Chapter 1
Infections in Patients with Cancer: Overview

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Abstract Patients with neoplastic disease are often highly susceptible to severe infections. The following factors influence the types, severity, and response to therapy of these infections: (1) Changing epidemiology of infections; (2) cancer- and/or treatment-associated neutropenia; (3) acquired immune deficiency states such as cellular immune defect; (4) recent development of new-generation diagnostic tools including widely available DNA amplification tests; (5) effective intervention for infection prevention; (6) empiric or presumptive therapy during high-risk periods; (7) availability of new classes of highly active antimicrobial drugs; (8) strategies to promote hosts' immune response; and (9) future measures. This introductory chapter intended for the reader to become familiar with the important historical milestones in the understanding and development in the field of infectious diseases in immunosuppressed patients with an underlying neoplasms and patients undergoing hematopoietic stem cell transplantation.

Keywords Cancer • Infection • Neutropenia • Immune defects • Diagnosis • Therapy

Patients with neoplastic disease are often highly susceptible to severe infections. These are inclined to be difficult to prevent, diagnose, and treat. There are a variety of reasons for this which will be discussed in detail in the chapters of this book. We will introduce this volume by reviewing the history and background of such infections, where we believe major advances have been made and what we believe will be necessary to effectively prevent and manage such infections in the future. The following factors influence the types, severity, and response to therapy of these infections: (1) Changing epidemiology of infections; (2) cancer- and/or treatment-associated neutropenia; (3) acquired immune deficiency states such as cellular immune defect; (4) recent development of new-generation diagnostic tools including widely available DNA amplification tests; (5) effective intervention for infection prevention; (6) empiric or presumptive therapy during high-risk periods; (7) availability of new classes of highly active antimicrobial drugs; (8) strategies to promote hosts' immune response; and (9) future measures.

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Historical Perspective

The introduction of chemotherapeutic regimens has expanded the population at risk, since many of these agents affect host defenses, most often causing neutropenia. However, even in acute leukemia, the malignancy with the highest frequency of infection, very little was published about infectious complications until the second half of the twentieth century. The paucity of published data is illustrated by a book on acute leukemia, published in 1958, which made no mention of infectious complications [1]. Indeed, at that time, some physicians attributed fevers in leukemia patients to a general hypermetabolic condition caused by the neoplasm.

By the 1950s, several antineoplastic agents became available which caused at least transient improvement in some malignant diseases. Nitrogen mustard caused responses in Hodgkin disease, aminopterin caused responses in acute leukemia, and methotrexate cured choriocarcinoma in women. The subsequent use of multiple drug combinations in acute lymphocytic leukemia and Hodgkin disease represented major advances [2]. Another important advance was the use of platelet transfusions to control and prevent hemorrhage in acute leukemia patients with thrombocytopenia [3]. In an autopsy study, the frequency of hemorrhage as a cause of death in acute leukemia patients decreased from 67 to 37% due to the use of platelet transfusions [4]. Unfortunately, infection remained a major cause of death. There have been many reviews of the subjects over the years, some with international contributors and continuity which are references here [5–11].

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Epidemiological Factors

Exposures to organisms in the distant as well as recent past should be considered in patients with neoplastic disease. Latent infections may be activated in the presence of waning immunity whether it be due to the disease itself or to the treatment. The classic example of this is reactivation of latent tuberculous in patients with treatment-induced helper T-cell dysfunction. Additional latent infections which may be activated, for example, are histoplasmosis, coccidiomycosis, disease caused by the Herpes group of viruses, toxoplasmosis, strongyloidiasis, and others. These demand consideration and many such as TB, herpes simplex, and strongyloidiasis can be effectively treated prophylactically. Recent travel or residence and hospitalization may expose patients to organisms which may incubate such as malaria after travel to an endemic area or colonization due to drug-resistant bacteria such as *Klebsiella*, *Pseudomonas,* and *Stenotrophomonas* species acquired during a previous hospitalization. Questions to investigate epidemiologic factors should include exposures at home along with work, habits, and hobbies. Also, a detailed history of recent and remote travel and recreational activities may provide clues for an otherwise improbable diagnosis. All of these can be a source of infection, some of which can be avoided with appropriate patient education.

Hosts' Susceptibility

It is not surprising that the frequency of infection is related to the type of underlying malignancy and most infections occur in patients who are failing to respond to their cancer therapy. Surveys in the 1960s found that about 80% of patients with acute leukemia, 75% with lymphoma, but less than 40% of patients with metastatic carcinoma developed infection [12, 13]. There are a wide variety of factors that may impact on the susceptibility of cancer patients to infection [11]. Local factors such as tumor masses that may obstruct the bronchial tree or urinary tract and necrotic tumors in the gastrointestinal tract can result in infection. In an autopsy study of children with metastatic carcinoma, 80% of cases of pneumonia were associated with pulmonary metastases, aspiration, or tracheostomy [14]. Antibiotic therapy is often of limited efficacy in these types of tumors, unless the local predisposing factor can be removed.

Immunological Factors

Neutropenia is the most important predisposing factor and can be due to the disease or its therapy. While there were some reports of the role of neutropenia in infection, a detailed analysis of 52 patients with acute leukemia was published in 1966 [15]. This study demonstrated that the risk of infection was related to the degree and duration of neutropenia. The risk increased when the neutrophil count was less than 1,000/mm^3, but increased substantially when it was below 500/mm^3. Also, the risk of developing infection increased the longer the duration of neutropenia. One hundred percent of episodes of severe neutropenia (<100 PMN/mL) lasting 3 weeks or longer were accompanied by identifiable infection compared to 65% of episodes lasting one week. Neutropenia diminishes the likelihood of detecting characteristic manifestations of infection. One study compared physical findings of infection in a group of patients with severe neutropenia with a group with adequate neutrophil counts [16]. Only 8% of patients in the former group with pneumonia were able to produce purulent sputum compared to 84% in the latter group. Similarly, among patients with urinary tract infections, pyuria was found in 11 and 97%, respectively. In an autopsy study, it was demonstrated that many pulmonary infections were not detected on routine chest radiographs antemortem [17]. Likewise, among patients with gram-negative bacillary pneumonia, 85% of those with initially abnormal chest radiographs had >1,000 neutrophils/mL, whereas 81% with normal roentgenograms had <1,000 neutrophils/mL [18]. The lack of signs of infection in febrile neutropenic patients impairs the physician's ability to determine whether or not fever is due to infection. In one study of fever in neutropenic patients, physicians were required to conclude whether infection was present or not before instituting therapy [19]. The physician's initial diagnosis (infection or fever of unknown origin) was incorrect in 33% of the cases.

White blood cell (WBC) transfusions were initiated in an effort to improve the outcome of infections in severely neutropenic patients. Since it was difficult to collect sufficient neutrophils from normal donors, initially, patients with chronic myelogenous leukemia with high neutrophil counts were used as donors [20]. Later, the development of the continuous cell separating machine made it possible to collect adequate cells from normal donors [21]. Studies demonstrated that there was a direct relationship between the number of cells transfused and the increment in the recipient's neutrophil count. In one study of 128 neutropenic patients who had fever unresponsive to antibiotic therapy, 49% responded after WBC transfusions, including patients with pneumonia and gram-negative bacillary septicemia [22]. Unfortunately, potential adverse effects occurred in some recipients. In one study when WBC transfusions were administered with amphotericin B, 64% of patients developed acute dyspnea, respiratory deterioration, and new pulmonary infiltrates compared to only 6% of patients who did not receive amphotericin B [23]. Several other studies failed to observe this toxicity. Another potential adverse event primarily for bone marrow transplant recipients was

acquisition of cytomegalovirus (CMV) infection [24]. Reports of graft-versus-host disease (GVHD) in a few recipients has led to routine irradiation transfused cells, but questions have been raised about adverse effects of radiation on the function of the transfused neutrophils. In a review of seven prospective randomized trials of WBC transfusions in neutropenic patients with infection, it was concluded that the transfusions were of some benefit in five studies but the number of patients in each study was small [25]. A problem with many was the ignoring of the number of neutrophils administered; hence, some patients received an inadequate dose. The use of WBC transfusions diminished by the 1980s because there was inadequate evidence of their efficacy from prospective comparative studies. However, there has been a resurgence of interest in increasing available neutrophils since recombinant myeloid growth factor granulocyte-colony-stimulating factor (G-CSF) has become available. Administration of G-CSF to donors improves the number of neutrophils collected as well as increases their activity against infection [26].

Protected Environment. Because of the risk of infection during periods of chemotherapy-induced neutropenia, efforts were made to provide a sterile environment for these patients. The first type of unit was a bed surrounded by a plastic canopy with filtered air (Fig. 1.1). Later, laminar air flow rooms were designed [27]. These units provided filtered air, sterile water supply, sterile room, specially prepared food, and toilet facilities. The patients were given specifically prepared "sterile" food and prophylactic oral and topical antibiotics. These rooms, air, food, and patients were carefully monitored for microbial contamination [28, 29]. The program reduced the frequency of infection and permitted the use of more intensive chemotherapy in the premyeloid growth factor era. Unfortunately, more intensive chemotherapy in this setting did not result in higher remission rates for several malignancies including acute leukemia [30], lymphoma [31], and sarcoma [32]. One review of protected environment entitled "Protected Environment are discomforting and expensive and do not offer meaningful protection" summarized the discussion as follows "The one constant in almost every controlled study is that life has not been prolonged, remission induction increased, nor remission prolonged" [8].

In the late 1940s and early 1950s, patients with neoplasms were originally found to be infected with organisms from the flora in their nasopharynx and the gastrointestinal tract due to neutropenia caused by their disease or subsequent therapy. Exceptions were those with cellular immune defects due to the neoplasm such as Hodgkin's disease, who might present with cryptococcosis or those with multiple myeloma who might present with pneumococcal septicemia because of their decreased production of normal immune globulins. In the neutropenic patient, the organisms invading from the nasopharynx were usually *Streptococcus pyogenes* or *Staphylococcus aureus* (penicillin susceptible). From the orointestinal tract, *Escherica coli* and *Klebsiella* or *Proteus* species were responsible; these bacteria were sensitive to most available antibiotics during early 1950s. Gradually, but steadily, resistance developed in most of the organisms except *S. pyogenes*. *S. aureus* resistant to penicillin and *Pseudomonas aeruginosa* resistant to all antimicrobials except polymyxin appeared in the late 1950s [4, 33, 34]. Antimicrobial resistance developed over the years among the orointestinal isolates and the Gram-positive cocci increased to become predominate by the 1980s with MRSA and penicillin-resistant

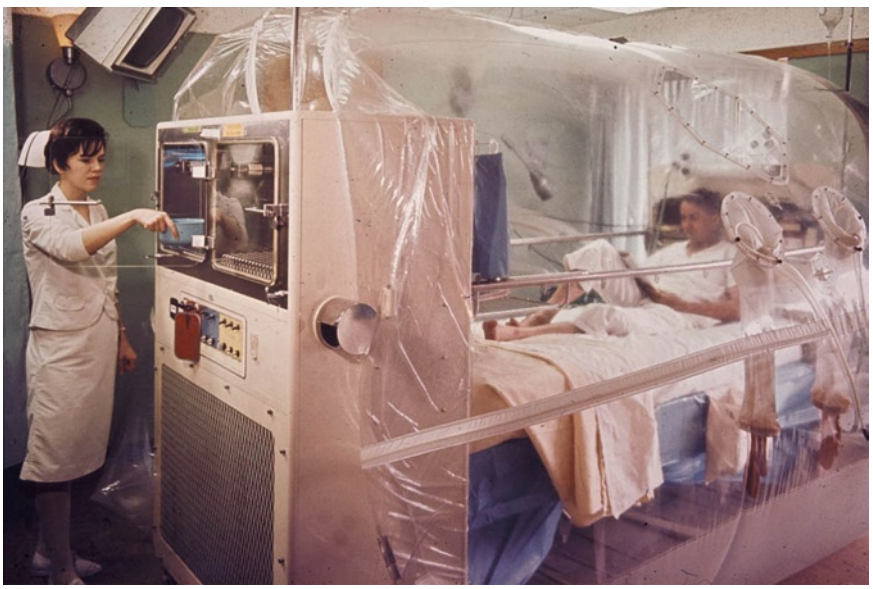

Fig. 1.1 First type of protective environment for severely neutropenic patients. Note, sleeves in the side of canopy to perform tasks on patient and chambers at the foot that irradiated items placed into unit

alpha streptococci appearing. Many of the effective anticancer treatment regimens result in neutropenia so that these types of infection remain a major problem in patients with neoplastic disease.

In contrast, patients with cellular immune defects due to their basic disease or its therapy are prey to a different array of organisms. Predisposing diseases include Hodgkin's disease, T lymphocyte lymphomas and leukemias, and hairy cell leukemia. Various transplantation procedures and GVHD along with treatments for them including cyclosporine, antithymocyte globulin, tacrolimus and adrenocorticosteroids induce defects which result in such opportunistic infections. The diseases are due to organisms from all categories including *Salmonella* spp., *Histoplasma capsulatum*, *Leishmania* spp., and CMV. In the early 1980s and with the advent of the AIDS epidemic, investigators with access to laboratories where T cells could be measured began systematic studies that revealed that patients with levels in the 200 range or lower would develop one or more of these opportunistic infections, especially PCP. It became apparent that as the T cells fell, it could be predicted which organisms would cause disease [8, 35]. Now with the measurements of endogenous cytokines, T-cell subset populations, and functional analysis, this is even more predictable and offers opportunities for treatment and prevention.

B-cell defects have been well described occurring in certain groups of patients with certain underlying neoplastic diseases such as multiple myeloma and chronic lymphocytic leukemia or those after bone marrow transplantation. In these instances, the organisms to be anticipated are *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neiseriae meningitimus,* or late after transplantation, Echoviruses. Vaccine studies in this group of patients and others are underway to try to achieve protection.

An altered integument allows access to a large variety of organisms to invade patients with neoplastic disease. Areas at risk include the entire orointestinal tract where chemotherapy-induced mucusitis with ulcers allow organisms' entry into tissues and the bloodstream. Intravascular catheters allow direct entry into the bloodstream and other catheters such as bladder, intraperitoneal or intracranial devices are sources of infection especially in the neutropenic patient. In addition, life-threatening infections may result from infusion of blood products or transplanted organs. These may vary from HIV and HTLV-I [36] to *Salmonella* spp., *Candida* spp., and *Trypanasoma cruzi* among others.

Knowing the immunological defect in a patient with neoplastic disease suspected of having an infection is extremely important. From the clinical picture, the appropriate tests can be done to confirm the diagnosis, and if indicated, empiric therapy can be started. A fine example of this is the empiric therapy of the neutropenic patient with appropriate antibiotics for anticipated organisms in the clinical setting such as a particular hospital. In the early 1960s, a clinical study from the NCI documented the association of the fall of the neutrophil count with the rise of the severe infections [15]. An example of a population at risk for a specific infection due to an immune defect was the prevention of Pneumocystis pneumonia in children with acute lymphoblastic leukemia carried out at St. Judes Hospital in Memphis TN [37]. Almost 100% protection was achieved. Knowledge of the perturbations in immune function following bone marrow transplantation has enabled clinicians to use preemptive therapy for suspected infections such as those caused by CMV.

Finally, immune defects involving innate and adaptive immune responses may occur in patients who have received prolonged courses of chemotherapy, neoadjuvant antineoplastic monoclonal antibody therapy, or immunosuppressive agents for treatment of GVHD following allogeneic stem cell transplantation.

Diagnostic Evaluation of Infection

There have been remarkable advances in diagnostic tests for the evaluation of infection in the past five decades, especially in diagnostic microbiology allowing us to make earlier and more specific microbial diagnoses. Gram stains, invented in 1884 by Hans Christian Gram in Denmark, and variations on dye techniques are still routine and useful for early presumptive diagnoses, but immunological methods using direct fluorescent antibody stains have been developed and are regularly used especially for viruses. In unusual circumstances such as suspected polyoma virus infection, electron microscopy may be used. New culture methods include isolator lysis centrifugation tubes which are used for continuous around-the-clock monitoring employing a fluorescent carbon dioxide detection system. An automated broth system can be used for quantitation by colony counts of centrifuged sediments and these systems are more sensitive for the isolation of some fungi, mycobacteria and *Bartonella* species. In addition, the broth can be examined by nucleic acid probes and HPLC for rapid organism identification. Automated broth Minimum Inhibitory Concentration (MIC) antimicrobial susceptibility tests yield more rapid results which can be entered into online computer systems for clinicians and recorded for antimicrobial susceptibility patterns for hospital infection control. To help select antimicrobial regimens for empiric therapy, these data can also be available for local and national Health Departments as well as the hospital.

Polymerase chain reaction (PCR) techniques to recognize copies of nucleic acid fragments in various specimens have been developed and are being used. Many are undergoing FDA approval and some may be available only in special laboratories. These techniques may well replace earlier tests

using antigen detection by poly or monoclonal antibodies and chemical tests for specific cellular elements such as arabinatol, beta D-glucan, or galactomanans of fungi.

Antibody tests are much easier to perform since the enzyme-linked antibody (ELISA) test has replaced the compliment fixation (CF) test, and for specificity, the Western blot has become the "gold standard". However, for cancer patients and those following allogeneic stem cell transplantation, serologic diagnosis may provide limited information regarding active versus remotely acquired disease. Furthermore, a negative serology cannot be interpreted with certainty due to potential defects in B-cell function.

Radiologic testing with CT scans and MRIs has better defined anatomic lesions for presumptive diagnoses, and recent advances in safe tissue sampling can be used by interventional radiology techniques for specific diagnoses. Bronchoalveolar lavages have virtually replaced open lung biopsies for investigating pulmonary lesions; however, similar to diagnostic reliability of serologic diagnosis, a negative BAL sample smear or culture dose not exclude the possibility of opportunistic lung infection. Radioactive labeling of the patient's own neutrophils and injecting them for localizing foci of infection can sometimes be helpful as can technetium scans. Efforts to localize infected sites using antibody for specific organisms are presently under study and this method could also offer treatment opportunities. Similarly, PET scan are now commonly used for tumor burden and disease recurrence monitoring; this new technology appears promising as an adjuvant diagnostic tool.

Pathogens of Interest

Most infections occurring in patients with nonhematological malignancies are caused by organisms commonly associated with the site of the tumor or nosocomial pathogens except when on chemotherapy. Infections in patients with hematological malignancies are usually caused by organisms that are prevalent in association with specific deficiencies in host defense mechanisms or are due to nosocomial pathogens. Only a few examples will be presented in this discussion, primarily focused on those infections prevalent in neutropenic patients.

Bacterial Infections

Early studies of infection in patients receiving chemotherapy for hematological malignancies found that *S. aureus* developed resistance to penicillin. It became the predominant cause of fatal infection in neutropenic patients [4]. Once effective antibiotics became available for treatment of penicillin-resistant *S. aureus*, gram-negative bacilli emerged as the most common cause of fatal infections. *Pseudonomas aeruginosa* became a major cause of infections, especially among neutropenic patients [29, 37, 38]. Although polymyxin B and colistin were very active in vitro against the pathogen, they were ineffective for therapy in neutropenic patients and were of limited benefit in other patients. Their efficacy in neutropenic patients depended upon the recovery from neutropenia. The availability of carbenicillin, the first β lactam with anti-pseudomonal activity, had a dramatic impact on the therapy of life-threatening *Pseudomonas* infections [39]. Other gram-negative bacilli emerged as significant pathogens, including *Klebiella* spp. and *Serratia marcescens*. Cephalothins were the first β lactam available for the treatment of some of these infections [40]. Over the years, multiplicity of antibiotics has been developed including potent broad-spectrum cephalosprosins, carbapenims, and fluoroquinolones [41]. Despite these important advances, bacterial infections remain a serious threat to cancer patients, due in large part to the ability of organisms to develop resistance to multiple antibiotics. Recent increase in nonpseudomonal nonfermentative Gram-negative bacteria such as *Stenotrophomonas maltophilia* has been associated with difficult-to-treat healthcare-associated infections; these bacteria may also cause less severe community-acquired infections [42]; high-dose trimethoprim-sulfamethoxazole remains the treatment of choice, although occasionally a multidrug-resistant organism poses a serious challenge [43]. Emergence and spread of extended-spectrum beta-lactamases (ESBL) *Enterobacteriaceae* and recently identified carbapenemases producing *Klebsiella* species (KPC) and spreading to other gram-negative disease-associated bacteria herald alarming limitation in choice for effective antimicrobial therapy against these new groups of MDR-gram-negative bacterial infections [44].

Listeria monocytogenes was one of the first bacterial infections reported as occurring more frequently in patients with cellular immune defects [8, 45] and it continues to be a problem [46]. It soon became apparent that *Salmonella* spp., *Nocardia asteroids*, and *Rhodococcus equi* were also opportunistic bacterial pathogens in this setting. *Mycobacterium hemphilum* [47] was thereafter established as a *Mycobacterium* to be anticipated in T-cell-deficient patients, in addition to the classic example of *M. tuberculous* [48] and subsequently *M. avium-intracellulare* complex.

Principles of Antibiotic Therapy in Neutropenic Patient

This discussion will be limited to general principles. Discussion of specific antibiotic therapies is presented in other chapters of this book. After multiple antibiotics became

available and the potential for emergence of resistance became apparent, it became the standard practice to withhold antibiotic therapy in the febrile patient until the infecting pathogen was identified. However, early studies of antibiotic therapy for fever in neutropenic patients clearly indicated the importance of instituting antibiotic therapy promptly to neutropenic patients when they become febrile. It has been demonstrated that mortality rates increase substantially if therapy is not administered promptly. The choice of initial antibiotic therapy should provide broad-spectrum antibacterial coverage against gram-positive cocci and gram-negative bacilli. Most infections are caused by aerobic gram-negative bacilli and anaerobic infections tend to be uncommon. It is of critical importance for physicians caring for neutropenic patients to be aware of the common pathogens causing infections at their hospitals and their antimicrobial susceptibilities so that appropriate antibiotic regimens will be selected. Antibiotics that are bactericidal should be selected when possible. The greatest experience has been obtained with broad-spectrum β lactams and aminoglycosides. Aminoglycosides are less effective as single agents in neutropenic patients and should not be used alone [49].

Some studies have indicated that synergistic combinations that provide high serum cidal levels such as a β lactam plus an aminoglycoside are more effective than single agents [50]. However, aminoglycosides have potential nephrotoxicity, which are more prevalent in the elderly and patients with cancer such as multiple myeloma or cancer therapy induced reduced renal reserves.

Various regional, national, and international groups have met and are still meeting to study questions of treatment and how to conduct studies to evaluate treatment of bacterial infections. These have included The Infectious Diseases Society of America [51], The European Organization for Research and Treatment of Cancer [52], and The Immunocompromised Host Society [53]. For empirical antibacterial treatment, it is evident that regimens should be aimed at the most prevalent organisms with reliable knowledge of their susceptibility infecting the patient at a given hospital. It must be stressed that continued efforts at prevention, e.g., scrupulous hygiene, are most important.

Patients with fever of unknown origin that persists after several days of broad-spectrum of antibiotic therapy represent a difficult problem. Careful reevaluation and collection of additional appropriate diagnostic tests need to be performed and additional therapeutic measures should be considered. These may include other antibacterial, antifungal, or antiviral agents. Antifungal agents should be given serious consideration in these patients. Some investigators have advocated that antibiotic therapy be continued in patients with documented infections until the neutrophil count recovers. There is considerable evidence to indicate that this is unnecessary and can encourage superinfection. A more appropriate approach is to discontinue the therapeutic agents, watch carefully.

Mycobacterial Infections

Tuberculous is a well-recognized, albeit uncommon, complication even in patients with severe cellular immune defect [48]. Patients with solid organ cancer may be as susceptible to active *Mycobacterium tuberculous* infection as patients with hematologic malignancy and those undergoing hematopoietic stem cell transplantation [54]. It remains important to realize that tuberculous, being an indolent disease, may be mistaken for a slowly progressing neoplasm and may lead to unnecessary large excisions that can be avoided by initial fine needle aspiration and biopsy of the suspected mass [55].

Nontuberculous mycobacterial disease due to slow-growing mycobacteria is on the rise. Cancer patients with *Mycobacterium intracellulare* lung infections are often postmenopausal women [56], with a selective defect in interferon gamma production or presence of interferon gamma inhibitor [57, 58]. Rapidly growing mycobacterial (RGM) lung disease is uncommon and mostly seen in patients undergoing chemotherapy and in individuals with pervious pulmonary involvement with cancer [59]. *Mycobacterium chelonae* and *Mycobacterium fortuitum* were the prominent RGM associated with lung disease [59, 60]; recently, *Mycobacterium abscessus* has been a predominate RGM pulmonary pathogen [61]. *M. abscessus* infections are difficult-to-treat due to high level of drug-resistance [61] and issues related with drug intolerance. Patients with severe cellular immune defects have significantly poor outcome with disseminated RGM end-organ infection [62], with the exception of *Mycobacterium mucogenicum* catheter-associated infection that responds to prompt removal of the infected catheter and a short course of combination antimicrobial therapy [61].

Fungal Infections

Fungal infections emerged as a significant complication of patients with hematological malignancies after effective chemotherapy became available. The major predisposing factors to these infections were determined to be prolonged neutropenia and adrenocorticosteroid therapy, which interferes with macrophage function. These infections are also prevalent among HSCT recipients who develop graft vs. host disease and receive adrenocorticosteroid therapy.

As early as the mid-1950s, an increasing proportion of patients with acute leukemia developed fungal infections, predominantly candidiasis and aspergillosis [63]. In recent years, infections caused by Zygomycetes, *Fusrium* species, and *Scedasporium* species have become increasingly frequent [64, 65].

There are multiple species of *Candida*, with different antifungal susceptibilities and patterns of infection [56, 66–68]. Superficial candidiasis occurs in cancer patients receiving radiation therapy and those with impaired T-cell function. Infections involved the oropharynx, esophagus, larynx, urinary tract, and gastrointestinal tract and serve as the origin of disseminated infection, especially in those with neutropenia and long-term intravenous catheters. Disseminated infection is often difficult to diagnose because there may be few signs and symptoms except fever and progressive debilitation and the organism is often not cultured from blood specimens. About 10% percent of patients have multiple skin lesions [69]. There is a chronic form of disseminated candidiasis that occurs in neutropenic patients, which persists after neutrophil recovery and is characterized by persistent fever, debilitation, weight loss, and in some patients, hepatosplenomegaly and right upper quadrant pain [70–72].
Mortality rates have been as high as 70% among patients treated with amphotericin B. Fluconazole prophylaxis has been associated with a significant increase in drug-resistant *Candida krusei* and *Candida glabrata* breakthrough disseminated infections [73–75]. Other alternatives are lipid formulations of amphotericin B and echinocandins. Neutrophil recovery is a critical factor in recovery from candidiasis. Prolonged therapy with fluconazole has been effective for chronic candidiasis and recent experience suggests that anti-inflammatory agents may be useful.

Aspergillosis. The major sites of infection are the lungs and sinuses. Disseminated infection is uncommon. Infection is acquired by inhalation of spores and epidemics have occurred during construction in hospitals. The hyphae invade blood vessels causing thrombosis and infraction and can erode through facial planes, cartilage, and bone. Patients with pulmonary infection may present with symptoms suggesting acute pulmonary embolism. Characteristic nodular infiltrates can be detected on pulmonary CT scans "Halo sign" when radiographs are normal [76]. Culture specimens are often negative, but blood galactamannan tests are helpful in establishing the diagnosis and evaluating treatment response [77]. Sinus infections often present with black eschars on the nose or palate. Progressive infection causes proptosis, endophthalmitis, or cerebral infraction. Therapy consists of effective new *Aspergillus* active triazole-based drugs such as voriconazole and posaconazole, and echinocandins such as caspofungin and micafungin in combination or as a single agent [78]. Lipid formulations of amphotericin B are also used in combination with other mold-active drugs. Neutrophil recovery and discontinuation of systemic immunosuppressive therapy, especially adrenal costicosteroids, are important for recovery from the infection. Surgical resection of the infected tissue may benefit some patients and resection of residual cavitary lesions may be necessary to prevent pulmonary hemorrhage and late-recurring bacterial superinfections.

Patients at risk of developing cryptococcosis have impaired cellular immunity or are receiving adrenal corticosteroids; hence, patients with CLL or lymphoma or HSCT recipients are at greatest risk. Infection is acquired by inhalation of organisms; hence, the lung is the primary site of infection, although less than 40% of infected patients present with symptoms of pneumonia. The infection can progress rapidly leading to death. Over 50% of cancer patients develop meningitis and some have widely disseminated infection. The latex agglutination test detects cryptococcal antigen in cerebrospinal fluid or blood of infected patients [79]. Optimal treatment consists of initial systemic therapy with amphotericen B plus low-dose flucytosine [80]; for patients with mild-to-moderate infection, high-dose oral fluconazole may be given for maintenance therapy.

Zygomycosis, caused by molds of the order Mucorales, are increasing in frequency [81]. These infections share the same characteristics as aspergillosis, but mortality rates exceed 70% despite amphotericin B therapy. Newer azoles such as posaconazole may be effective therapy [82]. Over 80% of *Trichosporon* infections are disseminated and the organism can be cultured from blood specimens of most patients. Other infections include endophthalmitis, pneumonia, meningitis, and osteomyelitis [83]. Optimal therapy may be a combination of amphotericin B and fluconazole, but the mortality rate is high in neutropenic patients despite therapy; high-dose voriconazole may be effective in patients with disseminated or hepatosplenic *Trichosporon* species infection [84]. Breakthrough *Trichosporon* infection may occur in patients receiving mold-active drugs such as echinocandins or oral broad-spectrum triazoles [85, 86].

Fusarium spp. cause infections predominantly in the sinuses and lungs. Fusariosis like *Aspergillus* species infection are angioinvasive; pulmonary nodular or mass-like disease is indistinguishable from other mold infections [87]. About 75% of infections in neutropenic patients disseminate and the organism often can be cultured from blood specimens. Nearly half of patients are fungemic and up to 80% or more present may develop multiple (>10) nodular skin lesions that develop necrotic center; skin biopsy is diagnostic and should be performed promptly. Mortality remains high despite the availability of highly active triazole drugs against this organism [87].

Unresolved immune suppression continues to influence treatment response among cancer and hematopoietic stem cell transplant (HSCT) recipients with systemic fungal disease [88]. Various strategies including donor granulocyte transfusions in patients with severe neutropenia have not shown significant improvement in outcomes in recent clinical trials [89]. Combined therapy using effective antifungal agents plus recombinant cytokines to boost macrophage, helper, and cytotoxic lymphocyte functions have been explored; a nonrandomized study using granulocyte-macrophage colony-stimulating

factor (GM-CSF) and interferon gamma (IFNγ) which were safe and appeared to have a favorable impact in patients receiving donor granulocyte transfusions [90]. Safety of IFNγ has been a concern due to potential cytokine-induced graft compromise and/or GVHD in recipients of allogeneic HSCT; these concerns were not observed in our patients with life-threatening fungal infections [91], although larger, randomized studies are needed to explore this important issue further. Similarly, drugs that may promote pathogen-directed immune capture by introducing configurational changes in these pathogens are being explored [92, 93].

Viral Infections

For many years, little attention was focused on viral infections in cancer patients due to the lack of rapid diagnostic tests and effective therapy. For example, only in recent years have community respiratory viral infections been recognized as potentially serious to immunocompromised patients. Table 1.1 lists most of these viral infections and available therapy. Many acute viral infections represent reactivation of long-standing latent infection.

Human herpes viruses are among the most common causes of viral infections in cancer patients and are associated with significant morbidity and mortality in severely immunocompromised hosts. Herpes simplex viruses cause oropharyngeal and esophageal disease and may disseminate to other organs. Reactivation of varicella-zoster virus occurs mainly in patients with leukemia and lymphoma and can result in localized infection (shingles), disseminated cutaneous infection, pneumonia, encephalitis, hepatitis, or small bowel disease [94]. CMV infection is most often due to reactivation of latent infection, but has also been attributed to transmission by white blood cell transfusions [24, 95]. It is a special risk to HSCT recipients who may receive infected tissue. CMV may cause hepatitis, meninoencephalitis, pneumonitis, or gastroenteritis [96, 97]. The disease has immunosuppressive effects that increase the risk of other infection. Prophylaxis or preemptive therapeutic strategies are necessary for patients undergoing stem cell transplantation [98]. Epstein–Barr virus can cause a fulminant fatal lymphoproliferative disorder in occasional patients following allogeneic stem cell transplantation. Immunocompromised cancer patients occasionally develop interstitial pneumonitis, encephalitis, or hepatitis due to human herpes virus 6 infections.

Progressive multifocal leukoencephalopathy is a demyelinating disease of the brain caused by the JC virus which occurs infrequently among patients with CLL and Hodgkin disease. The disease is due to reactivation of latent infection that is prevalent in normal adults. Symptoms include visual disturbances, speech defects, and mental deterioration leading to dementia and coma with 80% of patients dying within one year. Parvovirus B19 may cause anemia in cancer patients which may be followed by severe polyarthritis. Most patients have been infected with polyomavirus (BK) virus that persists in the genitourinary tract and is a major cause of hemorrhagic cystitis in HSCT recipients [99].

Community respiratory viral infections cause about 30% of respiratory infections in cancer patients during winter and spring and can be a serious threat to transplant recipients and patients with acute leukemia who may develop viral pneumonia or superinfection with bacteria or fungi [100, 101]. Epidemics have occurred in transplant and leukemia units. Some of these patients have very prolonged viral shedding after resolution of symptoms. Viruses causing infection include influenza A and B, respiratory syncytial virus (RSV), parainfluenza (PIV), and adenovirus. In stem cell transplant recipients following PIV and RSV infections, pulmonary obstructive defects were recently recognized; these may be severe and complete resolution may take longer than 12 months after the initial viral infection [102]. Novel respiratory viruses recently recognized to cause serious life-threatening disease include human metapneumovirus, human cornonavirus NL63 and HKU1, agent of severe acute respiratory syndrome (SARS), and human bocavirus [103, 104]. Adenovirus also causes gastrointestinal infection, hepatitis, hemorrhagic cystitis, pancreatitis, and encephalitis; fatal disseminated adenovirus infections are seen in adults and pediatric patients with profound cellular immune defects such as cordblood transplant recipients with GVHD [105].

Parasitic Infections

Neuro-hepatic toxoplasosis is more common in cancer and transplant recipients in the northeastern United States, whereas strongyloidiasis infestation rates are mostly seen in habitants of southeast and south-central US states. Similarly, amebiasis and giardiasis are infrequently seen in patients from rural residences who consume water from shallow contaminated wells. Latent *Toxoplasma gondii* infection is difficult to diagnose on the bases of travel, food consumption, or history of domestic feline exposure; serology may be diagnostic, although in patients with B-cell defects PCR analysis may be needed. Malaria is mostly seen in patients traveling to endemic regions without prophylaxis or receiving ineffective chemoprophylaxis due to drug-resistant strains of *Plasmodium* species. "Airport malaria" has also been seldom reported in patients who reside near airports with frequent international flights. Transfusion malaria has been observed in patients with neoplastic diseases and should be considered and explored in the presence of unexplained fever [106]. Chaga's disease has also been transmitted by transfusions

Table 1.1 Infections causing pneumonia in cancer patients based on the underlying immune defect

Immune defect	Bacteria	Fungi	Parasites	Viruses
Granulocytopenia	*Staphylococcus aureus*	*Aspergillus fumigatus;* and other *Aspergillus* spp.		Herpes simplex virus I and II
	Streptococcus pneumoniae	Non-*Aspergillus* hyalohyphomycosis		Varicella-zoster virus
	Streptococcus species	Such as *Pseudallescheria boydii*, *Fusarium solani.*		
	Pseudomonas aeruginosa	*Mucorales* (zygomycoses)		
	Enterobacteriaceae	Dematiaceous (black) fungi such as *Alternaria*		
	Escherichia coli	*Bipolaris*, *Curvularia*, *Scedosporium apiospermum*		
	Klebsiella species	*Scedosporium prolificans*		
	Stenotrophomonas maltophilia			
	Acinetobacter species			
Cellular immune	*Nocardia asteroides* complex	*Aspergillus* and non-*Aspergillus* filamentous molds	*Toxoplasma gondii*	Cytomegalovirus
Dysfunction	*Salmonella typhimurium* spp.	*Pneumocystis jiroveci* (*P. carini*)	*Microsporidium* spp.	Respiratory viruses
	Salmonella enteritidis	*Cryptococcus neoformans*	*Leishmania donovani*	Influenza A and Influenza B
	Rhodococcus equi	Endemic mycoses due to *Histoplasma capsulatum*	*Leishmania infantum*	Parainfluenza type-3
	Rhodococcus bronchialis	*Coccidioides immitis, Blastomyces dermatitidis*	*Strongyloides stercoralis*	Respiratory syncytial virus
	Listeria monocytogenes	*Penicillium marnefie*		Adenovirus
	Mycobacterium tuberculous			Varicella-zoster virus
	Nontuberculous mycobacteria			HHV 6
				JC and BK virus
				Parvovirus B19
				SARS-associated coronavirus?
				Paramyxovirus?
				Hantavirus?
Humoral immune	*Streptococcus pneumoniae*	*Pneumocystis jiroveci* (*P. carini*)?	*Giardia lamblia*	VZV
Dysfunction	*Haemophilus influenzae*		*Babesia microti*	Echovirus
Splenctomy	*Neisseria meningitidis*			Enterovirus
	Capnocytophaga canimorsus			
	Campylobacter			
Mixed defects	*Streptococcus pneumoniae*	*Pneumocystis jiroveci* (*P. carini*)	*Toxoplasma gondii*	Respiratory viruses
	Staphylococcus aureus	*Aspergillus* spp.	*Strongyloides stercoralis*	Influenza
	Haemophilus influenzae	*Candida* spp.		Parainfluenza
	Klebsiella pneumonia	*Cryptococcus neoformans*		Respiratory syncytial virus
	Pseudomonas aeruginosa	*Mucorales* (zygomycoses)		Adenovirus
	Acinetobacter spp.	Endemic mycoses (severe systemic dissemination)		VZV
	Enterobacter spp.			
	Stenotrophomonas maltophilia			
	Nocardia asteroides complex			
	Listeria monocytogenes			
	Legionella spp.			

Patients with mixed immune defects include recipients of allogeneic hematopoietic stem cell transplant; acute or chronic graft versus host disease; myelodysplastic syndrome; adult T-cell leukemia lymphoma; antineoplastic agents like cyclophosphamide, fludarabine, and HHV6: Human herpesvirus 6 *L. donovani* and *L. infantum* may lead to serious visceral leishmaniasis. *L. donovani* is seen in Africa and Asia, *L. infantum* is seen in Africa, Europe, Mediterranean, and Central and South America. VZV is rarely associated with systemic dissemination in patients with humoral immune defects, or even those with mixed immune dysfunctions. *Strongyloides stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects

causing fevers and pericardial effusions [107]. This disease may become more common as the number of potential donors coming from endemic areas increases and also the reduvid bug appears to be moving north into southwestern states. Screening donors may become necessary. A recent increase in fatal *Babesia* species infection reported since

November 2005 in the US has raised concerns of this rare intraerythrocytic parasite disease [108].

Hydated cyst due to *Echinococcus granulosus* and *E. multilocularis* and neurocycticercosis is difficult to distinguish from cystic brain tumor or bacterial or fungal brain abscess. Liver hydrated cyst may present as polymicrobial bacterial abscess in patients from the developing world.

End-Organ Infection

Septicemia including disseminated infection and pneumonia are the most common sites of infection; urinary tract, skin, and central nervous system infection occurs less commonly. The site of infection is often related to the site of the primary tumor, a metastasis, or a surgical procedure. Septicemia is most likely to occur in patients with impaired host defenses. The frequency of infection has been determined in several autopsy studies.

Pneumonia

The management of pneumonia in the cancer patient is often frustrating and difficult. The spectrum of potential pathogens is exceptionally broad including those that infect normal hosts and those that occur predominately in immunocompromised hosts; predisposing factors include deficiencies in host defense mechanisms such as neutropenia or hypo IgG, bronchial obstruction or ulceration due to tumor, mucosal damage due to chemotherapeutics agents, and the use of mechanical ventilation. Cancer patients may develop pulmonary infiltrates due to noninfectious causes such as hemorrhage, radiation pneumonitis, and leukoagglutinin reaction. Several neutropenia patients are unable to produce adequate inflammatory responses and thus may fail to produce persistent sputum, develop clinic signs and symptoms, or develop abnormalities on chest radiographs.

In a study of gram-negative bacillary pneumonia in cancer patients (most of whom had hematological malignances), only 64% had abnormal radiographs at the onset of their pneumonia and 20% never developed abnormalities [109]. Identification of the infecting pathogen is often difficult. Adequate sputum specimens are often not available. The diagnostic yield from invasive procedures such as bronchoalveolar lavage is suboptimal. Biopsies are often contraindicated because of the risk of hemorrhage due to thrombocytopenia or coagulopathies. The use of CT scans and blood tests such as galactomannon detection for Aspergillosis have improved diagnostic capabilities [76].

Abdominal Infections

A wide variety of infection agents may infect the gastrointestinal tract due to obstruction, ulceration, and other factors. This discussion will focus on two infections with potentially serious consequences in neutropenic patients: typhlitis and perianal infections. Typhlitis or neutropenic enterocolitis is characterized by well-demarcated ulcers, hemorrhage, and large masses of organisms with few inflammatory cells usually limited to the cecum, but can be more extensive. Computed tomography scans provide superior images of the intra-abdominal organs and may be able to diagnose subclinical small bowel perforations, infected collections, and pneumatosis intestinalis, a serious complication which requires intense bowel management and presents as surgical dilemma [110]. Bacteremia occurs in 70% of patients. Therapy consists of broad-spectrum antibiotics, and anti-*Candida* agents, bowel rest, and decompression are important [110].

Perianal infections are most common in patients with acute monocytic leukemias. The prominent symptoms are fever and pain on defecation. Lesions often arise adjacent to a hemorrhoids and are indurated and ulcerated, often with extensive necroses. It is important to evaluate for recrudescent Herpes virus infections and perirectal abscess. Evaluation of surgical intervention may be obtained if there is not a prompt response to antimicrobial therapy or if a drainable focus is identified.

Catheter-Related Infections

Most cancer patients receiving antineoplastic therapy have indwelling central venous access. Catheter infections are an important cause of delay in chemotherapy, hospitalization, cost of care, and deaths [111, 112]. Coagulase-negative *Staphylococcus* (CoNS) and other skin gram-positive bacteria are common pathogens. Catheter removal reduces risk of infection recurrences [113], and in patients with high-grade bacteremia or candidemia with or without hemodynamic compromise, the catheter should be removed immediately. A thorough evaluation for underlying endovascular infection such as septic thrombophlebitis may yield a source of persistent bacteremia, lack of complete response, and influence duration of systemic antimicrobial therapy. Factors that influence antimicrobial choice include (a) penetration of drug in the biofilm, (b) antimicrobial activity within the biofilm, and (c) activity against the nonplanktonic stationary phase of the microorganisms [114]. A detailed discussion of this important topic is presented in two chapters.

This introductory chapter intended for the reader to become familiar with the important historical milestones in the understanding and development in the field of infectious

diseases in immunosuppressed patients with an underlying neoplasm and patients undergoing hematopoietic stem cell transplantation.

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