitis, septic emboli, and abscesses). It is crucial that the physician should differentiate between a complicated *S. aureus* bacteremia and an uncomplicated one. An uncomplicated bacteremia should be treated for at least 10 days with intravenous antistaphylococcal antibiotics (semisynthetic penicillins or vancomycin) [135]. However, the duration of therapy need not exceed 2 weeks. For a bacteremia complicated by deep-seated infections or septic thrombosis, optimal treatment should consist of at least 4 weeks of intravenous antibiotics [140]. Simple clinical parameters might help the clinician differentiate between complicated and uncomplicated course. In a study of 55 patients with catheter-related *S. aureus* bacteremias, we have shown that fever and/or bacteremia persisting for >3 days after catheter removal, while the patient is on active intravenous antibiotics, strongly suggests a complicated course [135]. Catheter removal is more favored in the case of *S. aureus* bacteremia than in the case of coagulase-negative staphylococci. Dugdale and Ramsey have shown that in patients with Hickman catheter-associated *S. aureus* bacteremia, retention of the catheter results in a high rate of relapse and sepsis-related death than when the Hickman catheter is removed [138].

Yeasts. Catheter-related candidemia could be treated with a short course of amphotericin B, consisting of 4.5–8.5 mg/kg. Fluconazole given at 400 mg per day for 10–14 days could be equally effective. Like *S. aureus*, the physician should limit the short-course therapy to uncomplicated cases. A thorough evaluation including fundoscopic examination is necessary to rule out retinitis. A high-grade candidemia after catheter removal (>2 days of candidemia on antifungal therapy) should necessitate an echocardiogram to rule out endocarditis and a venogram to rule out septic thrombosis of the central vein [124]. Whether catheter removal is necessary in uncomplicated cases remains a controversial issue. Eppes et al. reported retrospective data suggesting that failure to remove the catheter would result in increased morbidity and mortality, as well as prolonged duration of candidemia [141]. Quantitative blood and catheter cultures were not done in this study, and no evidence was included that would ascertain that the candidemia episodes reported were catheter related. There are no solid data at this point that would compel the clinician to immediately remove a surgically implantable CVC in the setting of a catheter-related candidemia. Pending further prospective data, the clinician should consider removing the CVC if the patient fails to respond to antifungal therapy within 96 hours or if the candidemia persists for longer than 48 hours while the patient is on appropriate intravenous antifungal therapy.

Gram-negative bacilli. Enteric gram-negative bacilli, such as *E. coli* and *Klebsiella pneumoniae*, rarely cause catheter-related sepsis. Other bacilli acquired from the hospital environment, such as non-aeruginosa *Pseudomonas* species, *Acinetobacter* spp., *Achromobacter* spp. and *X. maltophilia*, have been associated with catheter-related sepsis. Trimethoprim-sulfamethoxazole is the antibiotic of choice in the

treatment of *X. matophilia* bacteremia, whereas third-generation cephalosporins, carbapenems, monobactams, aminoglycosides, and quinolones could be useful in the treatment of the other gram-negative bacillemiias. The duration of parenteral therapy should not exceed 1 week. Benezra et al. [78] demonstrated that antibiotic therapy alone does not generally cure catheter-related infections caused by *Pseudomonas* species; for these infections, the CVC must also be removed. At the M.D. Anderson Cancer Center, Elting and Bodey [79] reported 149 episodes of septicemia caused by *Xanthomonas* and non-aeruginosa *Pseudomonas* species. The CVC was the most frequently implicated source of the septicemia. Failure to remove the CVC resulted in a significantly higher rate of treatment failure and recurrence. However, 100 percent of the patients whose CVCs were removed were cured of their infections, whereas only 53 percent of those whose CVCs remained in place were cured ($p = .00001$).

Gram-positive bacilli. *Corynebacterium jeikeium* and *Bacillus* species have also been associated with catheter-related bacteremia [142–149]. Vancomycin remains the antibiotic of choice in the treatment of such infections [143,147]. Infection with *Corynebacterium* group JK can result in serious complications, such as endocarditis [142]. Removal of the catheter has been recommended for the successful management of such infections [147,149]. However, more prospective data gathered using strict criteria to define catheter-related infections are required to determine the impact of catheter removal on the treatment of these infections.

Atypical mycobacteria. Rapidly growing mycobacteria, such as *Mycobacteria fortuitum* and *M. chelonae*, have been shown to cause catheter-related infections. We recently reported 15 cases and reviewed 14 additional cases from the literature [123]. Catheter removal was found to be crucial for the successful management of catheter-related bacteremias due to *M. fortuitum* and *M. chelonae*. Parenteral antibiotic therapy with a combination of cefoxitin and amikacin provided the best coverage.

Catheter type and underlying condition

Fungemia or staphylococcal bacteremia in patients with a surgically implantable CVC, such as the tunneled Hickman or implanted subcutaneous ports, is often a management challenge. The option of exchanging the CVC over a guidewire for diagnostic purposes (to obtain quantitative catheter culture) does not exist. Quantitative blood cultures might not be readily available. Hence, the diagnosis of CVC-related septicemia is often presumed and the CVC is often retained in the case of coagulase-negative staphylococci or is often removed in other situations. It is important to note that the source of gram-negative bacteremias and candidemias in neutropenic patients is the gastrointestinal tract and not the CVC. Simultaneous quantitative blood cultures through the CVC and peripheral vein are necessary to rule out a catheter infection in cancer patients with a surgically implantable venous access device [31–35].

Surgically implantable vascular devices have been considered as the only alternative that provides long-term venous access with a low rate of infectious complications [1–5]. A recent prospective study from M.D. Anderson has demonstrated that nontunneled silastic catheters could have low infection rates and long durability, which are comparable to the Hickman or Groshong catheters [28]. Historically, the change from nontunneled polyethylene catheters to tunneled silicone catheters containing a cuff was made without the intermediate steps of nontunneled noncuffed silicone catheters. The comparable durability and safety (i.e., low infection rate) of nontunneled and tunneled catheters in adults should be viewed in light of the great cost differences between the two types. At M.D. Anderson the cost of inserting a Hickman CVC is around \$3000, compared with \$582 for a nontunneled subclavian CVC [28]. The durability is around 100 days for the two types of catheters, and the infection rate is 1–3 per 1000 catheter days.

Several studies have compared the infection rates of silastic tunneled catheters and implanted subcutaneous ports [3–5]. The device-related infection rate was three- to fourfold lower for ports. This difference has been attributed to the migration of skin flora through the cutaneous insertion site of the external tunneled CVC [5].

In at least two studies, patients with hematologic malignancy (leukemia) were significantly more likely to develop CVC-related infection compared with solid tumor patients [5,28]. The reasons for the difference has been attributed to the frequency with which devices are accessed, the frequency of blood transfusions, and the duration of neutropenia [5].

Therefore, the decision to remove the CVC is not only determined by the type of organism causing the device-related septicemia. The reluctance to remove a surgically implantable venous access device or a CVC in a profoundly thrombocytopenic patient is well recognized. Under these circumstances, the ultimate decision should be based on the response of the infection to antimicrobial therapy before the CVC is removed.

Conclusions

Infection is one of the leading complications of indwelling vascular catheters. The diagnosis of catheter-related septicemia should be considered in the case of a staphylococcal or candidal septicemia with no other apparent source. Definitive diagnosis requires either quantitative catheter cultures or differential quantitative blood cultures. Coagulase-negative staphylococci, *S. aureus*, and *Candida* are the most common organisms reported to cause catheter-related infections. The skin and catheter hub are the two major sources for the introduction of the colonizing organisms. Risk factors predisposing to infections include prolonged catheterization, frequent manipulation of the catheter, improper aseptic insertion and maintenance techniques, poor placement of the catheter, the use of thrombogenic catheter material, occlusive transparent plastic dressings, and contaminated skin solutions.

Preventive measures against these infections include placement and maintenance by a skilled infusion therapy team, coating of catheters with antiseptic and antimicrobial agents, and the use of silver-impregnated cuffs (for short-term CVCs),

topical disinfectants such as chlorhexidine, and maximal barrier precautions. The exchange of CVCs over a guidewire might be useful diagnostically but has not been proven to be of any therapeutic or preventive value.

Management depends on several factors, particularly the extent of the infection and the causative organisms. Exit infections can be treated by local care and antibiotics without catheter removal. Tunnel infections are more serious and usually require catheter removal and antibiotic treatment. Coagulase-negative staphylococcal bacteremia can be treated without catheter removal, but there is a slight risk of relapse if the catheter is retained. Catheter-related *S. aureus* bacteremia is associated with a high rate of serious complications. Data suggest that the catheter should be removed and the patient treated for at least 10 days with appropriate intravenous antibiotics. Catheter-related candidemia can be treated with a short course (10–14 days) of antifungal therapy; however, the issue of catheter removal remains controversial.

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11 Indications for intensive care in the management of infections in cancer patients

Jean-Paul Sculier

Intensive care physicians manage cancer patients with infections principally under two different conditions. In the first, patients are admitted for severe infectious complications due to the neoplastic disease and/or its treatment. Management has to include specific treatment of the complication, as well as critical care to support associated organ failure(s). In the second, patients are admitted for reasons not related to infection, but the patient develops infectious complications during the intensive care unit (ICU) stay, eventually requiring critical care support. It is important to be aware that cancer patients can be admitted to the ICU for many reasons [1]: (1) postoperative recovery, with advantages that are the same as those for any high-risk postoperative patient; (2) critical complications of the underlying disease and its treatment; (3) administration or monitoring of intensive, new, or risky anticancer treatment; and (4) acute disease unrelated to the underlying disease and its treatment.

When caring for an infectious problem in a cancer patient, intense care physicians have to take into consideration [2] the host defense defects associated with the disease and its treatment: neutropenia, cellular (T-lymphocyte) and humoral (B-lymphocyte) immune deficiencies, visceral (mainly respiratory, gastrointestinal, and urinary) neoplastic obstruction, disruption of cutaneous and mucosal barriers, risks due to invasive procedures, and blood product transfusion. These defects may be associated with infections with pathogens (Table 1) that are not common in immunocompetent critical care patients, such as *Pneumocystis carinii* or cytomegalovirus.

Indications for intensive care in the management of infections [3] are multiple, including severe sepsis and septic shock, life-threatening respiratory infections, postoperative infectious complications such as mediastinitis or peritonitis, central nervous system infections, and endocarditis. Specific data about infections requiring intensive care in cancer patients are sparse, and most information is found in the hematological and oncological infections literature, where the distinction between patients treated in the ICU versus the standard care setting is very rarely made. However, infections that are frequent in cancer patients, are a major cause of death during the evolution of the neoplastic disease, as shown by an analysis of the type of lethal complications in an oncology unit among patients treated for febrile neutropenia in cooperative trials [4]. In this study, patients were randomized to

Table 1. Host defense defects and commonly associated pathogens in patients with cancer

Defect	Bacteria	Fungi	Viruses	Parasites
Neutropenia	Gram-negative bacilli <i>Ps. aeruginosa</i> <i>E. coli</i> <i>Klebsiella pneumoniae</i> <i>Enterobacter</i> spp. Gram-positive cocci <i>Staph. aureus</i> <i>Staph. epidermidis</i> <i>Streptococcus</i> spp. <i>Corynebacterium</i> spp.	<i>Candida</i> spp. <i>Torulopsis glabrata</i> <i>Aspergillus</i> spp. Mucoraceae		
Cellular (T-lymphocyte) immune deficiency	<i>Listeria monocytogenes</i> <i>Mycobacterium</i> spp. <i>Nocardia asteroides</i> <i>Legionella pneumophila</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> Staphylococci Streptococci Colonizing bacteria	<i>Candida</i> spp. <i>Cryptococcus neoformans</i>	Herpes simplex Varicella-zoster Cytomegalovirus Epstein-Barr virus	<i>Pneumocystis carinii</i> <i>Toxoplasma gondii</i> <i>Cryptosporidium</i> <i>Strongyloides stercoralis</i>
Humoral (B-lymphocyte) immune deficiency	Staphylococci Streptococci <i>Ps. aeruginosa</i> Gram-negative enteric bacilli Staphylococci <i>Corynebacterium</i> spp. Gram-negative bacilli	<i>Candida</i> spp. <i>Aspergillus</i> spp. <i>Candida</i> spp.	Herpes simplex	
Visceral neoplastic obstruction				
Disruption of cutaneous and mucosal barriers				
Invasive procedures (including catheters)		<i>Candida</i> spp.		
Blood product transfusion				Hepatitis B Hepatitis C Cytomegalovirus AIDS

receive a combination of amikacin and carbenicillin with or without cefazolin. Of the 230 granulocytopenic patients treated, 55 died during their hospitalization and an autopsy was conducted in 30 cases. Infection was microbiologically documented in 60 percent and clinically documented in only 2 percent. The direct cause of death was infection in 19 patients, hemorrhage in 15, neoplastic disease in 10, and other causes in 11. Sixteen patients died from bacterial infection: 12 with septic shock (including 10 microbiologically documented: 3 *Escherichia coli*, 2 *Klebsiella* spp., 5 *Pseudomonas aeruginosa*, 2 group D *Streptococcus* spp., and 2 patients with mixed infections), 3 from pneumonia, and 1 as a consequence of *Pseudomonas aeruginosa* meningitis. Three died from disseminated fungal disease. Overall mortality directly related to infection in this series was thus 8 percent (19 of 230).

In another study [5], we analyzed the causes of death in the ICU of an oncological hospital. Among 330 admissions, 55 percent were for a medical complication and 47 patients (28 percent) died in the ICU. Only one death was reported among the 150 patients admitted for monitoring during administration of an intensive or potentially toxic treatment. Autopsy was performed in 34 cases. In eight (23.5 percent) cases, the direct cause of death was a major infection (four aspergillosis, two candidemia, one CMV pneumonia, and one acute cholecystitis). It was neoplasia in only four patients. Other causes were noncardiac pulmonary edema in seven, acute bleeding in three, pulmonary embolism in two, cerebral stroke in one, cardiac tamponade in one, myocardial infarction in one, and multifactorial respiratory failure in one. Six deaths remained unexplained after postmortem examination.

These two reported studies emphasize the importance of infections as life-threatening complications of cancer and also show that the profiles of patients with infection are different in the ICU and in the general ward, even in the same cancer hospital. In fact, most of the patients who died with infection (14 of 19) in the first reported series [4] had very advanced neoplastic disease, having received all known effective anticancer treatments before their most recent admission. They would thus probably have not been admitted to the ICU. In the second series [5], nine patients were admitted for sepsis or septic shock, and three died, from complications other than the initial infection.

Specific considerations

Sepsis, septic shock, and multiple organ dysfunction syndrome

Bacteremia in critically ill patients is associated with a poorer prognosis, when occurring in patients with comorbidities such as active malignancy [6]. In a multivariate analysis performed in 176 surgical patients with bacteremia, Apache II and comorbidities were identified as the two independent predictors of mortality. Sepsis has also been shown to be a poor prognostic factor in the largest series of adults patients with hematological malignancies [7,8], with acute complications of bone marrow transplantation [9], or of children with hematological malignancy [10] admitted for intensive therapy. This type of data is not available for patients with solid tumors.

Despite the fact that polymorphonuclear cells can play a key role in the development of adult respiratory distress syndrome (ARDS) in some conditions [11], such as post-traumatic multiple organ dysfunction syndrome (MODS), many clinical observations [12–16] have shown that the bacteriemic neutropenic patient is not protected against ARDS. In these series, patients fulfilled the clinical criteria for the diagnosis of ARDS: the occurrence of a precipitating event (sepsis), diffuse bilateral pulmonary infiltrates on a chest radiograph, normal intravascular volume (as reflected by wedge pressure), and arterial hypoxemia. In a retrospective comparison of bacteremia patients [14], ARDS was not significantly less frequent in neutropenic than in non-neutropenic patients. Postmortem histopathology [12,14,16] showed an absence of neutrophilic infiltration of the lungs but diffuse alveolar damage consistent with ARDS. Thus for neutropenic patients, mechanisms other than neutrophils have to be operative, such as macrophages, platelets, clotting factors, kinins, cytokines such as interleukin 1 or tumor necrosis factor α , and other inflammatory mediators [17].

A postsepsis bradycardia syndrome has been described [18] in a small number of children with hematologic malignancies who were recovering from sepsis. These patients developed sinus bradycardia for 24–72 hours with heart rates <5 percent of normal heart rates for their age. Neither hypotension nor other symptoms were associated with the bradycardia. No therapy was necessary. It has been speculated that this syndrome may result from alterations in beta-adrenergic receptor function, an unidentified humoral factor produced by the invading organism, or as part of the host's response to sepsis.

The occurrence of cardiopulmonary arrest in the context of sepsis in cancer patients indicates a very poor prognosis. In a retrospective study [19] of 49 cancer patients presenting with cardiac arrest, cardiopulmonary resuscitation, even if immediately effective in 25 percent of cases, was associated with 100 percent fatality in the ICU when it was the ultimate complication of various problems such as septic shock.

A 'sepsis syndrome' is not uniformly caused by an infection in cancer patients. Table 2 shows the new definitions of sepsis established by the American College of Chest Physicians and the Society for Critical Care Medicine [20]. Cancer by itself can induce a systemic inflammatory response syndrome (SIRS). In fact, cancer induces during its development a chronic MODS due to activation of the cascade of immune cells and cytokines, as suggested, for example, by the presence of chronic disseminated intravascular coagulation or by the high rate of lesions of pulmonary edema found at autopsy [5]. In some cases, the clinical picture can become acute, such as in tumor lysis pneumopathy that causes ARDS [21] or in the capillary leak syndrome induced by treatment with granulocyte-macrophage-colony-stimulating factor (GM-CSF) [22,23].

Streptococcal bacteremias and ARDS

There is an increased frequency of bacteremia due to streptococci, particularly of the viridans group, in neutropenic patients [23,24]. Between 1986 and 1988, the

Table 2. New definitions of sepsis

<i>Infection</i>	Microbial phenomena characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
<i>Bacteremia</i>	Presence of viable bacteria in blood.
<i>Systemic inflammatory response syndrome</i>	Systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: Temperature >38°C or <36°C Heart rate >90 beats/min Respiratory rate >20 breaths/min or PaCO ₂ <32 torr (<4.3 kPa) WBC >12,000 cells/mm ³ , <4000 cells/mm ³ , or >10 percent immature (band) forms.
<i>Sepsis</i>	Systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection: Temperature >38°C or <36°C Heart rate >90 beats/min Respiratory rate >20 breaths/min or PaCO ₂ <32 torr (<4.3 kPa) WBC >12,000 cells/m ³ , <4000 cells/mm ³ , or >10 percent immature (band) forms.
<i>Severe sepsis</i>	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.
<i>Septic shock</i>	Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, and an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
<i>Hypotension</i>	Systolic BP of <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes for hypotension.
<i>Multiple organ dysfunction syndrome</i>	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

From Members of the American College of Chest Physicians . . . [20], with permission.

incidence in a cancer hospital [25] ranged from 5.5 to 7.6 per 1,000 admissions and represented 16 percent of all bacteremias. In another cancer hospital [26], the incidence between 1972 and 1989 increased from one case per 10,000 admissions to 47 cases per 10,000 admissions.

Some reports [26–28] suggest that *Streptococcus viridans* bacteremia responds poorly to standard empirical antibiotics, with a mortality of around 12 percent in both children and adults. Despite supplementation with adequate antibiotics, many patients will develop fatal ARDS [29], making *Streptococcus* spp. the main cause of ARDS and MODS in neutropenic patients. The rise in the frequency of streptococcal infections coincides with the increased use of quinolones—to which most streptococci are resistant—for prophylactic purposes. However, this *Streptococcus* emergency has also been reported in institutions not using quinolones, and thus the avoidance of quinolones will probably not resolve the problem. The main source of streptococci is the mucosa of the oropharynx (*Streptococcus mitis*, *S. sanguis*, *S. salivarius*, *S. anginosus*), gastrointestinal tract (*S. enterococci*), and

Table 3. Pathogens causing respiratory infections and failure in cancer patients

Bacteria	Fungi
Gram-negative bacilli	<i>Candida</i> spp.
Gram-positive cocci	<i>Torulopsis glabrata</i>
Mycobacteria	<i>Aspergillus</i> spp.
<i>Legionella pneumophila</i>	<i>Mucormycosis</i>
<i>Nocardia asteroides</i>	<i>Cryptococcus</i>
<i>Mycoplasma</i> spp.	
Viruses	Parasites
Cytomegalovirus	<i>Pneumocystis carinii</i>
Herpes zoster	<i>Strongyloides</i>
Herpes simplex	
Adenovirus	
Herpesvirus 6	

vagina (*S. anginosus*). Bacteremias from those sites are facilitated by mucosal damage due to cancer therapy or herpes simplex. Prevention of these lesions could reduce the risk for streptococcal infection. An alternative method would be to cover those pathogens in initial empiric therapy by adequate antibiotics.

Respiratory failure and infections

In neutropenic patients, the occurrence of diffuse bilateral pneumopathies that can rapidly result in respiratory failure is a difficult diagnostic and therapeutic problem [30]. Causes may be infectious or noninfectious (Table 3). The most frequent pathogens are *Pneumocystis carinii*, cytomegalovirus, fungi (*Aspergillus* and *Candida* spp.), and bacteria such as *Mycoplasma* or *Legionella* spp. Noninfectious causes are mainly diffuse neoplastic infiltration, cytostatic drug or irradiation lung toxicity, and leukoagglutinin transfusion reactions. Several factors may help in the diagnosis: patient history and context (cytotoxic drug therapy, corticotherapy, radiotherapy, immune status, previous antibiotic therapy, primary tuberculous infection, duration of neutropenia, bone marrow transplantation, previous transfusions and transfusion reactions), hospital-related epidemiology (nosocomial bacteria, *Legionella* spp., *Aspergillus* spp.), and geographic epidemiologic prevalence (tuberculosis, several fungi, *Pneumocystis carinii*). Clinical presentation frequently lacks specificity, but several aspects may be helpful: subacute and chronic course (frequent in drug-related toxicity; radiation toxicity; *Pneumocystis carinii*, *Nocardia* spp., and sometimes tuberculosis pneumonia); acute presentation (pulmonary edema associated with therapy, Ara-C, leukoagglutinin transfusion reactions, hemorrhage, leukostasis, sepsis-related ARDS), and the presence of systemic signs and symptoms (*Legionella* spp., miliary tuberculosis, gram-positive and-negative bacteria sepsis, mycotic emboli, graft-versus-host disease). Chest radiographs [31] and computed tomography scan [32], sputum analysis, serologic tests, and screening for extrapulmonary microbial colonization may be helpful but must be interpreted very carefully.

If the clinical diagnosis seems sufficiently accurate or if the patient's condition is rapidly deteriorating, empiric broad-spectrum therapy with high-dose trimethoprim-

sulfamethoxazole and erythromycin (and, if not already prescribed in the case of neutropenia, broad-spectrum antibiotics) should be given without delay, as supported by a recently published controlled trial [33]. If the patient's condition permits further diagnostic workup, a fiberoptic bronchoscopy should be performed to provide sputum aspiration, bronchoalveolar lavage, and bronchial brushings [34], and if indicated, transbronchial biopsies. Only in cases in which the diagnosis is unclear despite empiric therapy and the patient's condition is deteriorating should open lung biopsy be performed; it provides excellent diagnostic accuracy, but its true impact on patient survival is doubtful. Most authors therefore recommend a diagnostic workup with a good efficiency/morbidity ratio (for example, bronchoscopy with bronchoalveolar washing) followed by prompt broad-spectrum therapy of most suspected and readily treatable problems. Treatment may be further adapted according to the results of the analysis. The contribution of multiple causes to the underlying pulmonary process should never be overlooked, and easily manageable problems should clearly be excluded if left untreated.

The two most common pathogens involved in diffuse interstitial pneumonitis are *Pneumocystis carinii* and cytomegalovirus (CMV). For the first, co-trimoxazole (trimethoprim-sulfamethoxazole) administered at a high dosage is the treatment of choice [35,36]. Pentamidine should be reserved in case of failure. In the case of severe respiratory insufficiency, by analogy with AIDS data, corticoids should be associated with antimicrobial therapy [37]. Severe *Pneumocystis carinii* pneumonia can produce a hyperdynamic profile similar to bacterial pneumonia with sepsis [38]. In patients requiring respiratory assistance, continuous positive airway pressure (CPAP) using a face mask can provide a good means, in sufficiently compliant patients, to avoid endotracheal intubation [39,40]. Chemoprophylaxis with co-trimoxazole [41] or, in the case of allergy, with pentamidine [42], may be valuable in high-risk patients. For CMV, therapy has been recently improved, and some success, even in advanced cases supported by artificial ventilation, can be obtained [43]. Early treatment with ganciclovir in patients with positive surveillance cultures reduces the incidence of CMV disease and improves survival after allogeneic bone marrow transplantation (BMT) [44,45]. The combination of ganciclovir with immune globulin produces 35–50 percent response rates in the treatment of CMV pneumonia in BMT recipients [46,47].

Severe fungal infections

Patients, especially those with prolonged and severe neutropenia, are particularly susceptible to fungal pathogens such as *Candida* spp. and *Aspergillus* spp. Intensive care physicians are usually faced with two circumstances involving mycotic complications: life-threatening disorders directly caused by the fungi (i.e., septic shock due to candidemia, cerebral aspergillosis, and massive hemoptysis caused by lung aspergillosis) or secondary infection of patients undergoing critical care procedures (i.e., central venous catheter infection by *Candida* spp., lung aspergillosis during mechanical ventilation). Diagnosis is often difficult and late [48,49], which is why amphotericin B is now often started empirically when fever does not respond

to empiric antibacterial antibiotics. In an established infection, amphotericin B—the basic antifungal drug—produces variable results, particularly when neutrophil count recovery does not occur. It is a poorly water-soluble drug supplied for intravenous administration as a colloidal suspension with sodium deoxycholate as a dispersing agent, amphotericin B (Fungizone^R). This preparation induces many serious side effects, such as high fever, chills, bronchospastic attacks, and nephrotoxicity. A way to improve the therapeutic index of amphotericin B is to incorporate it into a liposomal preparation (ampholiposome). Ampholiposomes of small size made of egg phosphatidylcholine, cholesterol, and stearylamine (not commercially available) were much better tolerated than Fungizone, allowing intravenous administration of much higher doses [50]. Moreover, much higher serum amphotericin B levels were obtained, as well as increased antifungal activity, as suggested by cure of neutropenic and leukemic patients with fungal infection resistant to Fungizone [51–53]. New antifungal drugs, such as the triazole derivatives itraconazole and fluconazole, appear to have promising activities, but we have to obtain more data to define their exact place in the treatment of severe fungal diseases.

Neutropenic enterocolitis

Abdominal pain in neutropenic cancer patients is a common and serious problem [54,55]. The overall 30 day mortality rate ranges from 34 percent to 60 percent. Various abdominal complications can be observed, such as pancreatitis, hepatic candidiasis, diverticulitis, perforated bowel, large bowel obstruction, splenic infarction, cholecystitis with cholelithiasis, appendicitis, and gastritis. The most frequent cause, which is often a diagnosis of exclusion, is neutropenic enterocolitis. This condition includes a spectrum of involvement of the gastrointestinal tract, from transient small bowel edema to frank infarction of tissue. The most severe forms of the syndrome are also called *necrotizing enterocolitis*, *agranulocytic colitis*, and *typhlitis* (when it is limited to the cecum).

Although most cases are associated with chemotherapy, neutropenic enterocolitis has also been described with immunosuppressive therapy in transplant recipients and in aplastic anemia. The syndrome variously consists of fever, watery diarrhea, and diffuse or localized abdominal pain in the setting of neutropenia. These symptoms are nonspecific and neither plain radiologic studies nor laboratory tests are very useful in establishing the diagnosis. Computed tomography and/or ultrasonography are more sensitive.

The pathogenesis of neutropenic enterocolitis remains obscure. It might include leukemic infiltration of the bowel wall, direct toxic effects of chemotherapy, bacterial invasion of the bowel wall secondary to neutropenia, and alteration of the bowel flora by broad-spectrum antibiotics. The reason this complication often affects the ileocecal area is unknown, but any portion of the bowel may be involved with a thickened wall, transmural inflammation with infiltration and infection, and mucosal ulcerations, which may coalesce. The disease may range from mild, self-limited cecal inflammation to fulminating necrosis and perforation.

Prompt recognition of the syndrome is very important, and each case should be treated individually according to the severity and the presence of complications of the disease. In most cases, medical treatment will be initiated with bowel rest, gastrointestinal tract decompression, broad-spectrum antibiotics, and nutritional support. Close observation with serial examinations is mandatory. Surgery will be indicated in the case of bowel perforation, abscess, pneumatosis intestinalis, massive gastrointestinal bleeding, obstruction, and severe localized symptoms with systemic sepsis persisting more than 24 hours [56–60]. Overall mortality may be high, ranging from 8 percent to more than 60 percent according to one series [55]. Prognosis will mainly be influenced by the duration of neutropenia. Other poor prognostic factors might be abdominal distention, older age, occurrence of MODS, hypotension at presentation, bacteremia, and fungemia.

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12 Colony-stimulating factors: *Current applications and perspectives*

Dominique Bron and Frank Jacob

Neutropenia, and particularly prolonged neutropenia, increases the risk of infection [1]. In cancer patients, neutropenia often leads to chemotherapy dose reduction and/or delay, which may be responsible for a lowered response rate and possibly shorter survival. It has been known for at least 25 years that hematopoiesis is under the control of specific factors that act on early cells in the hemopoietic system to produce mature cells. Following the cloning of the genes for human colony-stimulating factor (CSF), the clinical development of recombinant CSF proceeded rapidly. Extensive knowledge of the biological properties of CSF allowed further investigation in hematology, immunology, and medical oncology. Five CSFs are now available for clinical use: erythropoietin (EPO), granulocyte-CSF (G-CSF), granulocyte-macrophage-CSF (GM-CSF), interleukin-3 (IL-3), and macrophage-CSF (M-CSF).

Although erythrocyte support is easily obtained through transfusion of red blood cells, the risk of transfusion-related problems and the quality of life of patients receiving monthly transfusions remain a matter of concern in cancer patients with anemia. Subcutaneous administration of EPO has been successfully used in various clinical situations, such as myelodysplastic syndromes [2], multiple myeloma [3], cisplatin-induced anemia [4], and after allogeneic bone marrow transplantation in which EPO production has been shown to be decreased [5]. In this review, we will focus only on myeloid CSF. These myeloid CSFs can be used in several ways, including prevention of infection, acceleration of neutrophil recovery, correction or improvement of granulocyte and monocyte functions, and recruitment of peripheral hematopoietic progenitor cells. All of these potential clinical applications will be discussed.

CSF and drug-induced neutropenia

Patients receiving chemotherapy for cancer are at risk of severe neutropenia, which is the major factor contributing to fever, infection, morbidity, and mortality. Up to now, six published randomized trials have addressed the question of the role of rHu G-CSF in the prevention of chemotherapy-induced neutropenia and febrile neutropenia [6–11]. In these studies, rHu G-CSF was generally administered at a

Table 1. Clinical applications of colony-stimulating factors in oncology

Acceleration of hematological recovery
Recruitment of peripheral blood progenitor cells
Use in chronic neutropenia
Collection of autologous blood (erythropoietin)
Correction of anemia (erythropoietin)

dose of 5 $\mu\text{g}/\text{kg}$ starting the day after chemotherapy for 10–14 days. These trials showed that rHu G-CSF administered as an adjuvant to chemotherapy had minimal side effects and resulted in a significant reduction in the incidence of febrile neutropenia as well as the incidence, duration, and severity of grade IV neutropenia. There were no differences in response rates and survival between the groups receiving rHu G-CSF or placebo. Indeed, these trials were designed to examine the impact of G-CSF on supportive care and not on response rate. In addition, the actual mortality of infectious complications was quite low due to the policy of early hospitalization and early antibiotic administration. Finally, with the types of tumors targeted in those series (lung cancer or advanced leukemia), it was unlikely to have any impact on survival due to the high risk of drug-resistant relapse.

A recent trial conducted in small cell lung cancer patients showed a decrease in dose reductions or treatment delay in patients treated with G-CSF but failed to demonstrate a really significant increase in the intensity of the dose [12]. Some uncontrolled studies have suggested a beneficial effect of G-CSF on neutropenia caused by combined radiotherapy and chemotherapy or fractionated radiotherapy [13].

GM-CSF has also been tested in randomized studies. A recent trial in non-Hodgkin's lymphoma patients receiving first-line chemotherapy showed that GM-CSF-treated patients experienced fewer days of neutropenia, fever, and hospitalization. The complete response rate was the same in the GM-CSF group as compared with the placebo group but was higher in the 'high-risk' lymphoma patients [14]. However, the analysis was potentially biased by the fact that 80 percent of the patients who dropped out early were in the GM-CSF-treated group. Current trials, well designed to study the adherence to treatment schemes in curable malignancies, will be more likely to show a benefit in terms of complete remission and overall survival rates.

An original comparative study compared GM-CSF and prophylactic antibiotics in patients receiving intensified combination chemotherapy. Even though neutrophil recovery was faster in the GM-CSF-treated group, patients receiving antibiotics had substantially fewer infections and required fewer transfusions. Significantly reduced neutropenia has also been documented in solid tumors such as sarcoma [15], breast cancer treated with adjuvant chemotherapy [16], and glioma [17], where a possible beneficial effect of GM-CSF on the thrombocyte count was occasionally observed.

Interleukin-3 (IL-3), also known as multi-CSF, acts on earlier hematopoietic progenitors, and preclinical studies suggested an effect on granulocytes and platelets [18]. In a placebo-controlled randomized study, d'Hondt and colleagues have shown that IL-3 stimulates both thrombopoiesis and neutropoiesis in small cell lung cancer

patients but does not improve the tumor response or the overall survival rate [19]. The most frequent side effects of IL-3 are fever (90 percent), headaches (60 percent), and myalgias (60 percent). Phase II doses of 300 $\mu\text{g}/\text{m}^2/\text{day}$ or less were recommended [20].

During the last 2 years several interesting studies have tried to enhance CSF activity by combining different CSFs. Unfortunately the appropriate modalities of administration, that is, the dosage and timing of these CSFs, have yet to be defined, and at present there is no evidence of real benefits of such combinations; the toxicity might be even higher than that encountered with immunotherapeutic approaches. However, a few uncontrolled papers reported on the better efficacy of combining IL-3 with other CSF [21,22].

In the setting of neutropenia or agranulocytosis induced by other medical drugs, it is clear that morbidity and mortality are directly related to the rapidity of neutrophil recovery. Accelerated recovery after rescue with CSF has been demonstrated in a large number of case reports after a median of 4 (1–15) days of CSF administration.

CSF in aplastic anemia and myelodysplastic syndromes

Aplastic anemia is an obvious indication for CSF intervention. More or less half of these patients will not respond to immunosuppressive approaches or will not find an allogeneic marrow donor for transplantation.

Both G-CSF and GM-CSF have been used with success in aplastic anemia, resulting in fewer infectious complications [23]. However, in severe aplastic anemia in which few precursors are present, responses are often disappointing, and when CSFs are discontinued, blood cell counts rapidly drop to baseline. The impact on the platelet count or transfusion requirement is even more infrequent. A promising approach may emerge from the combination of CSF with an immunomodulator such as antithymocyte globulins [24], but a clear impact on survival remains to be demonstrated.

In the setting of myelodysplasia (MDS), CSFs may have different applications. First, they can be used to increase the number of neutrophils with a direct impact on infectious episodes and related mortality. Second, CSFs can induce differentiation of leukemic blasts into functional mature blood cells. Third, CSFs can induce the entry of leukemic cells into the S phase, rendering the blast more sensitive to S-phase-specific cytotoxic drugs.

Increases in the granulocyte count and granulocyte function have been observed in the large majority of MDS patients treated with G or GM-CSF [25,26]. However, this rise is often restricted to the granulocytes with poor impact on the platelets or the red cells, and is rapidly reversible after withdrawal of the CSF. Major concern has been raised by the observation of a concomitant rise in the percentage of blasts, mostly in patients with an initial marrow blast count higher than 15 percent. However, it is difficult to prove that CSFs really change the natural course of the disease.

In a randomized comparison of 1.25 and 6.25 $\mu\text{g}/\text{kg}$ IL-3, neutrophils increased in 5 of 14 and 9 of 11 patients, respectively. Platelets increased in one and two

patients in the low- and high-dose arms. Conversion to acute myeloid leukemia occurred only in patients with refractory anemia with excess blasts (RAEB) and at a rate expected for untreated patients [27].

The role of CSFs in stimulating entry of blast cells into the cell cycle to increase the antileukemic effect of antitumoral agents such as cytosine arabinoside has been prospectively studied in 'high-risk' MDS (RAEB, RAEB-T), with promising results in terms of complete response; whether this observation will translate into a better clinical outcome remains to be seen [28].

CSF in bone marrow transplantation

Escalating doses of chemotherapy with autologous or allogeneic bone marrow transplant (BMT) support has been reported to improve significantly the response rates and cures in various tumors. These benefits are obtained at the price of a significant myelotoxicity, and CSFs appear to be unexpected drugs that reduce this hematological toxicity.

Prophylactic myeloid growth factors have been extensively used following both autologous and allogeneic BMT [29–37]. All of these studies report an acceleration in neutrophil recovery, even when G-CSF is started on day 8 [38], while some studies also demonstrate less severe mucositis, reduced hospitalization time, fewer documented infections, fewer days on parenteral nutrition, and reduced antibiotic usage. Very few randomized trials have been published, but in the controlled studies using CSF or placebo after allogeneic BMT, neither G- or GM-CSF have shown an exacerbation of the graft-versus-host disease. In addition, even in allo-BMT for acute myeloblastic leukemia, no increase in relapse rates was observed [39]. Unfortunately, a survival benefit has not been shown after auto- or allo-BMT, and the rationale for using CSF in the setting of BMT requires further cost-benefit analysis [40].

Besides the potential use in the reduction of neutropenia and infections, CSF can also be used in graft failure after BMT. Myeloid growth factors have been accepted as first-line treatment for poor engraftment and/or graft failure post auto- or allo-BMT. G-CSF and GM-CSF may rapidly increase the neutrophil count and therefore reduce the risk of infections, but combination of CSFs with a broader spectrum are required to restore total marrow function [41,42].

More recently, peripheral blood progenitor cells (PBPCs) have increasingly been used for autografting following high-dose chemotherapy with the universally reported benefit of more rapid engraftment for granulocytes as well as platelets, compared with bone marrow transplantation [43–45]. PBPCs can be detected after chemotherapy during the hematological recovery phase [46], but administration of CSF after chemotherapy for at least 5 days results in a dramatic improvement in the PBPC mobilization [47]. Three to five leukaphereses are required to collect enough PBPCs ($\geq 5 \times 10^6$ CD34⁺/kg) to restore normal hematological and immunological functions after intensive chemotherapy and/or total body irradiation. In the setting of allogeneic BMT, related or unrelated HLA-compatible donors will soon be able to undergo leukapheresis after 4–5 days of rHu G-CSF instead of bone marrow harvesting under general anesthesia [48].

CSF in severe chronic neutropenia

An increased risk of infection is significantly correlated with severe neutropenia (ANC $<1.0 \times 10^9/l$) and is becoming increasingly frequent with prolonged neutropenia, with neutrophils also being important to preserve the integrity of the mucosal surfaces.

Severe chronic neutropenia is a heterogeneous group of disorders with different causes (viral infection, autoimmune diseases, cirrhosis, sarcoidosis, chronic parasitic infections, neoplastic bone involvement, hematologic malignancies, etc.) or selective hematologic abnormality of unknown origin (congenital neutropenia, cyclic neutropenia, and idiopathic neutropenia).

Spectacular results have been observed in chronic congenital neutropenia (Kostman syndrome, cyclic neutropenia) [49]. Even low doses of rHu G-CSF (1–2 $\mu\text{g/kg}$) are capable of increasing neutrophil counts above infection levels, resulting in an improved quality of life for these patients. Long-term administration of G-CSF has been maintained for up to 5 years and could be the cause, in some patients (mostly Kostman syndrome), of osteopenia and splenomegaly. No patients have made a detectable antibody response. Long-term administration of myeloid growth factors should be limited to severe chronic neutropenia with at least three ANC $<0.5 \times 10^9/l$ within 6 months or 5 consecutive days of neutrophils $<0.5 \times 10^9/l$.

CSF in acute myeloid leukemia

Because of the intensive myeloablative chemotherapy required for the treatment of acute leukemia, a high degree of myelosuppression and the resultant infectious complications are the major obstacles. The clinical application of CSF in myeloid leukemia has been controversial because they stimulate leukemic cells as well as normal granulocyte progenitors *in vitro* [50–54].

One randomized study evaluating G-CSF after induction chemotherapy in patients with various relapsed or refractory leukemias has been reported [6]. In this series, neutrophil recovery was accelerated with fewer days of fever and fewer documented infections. However, the complete response rate and relapse rate in patients receiving the cytokine were not different from those observed in the control group. Other studies have reported a detrimental effect of CSF, and the use of CSF cannot be advocated, except in well-designed randomized trials. Strategies aimed at increase the toxicity of cell-cycle-specific drugs such as ara-C by inducing CSF-mediated blast differentiation are still under investigation.

CSF and febrile neutropenia

Recent observations of elevated endogenous levels of G-CSF in a variety of infections [55], added to the information that G-CSF enhance neutrophil functions against microorganisms [56], suggest that G-CSF may play a role in the host defense response to infections [57]. Although the efficacy of G-CSF has been proven in

animal models of prophylaxis and the treatment of serious infectious diseases, clinical data in life-threatening infections remain anecdotal. Mayordomo et al. [58], in a randomized trial comparing the addition of G-CSF (5 µg/kg), GM-CSF (5 µg/kg), or placebo to standard antibiotics in neutropenic patients (ANC <500/mm³) with fever (>38°C), reported a significant reduction in the duration of severe neutropenia and hospitalization. In another large series of neutropenic cancer patients (ANC <1,000/mm³) reported by an Australian group, the duration of neutropenia, fever, and days on treatment was reduced by G-CSF (12 µg/kg/day). The benefit was even greater in documented versus doubtful infections [59]. At present there are some encouraging results using GM-CSF or M-CSF in the treatment of fungal infections, but only in uncontrolled studies [60].

CSF and dose intensification

The importance of dose intensity has been investigated in animal models. However, as the biology of human tumors appears to be more complicated than experimental transplantable tumors in animals, many questions remain unanswered. A few reports of higher response rates with higher doses of alkylating agents have been reported in lymphoma. Similar conclusions have been drawn after retrospective analyses in breast and ovarian cancer, but these results have not been confirmed by others.

Today, dose-intensive programs have been accepted as the standard therapy in diseases such as acute leukemias or chemosensitive lymphomas. However, in all tumors the use of intensive chemotherapy with bone marrow or PBPC support remains under investigation.

Intensification of chemotherapy may vary with intensification of the dose, intensification of the frequency, or both. All these approaches are limited by serious neutropenia, and CSFs offer the possibility of reducing the complications of neutropenic infections [61]. As reported earlier in this chapter, after conventional chemotherapy CSFs allow better tolerance and better adherence to the treatment schedule.

In another series of lymphoma patients, the concept of intensification of chemotherapy was tested in combination with G-CSF. Overall survival was improved after the high-dose regimen, but because of the low number of patients involved these results need further confirmation [62,63].

The real role of CSF in dose intensification still needs to be defined, particularly administration modalities such as the dose and timing of CSF administration. Extramedullary toxicity and thrombopenia remain dose-limiting factors in most of the series. Prospective randomized trials using growth factor–mobilized PBPCs to reduce the duration of neutropenia and thrombocytopenia after intensive chemotherapy may well finally result in better survival and an improved cost-benefit ratio.

Conclusions and perspectives

In clinical practice, it is now evident that CSFs are able to reduce the duration of neutropenia, but after intensive chemotherapy neutropenic toxicity still remains inevitable. When myelosuppressive chemotherapy is administered with curative

Table 2. Potential clinical application of colony-stimulating factors

Use in acute nonlymphoblastic leukemia
Use in febrile neutropenia
Use in non-neutropenic infections
Antitumoral effect
Enhancement of gene transfer into hematopoietic stem cells

intent, CSFs are obviously warranted. However, when a moderate or minimal incidence of febrile neutropenia is expected, CSF prophylaxis is much more difficult to recommend. Our current approach is to use CSFs in case of febrile neutropenia or when there has been prolonged neutropenia during a previous cycle of chemotherapy. After myeloablative chemotherapy requiring BMT, when PBPCs can be reinfused, CSFs have little or no effect, taking into account the more rapid hematopoietic reconstitution.

We have learned a lot about the prevention of chemotherapy-induced neutropenia and recruitment of PBPCs with CSFs, but many questions remain to be investigated (Table 2).

- When should we start using CSFs after chemotherapy or BMT?
- How can we optimize CSF-mobilized PBPCs?
- What role do CSFs have in the treatment of acute leukemia?
- Do CSFs improve survival in febrile neutropenia?
- Which are the best combinations of CSFs to achieve complete marrow recovery and a better survival?
- Will new cytokines (such as IL-4, IL-6, IL-11, IL-12, SCF, or hybrid molecules) be of real usefulness in clinical oncology?
- What is the adjuvant antitumoral role of CSFs?
- Can we use these CSFs to expand the true hematopoietic cell without losing the 'stemness' of the cell?
- Will CSFs enhance gene transfer into hematopoietic stem cells?

With CSFs we have now entered a new era of more complex therapies combining chemotherapy, radiotherapy, bone marrow or PBPC transplantation, biological response modifiers, and hematopoietic growth factors in a constant effort to further improve the cure rate and quality of life of cancer patients.

Note

Due to the rapid development of this field and time needed for publication, this overview is not properly updated.

For current recommendations, see:

American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. 1994. *J. Clin. Oncol* 12:11:2471–2508.

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13 Drug interaction and pharmacological considerations during anti-infective therapy in cancer patients

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The purpose of this review is to indicate the drug–drug interactions that have true clinical relevance. Those interactions can be either the kinetic changes affecting the drug(s) combined with the antibiotic or, conversely, the antibiotic itself. Such interactions may be found throughout the entire pharmacokinetic process (oral absorption, tissue distribution, excretion). Some extended reviews have been published on this topic in the past 2 or 3 years, as well as a general review [1] and specific reviews of rifampin [2,3], macrolide antibiotics [4–7], and quinolone antibacterials [8–11].

Interactions at the site of entry, before or during absorption

We shall distinguish between two types of interaction: interactions between antacids and oral antibiotics, and interactions involving active oral transport.

Antacids and oral antibiotic drugs

Formation of antibiotic-cation chelates

Tetracyclines. The formation of nonabsorbable chelates between tetracycline and metal ions, such as Fe^{2+} , Zn^{2+} , Al^{3+} , Mg^{2+} , or Ca^{2+} , has been known since the famous publications of Albert in *Nature* in 1953 and 1956 [12,13]. The strength of this interaction is a function of the tetracycline under consideration and of the salt used to salt the cations [14]. Coadministration of magnesium or aluminum-containing antacids, or calcium carbonate or even dairy products, with tetracyclines reduces the bioavailability of these antibiotics by more than 80 percent, and, moreover, inhibits enterohepatic and enteroenteric recycling of the cyclines, with a 30 percent decrease in their elimination half-life in the case of doxycycline [15]. The same is observed with fluoroquinolones.

Rifampin. As with tetracycline, Mg^{2+} and Al^{3+} cations form a nonabsorbable chelate with rifampin. For example, its bioavailability undergoes a 30–35 percent decrease with Maalox [16].

Fluoroquinolones. The formation of nonabsorbable metallic chelates with fluoroquinolones was first described by Timmons and Sternglanz [17] for nalidixic acid. Since that time, much published data (Table 1) have widely confirmed the clinical relevance of this drug–drug interaction, including interaction with Ca^{2+} from dairy products. A 40–90 percent decrease in quinolone C_{max} and area under the curve (AUC) has been seen in the case of concomitant administration. When metallic antacids are given 2 hours before the antibiotic, the interaction remains significant [18–22]. To be negligible, the antacid must be administered either 2 hours after the fluoroquinolone [22,23] or 6–8 hours before the antibiotic [18,23]. However, this constraint seems rather incompatible with good drug compliance. Thus, coadministration of quinolone and a cation-containing drug should be avoided, including formulations with metallic salts in the excipient, as is the case with chewable tablet formulations of didanoside, which is marketed in North America [24]. Similarly, administration of a multivitamin tablet containing transition metal zinc (23.9 mg) and copper (4 mg) must be avoided because this induces a 25 percent reduction in ciprofloxacin bioavailability [25]. Because the formation of nonabsorbable chelates has been initially proposed to explain the mechanism of this drug–drug interaction, results from Tanaka et al. [26] strongly indicate that adsorption of quinolone by metal hydroxide, reprecipitated in the small intestine, would play an important role in the reduced quinolone bioavailability.

β -lactam antibiotics. Until the work of Ueno et al. [27], β -lactam antibiotics were not known to interact with cation-containing drugs. This latter study has documented a major drug–drug interaction between cefdinir and ferrous sulfate, with a dramatic drop of greater than 90 percent of the C_{max} and the area under the curve (AUC) of the antibiotic, likely due to the formation of a nonabsorbable chelation complex between the 7-hydroxyimino radical and the iron ion.

Alkalinization of digestive content

β -lactam antibiotics. Esterified β -lactam antibiotics are prodrugs that are readily water soluble at pH 1–2, while being rather lipophilic at neutral pH. So, alterations of gastric pH by antacids or by H_2 -receptor antagonists usually change the amount of antibiotic that is absorbed (i.e., bacampicillin, cefuroxime axetil [28], and cefpodoxime proxetil [29–31]), but not cefotiam hexetil [32] and cefetamet pivoxil [33]. Until now, and as far as we know, no negative drug–drug interaction has been described with nonesterified β -lactam antibiotics [32,34–36].

Antifungals. The oral bioavailability of ketoconazole is dramatically reduced (≥ 95 percent reduction) when gastric pH is in the neutral range, a situation observed when using antacids [37] but also in more than 75 percent of AIDS patients [38,39] and in numerous elderly people. Such an interaction has never been observed with fluconazole [40,41].

Macrolides. Oral bioavailability of macrolides, including clarithromycin [42] and azithromycin [43], has not been significantly modified, with the exception of non-enteric-coated formulations of erythromycin base.

Fluoroquinolones. Even if the solubility of these antibiotics is highly variable in the pH range 2–6, [10], the bioavailability of fluoroquinolones is never decreased by alkalization of the digestive content (see Table 1).

Which antacid for which antibiotic? If drug–drug interaction is a matter of elevated pH, then all kinds of antacid should be avoided (see section 1.1.2). In the event of the formation of nonabsorbable metallic chelates (i.e., tetracycline, fluoroquinolone, and rifampicin, discussed previously), any of the nonmetallic antacids will be allowed a priori. We can thus recommend the use of the H₂-inhibitors (Table 1), omeprazole [44], pirenzepine [45–47], benexate [68], or dimeticome [48,49]. In addition, we have to consider the case of cimetidine, which is a potent inhibitor of various cytochrome P450 families of human liver that are involved in the biotransformation of fleroxacin, pefloxacin, and temafloxacin. This explains the 20–40 percent rise in AUCs of the latter three quinolones observed when they are coadministered with cimetidine [50–52].

Drug–drug interaction concerning active oral transport

Amino-β-lactam antibiotics are transported via the H⁺/dipeptide carrier system in the intestinal brush-border membranes [78,79]. This process is saturable and the pharmacokinetics of numerous amino-β-lactam drugs are not linear with the dose after oral administration [80–82]. This active transport can be inhibited by amiloride, an inhibitor of the Na⁺/H⁺ pump, which in turn leads to a decrease of more than 25 percent in the bioavailability of coadministered amoxicillin [83].

Furthermore, and according to animal data, captopril and other angiotensin-converting enzyme (ACE) inhibitors, which are structurally close to dipeptides such as glycine-proline, are transported through the peptide carrier system and can therefore inhibit the oral absorption of cephradine [84]. In the same manner, cephradine highly decreases the oral bioavailability of captopril [85] and lisinopril [86] to an extent that is highly relevant clinically. The same question has to be raised with regard to fluoroquinolones, which are orally absorbed by a similar carrier-mediated process, like amino-β-lactam antibiotics [87]. Lastly, these active transport processes are facilitated by calcium antagonists, as indicated by an up to 70 percent gain in bioavailability for cefixime when coadministered with 20 mg of nifedipine [88].

Interactions during drug distribution

Plasma protein binding displacement interactions

One of the first clinically relevant findings concerning antimicrobial agents was published in 1956, when a clinical trial showed that sulfisoxazole displaced bilirubin

Table 1. Extent of antibiotic C_{max} and AUC decrease during coadministration with an antacid compared with antibiotic given alone (results are expressed in percent of decrease)

Antibiotic	Maalox		Sucralfate and Al (OH) ₃		Ferrous sulfate		Zinc		Calcium carbonate		Dairy products milk [yogurt]		H ₂ -inhibitors and [omeprazole]		Others		References
	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	C _{max}	AUC	
Amifloxacin	85	85															47
Ciprofloxacin	80-95	85-96	72-95	84-96	33-77	48-64	37	24	38-47	41-42	36-[47]	33-[36]	0	±10-15	5	+8	22, 23, 25, 44, 45, 54-63
Enoxacin	70	73	91	88					44-59	26-40			[11]	[13]			18, 64, 65
Fleroxacin			25	23													66
Levofloxacin			65	44	45	19			23	3			0	0			67
Lomefloxacin	46	41											+11	+4	0		Benexate 21, 44, 68
Norfloxacin	95	NP	90	98-99	75	73	56 (fu)	55 (fu)	66	63	51-[53]	48-[58]	[0]	[+9,5]			54, 62, 69-72
Otofloxacin	73	73			36	25			+3	+4	0-[18]	6-[8]					Pirenzepine 45, 56, 62, 73, 74
Pefloxacin	62	55											+8	+41			Dimeticone 48, 50, 51, 75
Rufloxacin	43	36															76
Sparfloxacin	48	44															77
Temafloxacin	59	61											+4	+22			52

NP = not published; ± = both sided variations; fu = urinary elimination; + = value increased.

from human serum albumin (HSA), which subsequently produced kernicterus in premature infants [89]. Protein binding displacement may actually have pharmacokinetic significance only when the binding percentage is high and the distribution volume is small. In addition, the displacing drug must achieve a high drug to binding protein concentration ratio (i.e., >10:1) to sufficiently modify the apparent association constant of the displaced drug. Thus, more selective and potent drugs, which will exert their effects at low concentrations, will be at low risk for clinically important drug displacement interactions.

Such interactions are rather uncommon with antibiotics. First, only few of them are highly bound drugs, either to HSA (i.e., ceftriaxone, isoxazolyl penicillins, doxycycline, rifampin, teicoplanin, sulfonamides, ketoconazole, itraconazole, fusidic acid, and polyphenol), to α_1 -acid glycoprotein (i.e., roxithromicin), IgA (i.e., vancomycin), or IgG (i.e., teicoplanin). Second, the ratio of both affinity constants K_a (AB): K_a (comp) for the carrying proteins [where K_a (AB) is the K_a of protein-antibiotic and K_a (comp) is the K_a of protein-competitor drug] is not in the range leading to clinical relevant interaction. For example, itraconazole, which is nevertheless 99.8 percent bound to HSA, does not compete for HSA binding sites with any of the following highly bound drugs: imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide, sulphamethazine, warfarin, and phenytoin [90].

A major exception to this rule concerns sulfonamides, which potentiate coumarin anticoagulant treatment, the hypoglycemic effect of tolbutamide, and the alkylating effect of methotrexate because of higher free concentrations of the latter three drugs following plasma protein binding displacement [91]. Consequently, sulfonamides should be given only with caution to patients receiving oral anticoagulants or methotrexate. However, very recently Kishore et al. [92] observe a complete atrio-ventricular heart block in a patient receiving slow-release (SR) verapamil and phenytoin. This accident occurred 1 hour after the combined administration of ceftriaxone and clindamycin, given intravenously, with both antibiotics being highly bound to HSA. A displacement of verapamil from its plasma binding sites can be suspected, leading to a sudden increase in the free concentration of verapamil that has favored the cardiac acute toxicity.

Tissue drug protein displacement interactions

β -lactam compounds are organic weak acids, and there are separate active transport systems in the body with which they interfere, located for instance in the retina area, the choroid plexus, the nonluminal side of the proximal tubular cell, and the plasma membranes of the liver (hepatic ligandin and protein z). Any competition with one or several of these active transport systems gives rise to a reduction in the excretion of the β -lactam antibiotic. The main drug used to interact with active transport systems is probenecid (Benemid®). When combined with β -lactam antibiotics, three different actions are sought. In the eye, systemically infused probenecid inhibits the retinal pump, which in turn forces the β -lactam compound to escape by the anterior route. Since this route is long and narrow, the vitreous half-life of the

antimicrobial agent is longer [93]. In the brain the same mechanism can explain why we observe sustained effective concentrations of β -lactam antibiotics in the cerebrospinal fluid (CSF). In the liver and kidney, probenecid inhibits the excretion of the associated agent, whose half-life is increased. In the United States, probenecid is extensively used for this purpose, but the importance of the interaction is highly variable according to the β -lactam antibiotic used [94].

Still in the field of tissue interactions, we have noticed two major drug–drug interactions. First is the inhibition of hepatobiliary excretion of cyclosporin (CS) by ceftriaxone (CTX) [95], and second is the inhibition of hepatic uptake and/or tubular secretion of methotrexate (MTX) by mezlocillin [96], amoxicillin [97], or probenecid [98,99]. In both cases (CS and MTX) serum concentrations increase toxic levels. Thus, when CS or MTX are coadministered with ceftriaxone, mezlocillin, probenecid, or other highly biliary eliminated weak organic acids, such as piperacillin, azlocillin, or rifampicin, it would be more than wise to monitor CS or MTX levels to avoid toxicity. Lastly, we have to keep in mind that the toxicity of MTX can be increased by concurrent use of CS itself, nonsteroidal antiinflammatory drugs (NSAIDs) or co-trimoxazole [57].

Tissue penetration

Bacterial meningitis and hearing loss is the main long-term sequelae encountered in this pathology. In an attempt to reduce its incidence, corticotherapy has been proposed. From this perspective, it is worth noting that dexamethasone (0.15 mg/kg, every 6 hours) does not modify the early diffusion of cefotaxim (50 mg/kg, every 6 hours) in the cerebrospinal fluid during bacterial meningitis treatment in children [100,223]. In pulmonary infections, mucolytic agents, such as bromhexine or N-acetylcysteine, could significantly increase the amount of antibacterial agents in bronchial secretions and lung, particularly amoxicillin [101,102].

Interactions involving brain receptors

In a rat model, quinolones have been shown to compete with GABA for the binding of GABA-A receptors in the CNS. As a result, the seizure threshold is lowered and the risk of seizures is increased [103–106]. Indeed, when administered with NSAIDs, the binding of lomefloxacin, norfloxacin, and ciprofloxacin to GABA-A receptors is strongly enhanced, and they are, to date, the most potent inducers of seizures among the fluoroquinolones in the mouse model (intraventricular injection in mouse brain).

In human, the frequency of hallucinations and seizures is around 5 percent when fluoroquinolones and NSAIDs are concurrently administered [107]. Similar manifestations have been observed during concomitant use of theophylline and imipenem [108]. Associated risk factors are age, hepatic dysfunction (in the case of quinolones highly metabolized such as pefloxacin), and theophylline treatment (even if the concentrations are in the therapeutic range) [8,107–109]. Such manifestations are mostly encountered with fenbufen and in descending order, according

to the following sequence: fenbufen > (maybe) flurbiprofen > naproxen > ketoprofen > sulindac [8].

Intracellular penetration and activity

Metabolism of *Coxiella burnetti*, the intracellular etiologic agent of Q fever, is enhanced at acidic pH, whereas antibacterial activities of doxycyclin and fluoroquinolone are markedly reduced at low pH. By using lysosomotropic alkalinizing agents such as chloroquine or ammonium chloride, the content of *C. burnetti* phagolysosomes is modified from pH 4.8 to pH 5.7 and 6.8, respectively, and the bactericidal activities of the two former antimicrobial agents are restored [110,111].

Interactions occurring during elimination processes

Renal and biliary excretion

Interactions acting upon the renal or biliary active transport systems have been described earlier. One must also consider the interaction observed between rifampin and enzyme-inducing agents such as phenobarbitone. Indeed, most of the inducing drugs markedly stimulate the synthesis of hepatic proteins Y (ligandin) and Z, and therefore increase the biliary clearance of *cholephiles* anions such as rifampin.

Metabolic excretion

Before elimination, most drugs undergo biotransformation in the body, mainly in the liver, but also in other tissues such as the lungs. In oxidative drug metabolism, such as N-demethylation or hydroxylation, the hepatic microsomal mono-oxygenase system is largely involved, and these enzymic reactions are catalyzed by cytochrome P450 (CYP) hemoproteins, the terminal electron acceptor of the system. It has been established that there are at least 25 human forms of CYP, each with a distinct, although overlapping, substrate specificity [112–114]. The main characteristic of that system is that many drugs or xenobiotics can either induce or inhibit the CYP activities, leading to numerous drug–drug interactions. A number of extensive reviews have appeared regarding the role of CYP enzymes in the metabolism of drugs [115–117]. Conversely, in conjugating drug metabolism, in which the parent drug (or its oxidized form) is covalently associated with a water-soluble ligand such as glucuronide or sulfate, no CYP is involved. This latter system of biotransformation appears to be much less implicated in drug–drug interactions. We can only notice an inhibition of zidovudine glucuronidation by chloramphenicol and by NSAIDs [118].

In addition, the intersubject variability in the activity (and, therefore, the efficacy) of some common metabolic pathways may be as large as 10- to 20-fold [119–122]. This provides a partial explanation to the fact that some patients are more sensitive to metabolic interactions than others and also to the fact that the bioavailability of drugs with a major hepatic first-pass effect is highly variable [123].

Induction of drug metabolism

Antibiotic–antibiotic interaction. As already mentioned, rifampin is a potent inducer of human hepatic CYP families and is one of the most implicated drugs for hepatic drug–drug interactions [2,3]. Combinations of rifampin plus fluoroquinolones or rifampin plus novobiocin are widely recommended for the treatment of serious staphylococcal infections. However, it is important to mention that rifampin highly reduces (by 30–60 percent) the elimination half-lives of novobiocin [124] and of the quinolones that are metabolized by an oxidative pathway in the liver (i.e., pefloxacin, fleroxacin) [125,126]. So, when such an association is prescribed, it will be better to choose a nonmetabolized quinolone such as ofloxacin, or even a quinolone with a mixed elimination pathway (renal and hepatic) such as ciprofloxacin [127]. In the same manner, one must recall that rifampin reduces doxycycline plasma concentrations by more than 50 percent [128,129].

Concerning antifungal drugs, rifampin, like other inducers (i.e., carbamazepine, phenobarbitone, phenytoin) leads to a three to four times decrease in the mean peak plasma ketoconazole and itraconazole concentrations because both azoles are extensively metabolized by CYP enzymes [1,2,130]; ketoconazole acts in the same way with rifampin [130]. In the case of fluconazole, rifampin interaction accounts for only a 20–25 percent decrease in the mean azole half-life and AUC [131]. Metabolic clearance of fluconazole accounts for only 20 percent of its total plasma clearance. Rifabutin, a rifampin structurally related drug, does not significantly modify fluconazole pharmacokinetics [132]. Lastly, based on the fact that dapsone with trimethoprim may be an effective alternative to co-trimoxazole to treat *Pneumocystis carinii* infections, it is of interest to notice that concurrent administration of dapsone and rifampin is associated with a decrease in dapsone serum half-life greater than 50 percent [133].

Rifampin and nonantibacterial drugs. Rifampin, being probably the most potent microsomal enzyme-inducing agent to date, significantly decreases plasma levels of numerous liver metabolized drugs, either markedly or partially. Quinidine half-life is divided by 3 and AUC by 4–6 when concurrently administered with rifampin [134]. Something very similar is observed with verapamil [135], diltiazem [136], and most probably with other calcium-channel blockers that undergo an extensive hepatic first-pass effect.

Plasma theophylline clearance is nearly doubled [138–140]. The same extent of increase is observed when rifampin is coadministered with the oral anticoagulants glycodiazine, tolbutamide, cortisol, digitoxin, oral contraceptives, methadone, ethosuximide, phenytoin, diazepam, haloperidol, tocainide, lorcinide, bunazosin, and disopyramide [2,3,141].

Induction of CYP isoenzymes by rifampin causes a substantial reduction in cyclosporin blood levels, sometimes leading to rejection episodes in transplant patients. From this perspective, the dose of cyclosporin should be initially increased by 50 percent in patients receiving rifampin and then monitored daily [142–144]. Recent work by Hebert et al. [145,146] and Gomez et al. [147] strongly suggests

that, contrary to the widely held opinion that rifampin induces the systemic hepatic metabolism of cyclosporin, rifampin could decrease the oral bioavailability of cyclosporin by altering its absorption and/or by inducing its presystemic metabolism (since intravenous cyclosporin pharmacokinetics were not modified by rifampin pretreatment). In connection with this, a recent *ex vivo* study of cyclosporin absorption suggests that the gastric mucosa and also the colonic mucosa may be major sites of first-pass metabolism for cyclosporin *in vivo* [148].

Some authors have suggested that pyrazinamide could replace rifampin in transplant patients affected by tuberculosis, but pyrazinamide itself seems to decrease plasma cyclosporin concentrations [149]. Lastly, when erythromycin, which is a potent CYP inhibitor, is added to rifampin and cyclosporin, the enzyme inductor effect of rifampin surpasses the erythromycin-inhibiting effect and the cyclosporin dosage has to be increased [150].

Among the antituberculosis drugs, we have to note that isoniazid is a specific inducer of the CYP2E1 isoenzyme, which is involved in the metabolism of acetaminophen. So concurrent administration of those drugs can result in increased acetaminophen metabolite concentrations (sometimes reaching the toxic range) and in depletion of glutathione, thus leading to hepatocellular injury [151].

What can we suspect when we use a drug with a biphasic effect such as isoniazid? In fact, according to Zand et al. [152] isoniazid has a biphasic effect. First, during the 7-day period of isoniazid administration, the authors observed a large inhibition, greater than 50 percent, of both the clearance of chlorzoxazone and the formation of acetaminophen thioether metabolites (both CYP2E1-dependent). Then, after discontinuation of isoniazid treatment, both kinetic processes were increased above the value measured before isoniazid treatment by 56 percent. This requires additional extensive studies before the clinical consequence that can be drawn out.

Inhibition of drug metabolism. Drugs that interfere with a specific CYP enzyme will markedly influence the elimination of the corresponding index drug from the body unless significant alternate metabolic pathways exist for this drug. For this, Table 2 indicates the main inhibitors and substrates corresponding to each of the individual CYPs. It will constitute a first help to identify the potential interactions when using a new drug known to interact with, or to be a substrate for, a specific CYP isoform.

Main mechanisms involved in P450 enzymes inhibition. From a practical and clinical point of view, the main points to remember are as follows [117]:

- First, the more commonly encountered interaction in oxidative drug metabolism is the reversible competition between substrates for the same substrate-binding site of the same CYP enzyme. Usually this does not lead to very significant modifications of elimination half-life of coadministered drugs. But it can highly reinforce proper inhibition of metabolic pathways by an inhibitory drug belonging to the two following subgroups described.

Table 2. Primary examples of cytochrome P450 inducers and inhibitors

		CYP (= Cytochrome P450)		
		1	2	3
Family				
Subfamily				
Specific enzymes				
Inhibitor				
Probable inducer				

1 A	2 C	2 D	2 E	3 A
1 A2	2 C8-10	2 D6	2 E1	3 A3-5 (mainly 3 A4)
Cimetidine	Cimetidine	Cimetidine	Disulfiram	Cimetidine
Fluvoxamine	Fluconazole	Fluoxetine	Methoxsalen	Ethinylestradiol
Furafylline	Ketoco/traconazole (±)	Paroxetine		Fluconazole (±)
Grapefruit juice (±)	Omeprazole	Quinidine		Fluoroquinolones (±)
Interferon α and β	Sulfaphenazole			Grapefruit juice
Methoxsalen				Interferon α and γ
Fluoroquinolones				Keto/traconazole
				Macrolides
				Omeprazole (±)
				Carbamazepine
			Alcohol	Glucocorticoids
			Isoniazid	Phenobarbital (±)
	Phenobarbital			Phenylbutazone
	Rifampin			Phenytoin
				Pyrazinamide (?)
				Rifampin
				Spironolactone
				Sulfapyrazone

Substrate	Acetaminophen	Barbiturates	Amitriptyline and analogues (Most) β -blockers	Acetaminophen	Alfentanil
	Caffeine	Diazepam	Captopril	Alcohol	Bromocriptine
	Dihydralazine	Mephentermine	Chlorpromazine and analogue	Chlorzoxazone	Carbamazepine
	Imipramine	Methsuximide	Dextropropofol	Various N- demethylation	Cyclosporine
	Phenacetin	Nialamide	Debrisoquine	Haloethane	Dapsone
	Theophylline (1-oxydation)	Omeprazole	Dextromethorphan/codeine		Dextrometorphan
	Warfarin	Papaverine	Diphenhydramine		Dihydropyridine calcium antagonists
	Zidovudine?	Phenylephrine	Domperidone		Disopyramide
		Propranolol	Encainide and analogues		Ergot alkaloids
		(side chain oxidation)	Haloperidol		Imipramine and analogues
		Sulfonpyrazole	Imipramine and analogues		Ketocof/traconazole
		Tienilic acid	Mexiletine		Lidocaine
		Tolbutamide	Papaverine		Midazolam/triazolam
			Paroxetine		Pentoxifylline
			Perhexiline		Procainamide
			Phenacetin		Quinidine
			Phenformin		Steroids
			Phenylephrine		Terfenadine
			Propafenone		Theophylline (8 hydroxylation)
			Quinidine		Valproic acid
			Sparteine		Verapamil/diltiazem
			Yohimbine		Warfarin

Data from references 1, 7, 112, 115–117, 122, 151, 157, 162–166, 199, 201–203, and 218–222.

Table 3.

	Theophylline alone	T+ cimetidine (400 mg, every 12)	T+ ciprofloxacin (500 mg, every 12)	T+ cimetidine + ciprofloxacin
$t_{1/2\beta}$	7.2	10.2 (+42%)	10.6 (+48%)	12.8 (+77.8%)

- Second, some drugs, such as macrolide antibiotics, methoxsalen, ethinylestradiol, chloramphenicol, cyclophosphamide, or secobarbital, have functional groups that are oxidized by CYP enzymes. What may happen, however, is that the metabolite formed binds strongly (even covalently) to the enzyme. The result is an *irreversible* inhibition in which the labelled CYP is unavailable for further oxidation. It may take a few days before the occurrence of this inhibition (time required for the formation of the metabolite), and therefore the synthesis of new enzyme is the only way in which activity can be restored. This also may take several days.
- Third, the majority of the inhibitory drugs interact *reversibly* with CYP enzymes but in a noncompetitive way. Among them are fluoroquinolone antibiotics, the drugs with an imidazole ring (i.e., antifungal drugs such as ketoconazole and itraconazole; cimetidine, but not ranitidine, which possesses a furan ring instead of an imidazole ring), sulfaphenazole, omeprazole, and probably grapefruit juice. Here, the inhibition appears quickly and disappears quickly as well, as soon as the interacting drug is withdrawn (except when a metabolite of the parent drug is involved, that is, self-inhibition of diltiazem oxidation by some of its metabolites and probably self-inhibition of pefloxacin metabolism by its own metabolites. This explains, in both cases, why the elimination half-life increases up to two-fold, following multiple doses of the drugs) [153].

Risk factors. The main risk factors are as follows:

- Coadministration of several substrates for the same CYP enzyme and/or concurrent administration of different enzyme inhibitors; for example, coadministration of a therapeutic dose of cimetidine and ciprofloxacin with theophylline is associated with a greater proportionate increase in the elimination half-life of theophylline (T), as compared with that observed with each agent administered alone with T (those two drugs impairing both the demethylation and the hydroxylation of theophylline) [154]. The summary of this interaction is presented in Table 3.
- Chronic liver disease, mainly hepatic cirrhosis, can be associated with altered P450 expression. However, if most of the CYP enzymes are downregulated, there is some evidence that the CYP2C subfamily is not modified (or slightly increased) in cirrhotic liver but is upregulated in patients with carcinoma (up to three times the normal liver content) [117].
- Viral hepatitis can be associated with decreased metabolic capacities.
- Viral and bacterial pulmonary infections can significantly alter nitrendipine, theophylline, and antipyrine metabolism. The mechanism of these effects could be direct downregulation of the pulmonary expression of P450 isoenzymes (lung

Table 4. Increasing factor for the elimination half-life of theophylline when coadministered with a fluoroquinolone

Enoxacin	× 2
Pipemidic acid	× 2
Pefloxacin	× 1.5–2
Ciprofloxacin	× 1.5
Tosufloxacin	× 1.5
Norfloxacin	× 1.2
Sparfloxacin	× 1.2
Fleroxacin	
Lomefloxacin	
Ofloxacin	× 1.0
Rufloxacin	
Temafloxacin	
Q35	

Data from references 8, 105, 106, 154, and 166–172.

as well as liver is a major tissue for drug metabolism) or a depressed P450 activity due to a release of interferon. Interferon α -2b decreases theophylline and antipyrine clearance but does not modify hexobarbital metabolism [155–161]. Similarly, an almost two-fold increase in the zidovudine elimination half-life is mediated by interferon- β [162], while interferon- γ suppresses the activity of CYP3A4 and the metabolism of erythromycin [156].

- Old age
- Grapefruit juice: Components of grapefruit juice GFJ, but not other citrus, inhibit CYP3A4 and thus subsequent metabolic pathways. CYP1A2 also seems to be concerned, but to a lesser extent [163]. Therefore, GFJ highly interacts with substrates of CYP3A4, such as calcium antagonists [164], cyclosporin [165], or terfenadine [208]. This food–drug interaction has potential clinical importance since citrus juices are often drunk at breakfast time, and sometimes together with drug treatment [164].

Major examples

Fluoroquinolone antibacterials. Quinolone antibacterials mainly inhibit CYP1A2 and, to a much lesser extent, CYP3A4 [8–11]. Consequently, cyclosporin, the metabolism of which is mediated by CYP3A4, does not interact with fluoroquinolones [8,9,143]. However, periodic monitoring in transplant recipients would be prudent [9]. If we investigate the interaction with cimetidine (see previously), the only clinically relevant drug–drug interaction known with quinolones concerns the interaction with theophylline, the elimination half-life of which can increase up to two-fold when coadministered with enoxacin or pefloxacin, as indicated in Table 4.

Macrolide antibiotics. Macrolides, particularly troleandomycin and erythromycin, are potent inducers of CYP3A, but however, an immediate secondary reaction

during which an iron–metabolite complex is formed leads to the final inactivation of CYP3A [4–7]. This complex is due to the strong binding of a nitrosoalkane metabolite of the former macrolide to iron of the heme moiety of CYP3A [5,173,174]. Thus, macrolides are able to interfere with the elimination of numerous drugs whose metabolism is mediated by CYP 3A (see Table 4), such as theophylline, cyclosporin, carbamazepine, warfarine, terfenadine (Table 5), midazolam-triazolam [175–179], bromocriptine, methylprednisolone [4–7], disopyramide, felodipine [164], and valproic acid [180,181]. Other substrates can be involved because the induction of the CYP3A subfamily can be associated with a relative decrease in the expression of other CYPs, particularly the CYP2C subfamily [5,182], or even the CYP2D subfamily, according to the reduced metabolism of amitriptyline and nortriptyline observed in the presence of josamycin [183].

Azole antifungal agents. As a rule, ketoconazole is a significantly stronger inhibitor of CYP3A4 than itraconazole or fluconazole, however, fluconazole is probably one of the strongest inhibitors of CYP2C among oral azoles, as indicated in Table 6 [1,198,199]. Thus, terfenadine normally undergoes a nearly complete (99 percent) hepatic first-pass effect, leading to the pharmacologically active acid metabolite, M_1 . M_1 is further oxidized to give a second inactive metabolite, M_2 . When concurrently administered with a CYP inhibitor such as oral azoles or macrolide antibiotics, the first metabolic step can be inhibited, leading to a detectable amount of terfenadine in the systemic circulation and to the possible dissolution of the cardiac toxicity of teldane itself. Many episodes of torsades de pointes with prolonged QT intervals have been described, along with such drug–drug associations involving mainly ketoconazole, itraconazole (but not fluconazole), and erythromycin [188,191,192,201–206]. Risk factors include hepatic disease [207], coexisting cardiovascular disease, hypokalemia (i.e., diuretic or laxative usage, coadministration of amphotericin B, cirrhosis), and concomitant intake of grapefruit juice [208]. Interestingly, no interaction occurs with the administration of cimetidine [209]. Last we have to notice that ketoconazole per se is responsible for a significant increase in QT [210], likely due to the blockade of cardiac potassium currents [211].

With regard to cyclosporin, mainly ketoconazole, but also the other two azoles, but to a lesser extent, inhibit the intestinal metabolism of the former immunosuppressor drug [147]. This drug–drug interaction has been proposed to reduce the cyclosporin dosage in an attempt to significantly reduce the cost of such an expensive therapy. From this perspective, the ketoconazole dosage proposed by First et al. [212] is 200 mg/day, and the cyclosporin intake, expressed in percent of a standard dose, is indicated in Table 7.

With itraconazole and fluconazole, the results are rather conflicting [197]. Actually, it seems with that the interaction between cyclosporin and fluconazole depends upon the dose of azole used, the problem of nephrotoxicity being expected only when the dose is greater than 300 mg/day [213,214]. If ketoconazole is used in overcoming multidrug resistance due to P glycoprotein, as has been proposed very recently by Siegsmond et al., then all the data concerning oral azoles is of

Table 5. Drug–drug interactions involving macrolide antibiotics. The level of the interaction is noted from grade 0 (none interaction) to +++ (major interaction).

Coadministered drug	Azithromycin	Clarithromycin	Dirithromycin	Erythromycin	Josamycin	Mideca/Myocamycin	Roxithromycin	Spiramycin	TAO
Theophylline	0	0 (2 × 250 mg/j)	0	++	+	ND	0/+	0	+++
Cyclosporine	ND	ND	ND	+++	+++	+++	+	0	ND
Carbamazepin	ND	0 (2 × 250 mg/j)	ND	+++	+	+	0/+	0/+	+++
Warfarin	0	ND	ND	+	ND	ND	0	ND	ND
Terfenadine	0	++	ND	+++	0/+	ND	ND	ND	ND

TAO = troleandomycine; ND = not documented; 0 = no interaction.

Data from references 4, 6, and 184–197.

Table 6. Drug–drug interactions involving azole antifungal agents, from grade 0 to +++

Coadministered drug	Ketoconazole	Itraconazole	Fluconazole	CYP concerned
Theophylline	0	0	0	1A2 + 3A4
Cyclosporine	++	+	0/+	3A4
Terfenadine	++	++	0	3A4
Phenytoin	0	ND	++	2C
Tolbutamide	0	ND	++	2C

ND = not determined.

Data from 198 and 200–206.

Table 7.

Previous length of treatment (month)	1	3	6	12
% of a standard dose	24	24	18	16

particular interest [215]. Grapefruit juice acts in the same manner and could replace ketoconazole as well [165].

Fluconazole affects significantly the plasma clearance of atevirdine (ATV), a non-nucleoside inhibitor of HIV-1 reverse transcriptase, which is believed to be metabolized by members of the CYP 3A subfamily, resulting in a 30 percent increase in steady-state plasma ATV levels [216]. Lastly, cimetidine and misonidazole which both have an imidazole ring structure, significantly increase the elimination half-life of 5-fluorouracil [99], which can be observed with other azole drugs as well.

Conclusions

Most drug–drug interactions seem predictable when the pharmacokinetic and pharmacodynamic properties of each medication coadministered are completely understood. We thus hope that this chapter might provide a rationale to predict and then to avoid or control the effects of such interactions. However, some drugs are potentially hazardous in this respect, leading to dramatic unexpected drug interactions [217].

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