
Epidemiology of Infections in Cancer Patients

Teresa R. Zembower

Abstract

Although major advances in the care of cancer patients over the past several decades have resulted in improved survival, infectious complications remain a significant cause of morbidity and mortality. To successfully identify, treat, and prevent infections, a comprehensive understanding of risk factors that predispose to infection and of commonly encountered pathogens is necessary. In addition, clinicians must keep abreast of the changing epidemiology of infections in this population. As therapeutic modalities continue to evolve, as established pathogens become increasingly drug resistant, and as new pathogens are discovered, successful management of infections will continue to present challenges in the years to come.

Keywords

Epidemiology • Infection • Cancer • Risk factors • Emerging pathogens

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T. R. Zembower (✉)
Division of Infectious Disease, Feinberg School of Medicine, Northwestern University, 645 N. Michigan Avenue, Suite 900, Chicago, IL 60611, USA
e-mail: t-zembower@northwestern.edu

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1 Introduction

Infectious complications are a serious cause of morbidity and mortality in cancer patients, especially those with underlying hematological malignancies where autopsy studies demonstrate that approximately 60 % of deaths are infection related [1–7]. Although fewer data exist on infectious mortality in patients with solid organ tumors, approximately 50 % of these patients are estimated to have an infection as either the primary or an associated cause of death [3, 5–9]. Because patients with underlying malignancies are a heterogeneous group, an epidemiologic review of risk factors and infections in these patients must take into account the diversity of the population.

Risk factors for infection include underlying immune deficiencies, associated comorbidities, and treatment-related adverse effects. Clearly, more than one predisposing factor may exist in a given patient, and their cumulative burden more accurately reflects the risk of infection. To some extent, however, these risk factors are associated with specific infectious pathogens, and an understanding of each individual risk factor can help direct strategies for diagnosis and treatment.

Patients with underlying malignancies are at risk for a wide array of infectious diseases. Bacterial infections predominate, followed by fungal infections. Viral infections occur not infrequently, often as a result of reactivation of latent disease, primarily in patients with hematological malignancies. Parasitic and other unusual infections are encountered less frequently but should be considered in individuals with appropriate exposure history [10–14].

Epidemiologic trends include recognition of emerging pathogens or syndromes and increasing antimicrobial drug resistance that is now commonplace among bacteria and fungi and is increasing among some viruses. The astute clinician must remain aware of these emerging issues to optimize care of the cancer patient.

This chapter will provide an overview of the risk factors for infection, review commonly encountered pathogens associated with specific malignancies, and examine emerging pathogens and epidemiologic trends.

Table 1 Factors predisposing to infection in cancer patients

Host factors
Disrupted anatomical barriers
Humoral immunodeficiencies
Cell-mediated immunodeficiencies
Organ dysfunction
Concurrent illnesses and past infections
Nutritional status
Psychological stress
Treatment-associated factors
Surgery
Radiation therapy
Immunosuppressant therapies
Chemotherapy
Biological response modifiers
Antimicrobial use
Diagnostic and invasive procedures
Central venous catheters
Urinary catheters
Tracheostomy
Blood transfusions

2 Risk Factors for Infection

For ease of understanding, factors that predispose to infection are divided into those that are host associated and those that are treatment associated. Host-associated factors include underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress. Treatment-associated factors include surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures [12]. Again, clinicians should be aware that in practice, multiple deficiencies are usually encountered simultaneously (Table 1).

2.1 Host-Associated Risk Factors

2.1.1 Immune Deficiencies

Host defense mechanisms are mediated by the immune system which has traditionally been thought to be composed of two major subdivisions: the innate or non-

Table 2 Innate versus adaptive immunity

	Innate immune system	Adaptive immune system
<i>Characteristics</i>	Discriminates self from non-self	Discriminates self from non-self
	General protection	Antigen specific
	Early phase of host response; immediate	Late phase of host response
	Does not require prior exposure	Requires prior exposure
	Response does not alter on repeated exposure; no memory	Response improves with successive exposures; immunological memory
<i>Components</i>		
Physical and chemical barriers	Skin, mucous and mucous membranes, tears, saliva, nasal secretions, sweat, defensins, surfactant	Lymphocytes at surfaces
Humoral components	Complement, coagulation system, lactoferrin, transferrin, lysozyme, interleukin-1, interferons	B lymphocytes
Cellular components	Monocyte-derived macrophages, dendritic cells, mast cells, natural killer cells, granulocytes (neutrophils, eosinophils, basophils)	T lymphocytes

specific immune system and the adaptive or specific immune system [12, 15, 16]. This categorization is somewhat artificial as the systems are highly interrelated. Despite this, literature still describes these systems separately, and there is some utility in doing so, as defects in their separate components predispose, in part, to specific infections. A detailed description of the immune system is beyond the scope of this chapter (see chapter [Host Impairments in Patients with Neoplastic Diseases](#)); however, a basic understanding of the key components of innate and adaptive immunity is important for clinicians caring for patients with malignancies (Table 2).

Deficiencies in Innate Immunity

The innate immune system is constitutively present, not antigen specific, and able to mobilize rapidly; thus, it provides the first line of defense for invading micro-organisms. The innate immune system is comprised of anatomical barriers, humoral factors that aid in the inflammatory response, and cellular components that facilitate phagocytosis.

Anatomical barriers of the skin and mucous membranes form protective layers that, when intact, prove impermeable to most of the infectious agents [8, 12, 17–19]. Protective processes such as desquamation of skin epithelium, ciliary movement, peristalsis, and production of tears, saliva, and respiratory and gastrointestinal (GI) tract mucus work in conjunction with these barriers to trap and remove harmful organisms. Substances such as fatty acids found in sweat; lysozyme and

phospholipase in tears, saliva, and nasal secretions; defensins and surfactant in the pulmonary tract; and defensins in the GI tract inhibit the growth of organisms, primarily bacteria. The acidic nature of sweat and GI secretions also helps prevent organism growth. In addition to the barriers themselves, the normal flora of these sites can prevent the colonization of pathogenic organisms by secreting toxic substances or by competing with pathogenic bacteria for nutrients or attachment to cell surfaces.

In cancer patients, these barriers can be compromised by malignant invasion, mechanical obstruction, or treatments such as radiation and cytotoxic chemotherapy [8, 12, 20–22]. Primary or metastatic skin tumors increase the risk for skin and soft tissue infections and for bacteremia with organisms such as *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pyogenes*, and *Corynebacterium* spp. Tumors of the oral cavity and nasopharynx damage the mucosa, resulting in local infection in the mouth, nose, throat, or sinuses and predisposing to infections with streptococci, *Haemophilus influenza*, and anaerobic necrotizing infections. Occasionally, these infections can spread to the meninges causing meningitis or locally invade the sinuses, resulting in osteomyelitis with or without subsequent cerebral abscess. Tumors of the GI tract can invade the mucosa, causing local abscess formation, bacteremia, or perforation and resulting peritonitis. In these infections, gram-negative bacteria predominate; however, fungal infections are also encountered, primarily in patients who have received broad-spectrum antibacterial agents. Gynecological malignancies disrupt barriers in the female genitourinary (GU) tract predisposing to infection with enterococci, enteric aerobic and anaerobic gram-negative bacilli, and *Clostridium* spp. Anatomical barriers are further compromised by cytotoxic chemotherapeutic agents such as anthracyclines, bleomycin, cytosine arabinoside, methotrexate, 6-mercaptopurine, and 5-fluorouracil, those most likely to cause skin breakdown, stomatitis, and GI mucositis. Dermatologic side effects are also increasingly reported in patients who receive thalidomide [23]. Radiation combined with chemotherapy further increases the risk of skin and mucosal toxicity.

Deficits in the humoral components of the innate immune system also predispose to infection [24–29]. Some important components include the complement and coagulation systems and substances such as lactoferrin, transferrin, lysozyme, interleukin-1, and interferons. Complement deficiencies predispose to infection through ineffective opsonization and through defects in lytic activity resulting from altered assembly of the membrane attack complex (MAC), components C5b through C9. These deficiencies predispose to infections with the encapsulated bacteria, *Streptococcus pneumonia*, *H. influenza*, and *Neisseria meningitidis*; mycobacteria; fungi such as the yeast *Saccharomyces cerevisiae*; and viruses. The role of complement in defense against viral infection is sufficiently important that pathogenic viruses such as *Herpesviridae* and *Coronaviridae* have had to develop strategies to evade complement activation. Alterations in coagulation can compromise vascular permeability and diminish chemotaxis of phagocytic cells. Additionally, deficiencies in the production of beta-lysin, a platelet-derived protein that acts as a cationic detergent, can diminish response to gram-positive bacteria.

Lactoferrin and transferrin bind iron, an essential nutrient for bacteria; lysozyme helps break down the bacterial cell wall; and interleukin-1 induces fever and the production of acute-phase proteins involved in opsonization. Deficiencies in these components increase the risk of bacterial infections. Deficiencies in interferon predispose to viral infections because it is vital to limiting viral replication within cells.

Once the anatomical and humoral defenses are breached, cellular innate defenses such as monocyte-derived macrophages, dendritic cells, mast cells, natural killer cells, and granulocytes (i.e., neutrophils, eosinophils, and basophils) also respond rapidly to microbial challenges. However, as these cells also initiate and modulate the response of T and B lymphocytes, they serve as important links between the innate and adaptive immune systems [12, 15, 16].

Macrophages exist throughout the body and are an important component of phagocytosis and intracellular microbial killing. They also function as antigen-presenting cells (APCs) to present ingested foreign antigens on their surfaces to other cells of the immune system such as T and B lymphocytes [30]. Likewise, dendritic cells, first described by Paul Langerhans (i.e., Langerhans cells) in the late nineteenth century, are another essential component of innate immunity. These cells originate in the bone marrow and are found in small quantities in tissues in contact with the external environment such as the skin, respiratory tract, and GI tract. When activated, they migrate to lymphoid organs where they also capture and process antigens and serve as highly efficient APCs. These APCs, through pattern recognition receptors, bind to lipopolysaccharides, peptidoglycans, lipoteichoic acids, mannan, bacterial DNA, and double-stranded RNA (collectively referred to as pathogen-associated molecular patterns or PAMPs) to aid in the recognition of pathogens [12, 31, 32].

Mast cells, while traditionally recognized for their role in allergic diseases, are also increasingly acknowledged for the important role they play in protection against infection [33]. They are leukocytes found in most tissues of the body, particularly in locations in close contact with the external environment, thus functioning as early immune sentinel cells at sites of pathogen entry. They contribute to host defense directly through phagocytosis and production of reactive oxygen species and antimicrobial peptides, and indirectly through release of histamine and other vasoactive mediators that increase vascular permeability and blood flow, and through their action on smooth muscle to help increase expulsion of mucosal parasites and to enhance mucus production to aid in pathogen immobilization and cytoprotection. Mast cells also produce chemotactic factors that can recruit inflammatory cells including eosinophils, natural killer cells, and neutrophils to sites of infection. Their role in protection against parasites including helminthes, nematodes, and protozoa is well known. More recently, their role in protection against bacterial infections, especially gram-negative infections, has been established. While there is some evidence that mast cells help mediate antiviral and antifungal immunity, this evidence is more limited. Cancer patients receiving corticosteroids and other immunosuppressive agents that decrease mast

cell activity may have compromised ability to respond in a timely manner to parasitic and bacterial infections.

Natural killer cells (NK cells) are lymphoid cells that, unlike T and B cells, lack antigen-specific receptors [34–37]. They are able to recognize cells as “self” versus “non-self” and to kill infected or stressed host cells very rapidly. As such, they are among the very early responders during infection. While they were originally recognized as playing a major role in the destruction of malignant and virally infected cells, it is now evident that NK cells play an important role in the effective control of a diverse array of pathogens, including viruses, bacteria, fungi, and parasites. While many of these infections can be contained in the absence of NK cells, clearance of these organisms is almost always more efficient and complete in the presence of a functional NK cell response.

Neutrophils are the single most important cells for defense against bacterial infection in cancer patients. They are recruited to the site of infection where they participate in phagocytosis and intracellular microbial killing. Neutropenia, commonly defined as an absolute neutrophil count (ANC) lower than 1,000 or 500 cells/mm³, primarily occurs in patients with acute leukemia or non-Hodgkin’s lymphoma and those who have received intensive myelosuppressive therapies for their underlying malignancies or as part of their hematopoietic stem cell transplantation (HSCT) [22, 38–40]. Patients with aplastic anemia are also likely to present with severe and persistent neutropenia, although unlike neutropenic patients with hematological malignancies, they may remain infection free for prolonged periods [41]. Although less common, solid organ tumors, such as metastatic carcinoma of the breast, prostate, lung, adrenal, thyroid, and kidney, can all infiltrate the bone marrow and result in neutropenia [22].

The absolute neutrophil count, the rapidity in the decline of the neutrophil count, the duration of neutropenia, and whether the count is rising or falling are all important determinants of infection risk. A large multicenter study by the European Organization for Research on Treatment of Cancer (EORTC) demonstrated that the change in granulocyte count was the most important factor in determining success or failure of antibiotic therapy for gram-negative bacteremia. Only 22 % of patients whose granulocyte count did not rise by at least 100 cells/mm³ during therapy were successfully treated, whereas 88 % of those whose count rose by at least 100 cells/mm³ had complete resolution of infection [42].

Whether due to the invasion and progression of the malignancy itself or to the treatments directed against it, destruction of anatomical barriers and deficits in non-specific humoral and cellular immunity diminish the host’s frontline, rapid response to infection.

Deficiencies in Adaptive Immunity

The adaptive immune system is antigen specific and exhibits immunological memory; thus, it requires time to react but can mobilize more rapidly, although not as rapidly as innate immunity, on repeat exposure to the same organism [16]. Adaptive immunity is comprised of both humoral and cellular components mediated through B and T lymphocytes, respectively.

Humoral immunity is mediated primarily by B lymphocytes that arise from precursor stem cells in the bone marrow and, following maturation, are distributed to the spleen and lymph nodes. Under proper antigenic stimulation, they differentiate into immunoglobulin (antibody)-producing plasma cells. These plasma cells produce opsonizing antibodies. Coating or opsonizing certain bacteria, particularly encapsulated bacteria, greatly enhances their phagocytosis. Patients with defects in humoral immunity lack opsonizing antibodies to the common encapsulated pyogenic bacteria and thus are susceptible to infections with organisms such as *S. pneumoniae*, *H. influenza*, and *N. meningitidis*.

Cellular immunity is mediated primarily by T lymphocytes. T lymphocyte precursors are released from the bone marrow and migrate to the thymus gland, where maturation occurs. Mature T lymphocytes then exit the thymus and are present in the circulation, the lymph nodes, and the spleen. During cell-mediated immunity, various T lymphocytes subsets are activated and develop into effector T cells, including cytotoxic T lymphocytes and T helper cells of the TH1 and TH2 subsets. TH1 cells secrete lymphokines that activate macrophages and mediate delayed-type hypersensitivity responses. TH2 cells secrete lymphokines that stimulate B-cell development and may help activate cytotoxic T cells.

Although Hodgkin's disease and human immunodeficiency virus (HIV) infection are the prototypical illnesses associated with cellular immune dysfunction, impairment of cell-mediated immunity can occur with most cancers, including acute and chronic leukemia; solid organ tumors such as breast, lung, brain, GI tract, and GU tract; and following HSCT [43–51]. Additionally, irradiation and medications such as azathioprine, cyclosporine, and corticosteroids can result in cellular immunodeficiency [52–54].

Several predominantly intracellular pathogens are associated with deficiencies of cell-mediated immunity. These include the bacteria *Listeria monocytogenes*, *Salmonella* spp., *Nocardia asteroides*, and *Legionella*; mycobacteria including both *Mycobacterium tuberculosis* and the non-tuberculous mycobacteria; fungi such as *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Pneumocystis jiroveci*; viruses such as varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV), and adenovirus; the protozoa *Toxoplasma gondii* and *Cryptosporidium*; and the helminth, *Strongyloides stercoralis* [27, 55–64].

2.1.2 Organ Dysfunction

Risk of infection due to compromise of epithelial and mucosal barriers is discussed above. In addition, risk is also increased due to organ compromise through tumor invasion, mechanical obstruction, and surgical resection.

Asplenia

The spleen, the largest reticuloendothelial organ in the body, contains monocytes, macrophages, dendritic cells, natural killer cells, and T and B cells, enabling it to perform many important functions of both innate immunity and adaptive

immunity. Its functions include recognition of antigens, clearance of opsonized and unopsonized particles from the bloodstream, and production of antibody, especially IgM, and other substances such as properdin, an important component of the alternate complement pathway and tuftsin, a peptide that potentiates granulocyte and macrophage motility, chemotaxis, and phagocytosis [65].

Cancer patients who have undergone splenectomy and those who are functionally asplenic such as HSCT recipients are at increased risk for infections with the encapsulated bacteria *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*. In fact, patients who undergo splenectomy for staging or treatment for a hematological malignancy have approximately a 5 % risk of developing overwhelming sepsis, usually with *S. pneumoniae*, at some time during their lifetime [66]. Although patients are at the greatest risk of sepsis within the first two years after splenectomy, one-third of cases may occur up to five years later, and cases have been reported after more than 20 years. Patients who have undergone splenectomy or who are functionally asplenic must be instructed regarding the risk of life-threatening infection. They should alert their healthcare providers about their asplenic state and should receive education regarding the need for early administration of oral antibiotic therapy for fevers; some authorities recommend lifelong prophylactic antibiotics for all immunosuppressed patients after splenectomy [67–69]. Asplenic patients should undergo immunization with pneumococcal, *H. influenzae*, meningococcal, and influenza vaccines, in addition to other vaccinations according to routine immunization schedules [70, 71].

Other Organ Dysfunction

Patients with primary or metastatic tumors of the central nervous system (CNS) are predisposed to a variety of infections. Those with either a partial or complete loss of the gag reflex are at increased risk for aspiration pneumonia. Patients with CNS tumors also frequently suffer from impaired micturition, leading to urinary retention and recurrent urinary tract infections, and from impaired mobility predisposing to skin breakdown with resulting decubitus ulcers and osteomyelitis. Interestingly, meningitis, encephalitis, and brain abscesses are uncommon in patients with CNS tumors unless related to problems of surgery [66, 72].

Patients with primary or metastatic lung tumors are particularly susceptible to recurrent pneumonia and to lung abscess formation due to decreased mucociliary clearance, bronchial obstruction, and postobstructive atelectasis. Local invasion of other malignancies such as those of the head and neck, breast, gastrointestinal and genitourinary tracts also predisposes to infection with the flora residing in these sites. In addition, malignancies such as lymphoma and carcinoma of the prostate, ovary, cervix, and rectum commonly obstruct the urinary tract, leading to urinary retention and recurrent urinary tract infections. Obstruction of the biliary tract by lymphoma, cholangiocarcinoma, or pancreatic cancer predisposes to ascending cholangitis. Tumors obstructing blood vessels and lymph nodes can cause septic thrombophlebitis, ischemia, and lymphedema, predisposing to infection. Importantly, when obstruction occurs as a result of tumor, eradication of the infection without relief of the obstruction is usually unsuccessful [11, 12].

2.1.3 Concurrent Illnesses and Past Infections

Increased infection risk has been noted in cancer patients with certain chronic illnesses. Studies have demonstrated that patients with type 2 diabetes and hyperglycemia have increased rates of wound and GU infections, fungal infections such as candidiasis and rhinocerebral mucormycosis, shorter remission periods, shorter median survival times, and higher mortality rates [73, 74]. One systematic review and meta-analysis by Barone and colleagues revealed that preexisting diabetes was associated with an increased risk of all-cause mortality compared to cancer patients without diabetes [75]. Although mortality risk reached statistical significance only for patients with endometrial, breast, and colorectal cancers, diabetes appeared to pose some additional mortality risk for all cancer types studied. In another systematic review and meta-analysis, Barone et al. found that cancer patients with diabetes were approximately 50 % more likely to die following surgery than their non-diabetic counterparts [76]. Risk of infection with pulmonary and rhinocerebral mucormycosis is also increased in cancer patients with iron overload treated with deferoxamine [77, 78].

Obesity also increases infection risk in cancer patients, especially those undergoing oncologic surgery [79–81]. Studies in patients with colon, breast, and bone and soft tissue tumors have demonstrated that patients with morbid obesity and those specifically with obesity defined by visceral fat area were more likely to suffer wound dehiscence and surgical site infection.

Cancer patients previously infected with certain organisms are at increased risk of infection reactivation, especially when undergoing immunosuppressive therapies; thus, obtaining a thorough infectious disease history prior to therapy is essential in this population. Questions should include exposures at home, work and in healthcare settings, habits, and hobbies. Also, a thorough travel history may provide clues for an otherwise improbable diagnosis. Organisms of concern include *Mycobacterium tuberculosis*; viruses such as HSV-1, HSV-2, CMV, VZV, and hepatitis B; fungi such as *Aspergillus* spp., histoplasmosis, blastomycosis, coccidioidomycosis, and *Pneumocystis jirovecii*; and parasites such as *Toxoplasma gondii*, *S. stercoralis*, and *Trypanosoma cruzii* [14, 82]. Physicians caring for these patients should familiarize themselves with the guidelines for monitoring and, in some cases, providing prophylaxis for these pathogens. *Clostridium difficile* disease is common in cancer patients and can recur or relapse, primarily due to ongoing receipt of antimicrobial agents; however, some chemotherapeutic agents have also been associated with *C. difficile* disease including methotrexate, paclitaxel, and carboplatin [83–89]. Likewise, previous infection and/or colonization with drug-resistant bacteria such as vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, fluoroquinolone-resistant gram-negative bacteria, extended-spectrum beta-lactamase-containing gram-negative bacteria (ESBLs), and, increasingly, carbapenem-resistant bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* is a risk factor for subsequent infection with these organisms. Clinicians should be aware of past

infection and colonization status with drug-resistant pathogens to help facilitate empiric antimicrobial choices when infections arise [14, 82].

2.1.4 Nutritional Status

Significant weight loss, defined as a loss of at least 10 % body weight within 6 months, and malnutrition are poor prognostic indicators and are common problems among cancer patients. In some studies, approximately 60 % of patients with lung cancer and 80 % of patients with upper GI tract cancers have significant weight loss at the time of diagnosis, and the prevalence of malnutrition ranges from 30 to 80 %, depending on the definition used and the underlying malignancy. For instance, patients with GI tract cancers, especially those of the head and neck, are the most likely to suffer from weight loss and malnutrition. In addition, nutritional status is often jeopardized by the natural progression of neoplastic diseases. Protein-calorie malnutrition stemming from inadequate intake of carbohydrate, protein, and fat to meet metabolic requirements and/or the reduced absorption of macronutrients is the most common secondary diagnosis in individuals diagnosed with cancer [90–93].

Many factors lead to these conditions, including anorexia, nausea, vomiting, diarrhea, constipation, stomatitis, mucositis, dysphagia, alterations in taste and smell, pain, depression, and anxiety. Anorexia is typically present in 15–25 % of all cancer patients at diagnosis, may occur as a side effect of treatments, is almost universal in patients with widely metastatic disease, and can hasten the progression to cachexia, the most severe form of malnutrition. Cachexia is characterized by the loss of lean body mass, muscle wasting, and impaired immune, physical, and mental function. It is estimated to be the immediate cause of death in 20–40 % of cancer patients, especially those with GI malignancies [90].

Cancer cachexia is a complex process that is thought to result from the actions of both host- and tumor-derived factors. Increasing evidence from both animal models and clinical studies supports that a systemic inflammatory response to the tumor, mediated in part by the dysregulated production of proinflammatory cytokines, induces an acute-phase protein response and produces alterations in lipid and carbohydrate metabolism. In addition, there is growing appreciation that cachexia represents the end product of an inappropriate interplay between these cytokines, neuropeptides, classic stress hormones, and intermediary substrate metabolism [90].

These nutritional deficiencies are associated with increased risk of infection, increased antimicrobial use, increased hospital stay, decreased quality of life, and increased mortality. A prospective study examined the effects of preoperative enteral immunonutrition on development of surgical site infections (SSIs) in patients with colorectal cancer [94]. Immunonutrition consisting of an enteral diet supplemented with arginine, dietary nucleotides, and omega-3 fatty acids was given to study subjects for five days prior to bowel surgery, and SSI outcomes were compared to a control group. Patients receiving the immunonutrition experienced fewer SSIs than the control group [95]. Similarly, reduced infection rates

were reported in a systematic review of immunonutrition in critically ill patients, including those with malignancy [93]. In addition to these studies, other investigators have reported that malnutrition impairs scar formation and increases the risk for surgical complications such as suture dehiscence and infections [96]. Because poor nutritional status is so prevalent and portends worse outcomes, early detection of risks for malnutrition and ongoing nutritional assessments should be a standard part of the quality of care in oncology practices [97].

2.1.5 Psychological Stress

For decades, clinical observations have suggested that psychological stress plays a role in susceptibility and response to certain infections. Recently, rapid advances in immunology have provided experimental evidence that acute and chronic stress can alter the immune response to viral challenges, vaccine response, and wound healing [98, 99]. One recent systematic review supports the concept that stress, anxiety, and depression are risk factors for acute viral respiratory tract disease acquisition and progression [100]. Stress activates the major neural pathways of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. The mediators they release can, in turn, induce pronounced changes in components of both the innate and adaptive immune responses, including cytokines, macrophages, natural killer cells, and T lymphocytes [101, 102]. Although individual response to stress varies, chronic high-level stress, as experienced by many cancer patients, is thought to be detrimental. Much remains to be learned regarding the complex interplay between physical health and psychological health in these patients [103].

2.2 Treatment-Associated Factors

Although essential to patient care, no procedure or treatment is without risk. The following treatment-associated factors have all been shown to predispose patients with underlying malignancies to an increased risk of infection.

2.2.1 Surgery

Extensive surgery, especially in the maxillofacial, gastrointestinal, or pelvic regions, increases the risk of infection in cancer patients [22, 104]. Although extensive procedures are often necessary, especially for advanced invasive tumors, they remove large areas of otherwise protective tissue and disrupt anatomical barriers that predispose to leakage of material already containing bacterial flora. The infectious complications following surgery vary depending on the site and extent of the operation and the type of procedure performed; even so, postoperative infections have been shown in one series to be twice as common in cancer versus non-cancer patients [105, 106].

Intra-abdominal procedures such as Hartmann's operation, which involves sigmoid resection with a diverting colostomy, are frequently complicated by

infection in patients with underlying malignancies [107]. Likewise, cancer patients undergoing craniotomy who have previously had a ventriculoatrial shunt placed are at increased risk of meningitis and/or sepsis [108]. Extensive surgery of the paranasal sinuses has also been shown to predispose to *Pseudomonas* meningitis in these patients [109]. Postoperative cellulitis is frequently reported after breast cancer surgery [110, 111]. The extent of the operation plays a major role in determining infection. As expected, the largest interventions are associated with the maximum risk. Other factors such as obesity and diabetes can also increase the infectious risk in these patients as previously described. Reduced infection rates may be associated with recent advances in minimally invasive surgery [112, 113] and, as previously stated, in patients who receive preoperative immunonutrition.

Neutropenic enterocolitis (typhlitis) is the most common gastrointestinal tract infection related to neutropenia and is the most ominous. In one review of 438 leukemic patients, the incidence of major gastrointestinal complications, including typhlitis, was 13 % [114]. Another study estimated the incidence of typhlitis to be at least 5 % in adult patients receiving chemotherapy for solid malignant tumors, with mortality rates ranging from 30 to 50 % [115]. The surgical management of patients with typhlitis is a frequently encountered although controversial issue. Along with the increased risk of infection, these neutropenic and usually thrombocytopenic patients have a high risk of operative mortality from the surgery itself. Consequently, the care of these patients should be individualized. Non-operative management with bowel rest, decompression, nutritional support, and broad-spectrum antibiotics is often successful and is usually recommended initially. Operative intervention is typically reserved for patients with bowel perforation and uncontrollable hemorrhage, or for those whose clinical condition deteriorates despite conservative management [115, 116].

2.2.2 Radiation Therapy

In addition to surgery, preoperative irradiation increases the risk of infection. In one series, preoperative irradiation given to patients undergoing surgery for breast cancer was associated with a twofold increase in infectious complications. However, postoperative irradiation was not associated with an increased risk [117]. Infection is also the most common complication in patients who receive preoperative irradiation prior to oncologic surgery of the upper respiratory or gastrointestinal tract. This is predominantly due to fistula formation or impaired wound healing [118] and has been well described in patients receiving radiation therapy for rectal cancer. In addition to causing local tissue damage, radiation can result in stenosing lesions, leading to obstruction [22].

Some studies have reported genital condyloma, following pelvic irradiation therapy [119]. Opportunistic infections such as *P. jirovecii*, *Aspergillus terreus*, and CMV have been reported following the use of radiation in combination with temozolomide, an alkylating agent, in the treatment for glioblastoma. Radiation of the spleen or lymph nodes can depress cell-mediated immunity and antibody production. Total body irradiation predictably results in substantial depression of

cellular immune function for months to years and can result in prolonged marrow depression and neutropenia [72].

Radiation reactions such as radiation enhancement and radiation recall predispose to infection due to local tissue inflammation and breakdown [120–124]. Radiation enhancement, also called radiation sensitization or radiosensitization, is defined as occurring within seven days of radiation exposure and is postulated to be due to the effect of medications that either enhance the initial radiation tissue damage or hinder repair of the tissues after exposure. Radiation recall, or radiation recall dermatitis, is an acute inflammatory reaction that occurs in previously irradiated areas precipitated by the initiation of certain drugs, primarily chemotherapeutic agents. By definition, it occurs more than seven days after the initial radiation exposure and can manifest weeks to years after initial radiation. These reactions frequently result in localized skin erythema but can progress to ulceration and necrosis. Although uncommon, radiation recall can also affect the gastrointestinal tract, lungs, muscles, and brain.

2.2.3 Immunosuppressant Therapies

Chemotherapy

Chemotherapeutic agents predispose to infection in a variety of ways [22, 125]. Many of these agents damage the body's anatomical barriers. Most notably, they can cause ulceration of the gastrointestinal tract, allowing for erosion and invasion by endogenous microorganisms. Other agents such as bleomycin and methotrexate are associated with skin lesions that can predispose to bacteremia with staphylococci and other skin flora. Agents such as BCNU, Ara-C, and daunorubicin irritate veins, increasing the risk of phlebitis and subsequent bacteremia. Many chemotherapeutic agents cause bone marrow suppression and neutropenia in a dose-related fashion. Some of these drugs can also inhibit neutrophilic migration and chemotaxis. Regimens that include corticosteroids inhibit the bactericidal activity of neutrophils. Humoral immunity is altered by agents such as methotrexate, cyclophosphamide, and 6-mercaptopurine. Deferoxamine, an iron-chelating agent, is associated with increases in bacterial infections and zygomycosis, most likely due to the increased availability of free iron necessary for fungal growth [77, 78].

Biological Response Modifiers

Biological response modifiers (BRMs) are naturally occurring substances often used in conjunction with chemotherapeutic agents that help boost, direct, or restore the body's immune response to cancer cells. They include interferons, interleukins, hematopoietic growth factors, monoclonal antibodies, components of vaccines and gene therapy, and non-specific immunomodulating agents such as bacillus Calmette–Guerin, used in the treatment for bladder cancer, and levamisole, sometimes used in combination to treat colon cancer. The immunotherapeutic actions of BRMs can be passive or active. The effects of monoclonal antibodies are passive in that they are targeted to antigens or receptor sites on cancer cell surfaces. When

the antibody binds to the target, a cascade of events leads to tumor cell death, usually without invoking an immune response. Conversely, other BRMs work by actively evoking either a non-specific immune response to cancer cells as with interferons and interleukins or a specific immune response as with cancer vaccines [126–130].

Clinicians should be aware that adverse effects of BRMs, especially monoclonal antibodies, interleukins and interferons, can mimic infection as they can precipitate a flu-like reaction with fever, chills, headache, myalgias, and arthralgias. Prolonged symptoms, however, should prompt an evaluation for infection [131]. Monoclonal antibodies such as alemtuzumab, rituximab, and trastuzumab may cause myelosuppression, and, in the case of alemtuzumab, profound and persistent lymphopenia, predisposing to viral and fungal infections. One study demonstrated that cancer patients with HIV receiving rituximab in addition to their chemotherapy had a 12 % increase in infection-related deaths and an increased rate of opportunistic infections [132]. Another study demonstrated that patients with lymphoma receiving rituximab maintenance therapy had higher rates of infection and neutropenia [133]. Because interleukin-2 induces a reversible but profound defect in neutrophilic chemotaxis, high doses used in the treatment for renal cell carcinoma and melanoma have been associated with infection rates between 13 and 38 %. These consist primarily of urinary tract infections and central venous catheter-associated bloodstream infections [134].

2.2.4 Antimicrobial Use

A patient's intact normal flora protects the surfaces of the skin and mucous membranes by competing with non-indigenous organisms for binding sites and by producing substances that inhibit or kill these microorganisms. The use of antimicrobial agents can radically alter host flora, predisposing to infection. To understand the changing microbial flora, it is important to understand a concept known as *colonization resistance*. Individuals are colonized with non-invasive flora that, in a sense, can be considered "protective." This normal flora prevents colonization and subsequent infection with more invasive, pathogenic bacteria. Patients who have lost their normal flora, such as those receiving broad-spectrum antibiotics, are at greater risk of colonization and infection with these more invasive organisms. In an animal model of infection, van der Waaij elegantly depicts this phenomenon. In this study, three groups of mice were used: One group was rendered completely germ free, a second group retained their anaerobic flora but were rendered free of aerobes, and the third group of normal mice served as the control. The mice were given different oral doses of streptomycin-resistant *E. coli* for ease of detection, and persistent colonization was determined by the evaluation of fecal flora. The control group required 10^7 *E. coli* to become persistently colonized, the mice with only anaerobic flora required approximately 10^5 *E. coli*, and the germ-free mice, who had no colonization resistance, required only 10^1 to 10^2 *E. coli* [135].

Dramatic changes in microbial flora can also occur in debilitated patients. In a study by Johanson and colleagues, throat cultures were obtained from normal volunteers and from patients hospitalized on a psychiatric ward, an orthopedic ward, and two medical wards. The patients on both medical wards had severe underlying medical illnesses; on one ward, they were receiving antibiotics, and on the other, they were not. Throat cultures from the normal volunteers and the psychiatric patients revealed normal flora. However, the throat cultures from 16 % of the orthopedic patients, 57 % of the medical patients without antibiotics, and 80 % of the medical patients with antibiotics revealed gram-negative bacilli [136]. This suggests that severity of illness and antibiotics, not hospitalization per se, is associated with changes in endogenous flora; in fact, of all the predisposing conditions, antibiotic use is the single most important factor leading to changes in host flora.

Although necessary for both infection prophylaxis and treatment, antimicrobial agents can cause rapid and radical alterations in endogenous flora. Certain antimicrobial agents such as penicillin, rifampin, clindamycin, macrolides, bacitracin, and vancomycin significantly impair colonization resistance, probably because they inhibit gram-positive, non-sporulating, lactic acid-producing bacilli, such as *Bifidobacterium* spp. Other agents such as chlorhexidine mouthwashes used to minimize plaque and gingivitis and H2 receptor antagonists that reduce gastric acidity also influence the microflora. Loss of gastric acidity and passage and survival of oral flora such as alpha-hemolytic streptococci into the bowel may account in part for its pathogenesis in cancer patients. Another common example is *C. difficile* colonization and infection induced by antibiotic therapy [83, 137]. In general, however, broad-spectrum antibiotics are more apt to suppress normal, non-invasive flora, particularly anaerobes, and to cause a shift toward gram-negative bacteria and yeast. Increasing data demonstrate that interactions between hosts and the microflora are markedly dynamic, and these interactions are an area of intense research interest [12, 138–142].

In addition to altering the type of microflora, antimicrobial use selects for resistant organisms [12, 143, 144]. Examples of this have been proven repeatedly in cancer patients. Historically, trials of non-absorbable antibiotics were used to decrease colonization of the alimentary canal. These trials were halted in part due to the emergence of resistant organisms. In one study, surveillance cultures were monitored in 10 patients receiving ampicillin for 3 weeks. Nine of these patients became rapidly colonized with ampicillin-resistant gram-negative bacilli, and several isolates were multiply drug resistant, while only one patient in the control group acquired a multidrug-resistant organism [145]. The total amount of ceftazidime, the duration of therapy, and the number of days of therapy with this agent have all been implicated in the emergence of vancomycin-resistant *E. faecium* bacteremia. Fluoroquinolone use in neutropenic cancer patients is associated with an increase in infections with resistant staphylococci, streptococci, and anaerobes, as well as increased fluoroquinolone resistance in gram-negative bacilli. Likewise, incidence of antimicrobial-resistant fungal infections is related to prophylaxis and treatment. Fluconazole prophylaxis has resulted in the development of resistant

strains of *C. albicans* and non-*albicans Candida* spp. [146–149] and to outbreaks of inherently fluconazole-resistant *Candida krusei* [150, 151].

Although antibiotic use in cancer patients is essential in many situations, the emergence of resistant organisms is dramatically increasing, can be directly linked to antibiotic selective pressure, and poses a major health threat to all patients, especially to those who are immunocompromised.

2.2.5 Diagnostic and Invasive Procedures

Any procedure that breaks the natural protective barrier between the internal environment and external environment can allow entry of microorganisms and predispose to infection. Biopsies, bone marrow aspirations, endoscopy, and indwelling vascular and urinary catheters are but a few examples. Strict attention to sterile technique, when applicable, can decrease but cannot completely eliminate the infectious risk associated with these procedures.

Central Venous Catheters

Although indwelling venous access devices are commonly required in cancer patients, infection is a common and often severe complication. Each year in the United States, more than five million central venous catheters are inserted, resulting in up to 80,000 catheter-related bloodstream infections and up to 28,000 deaths [152–154]. The risk of infection varies with the device used, duration of placement, and extent of the patient's immunosuppression. In general, the risk of infection is the greatest for non-tunneled catheters, followed by peripherally inserted central catheters (PICCs), tunneled catheters, and implanted ports. Multilumen catheters may increase the risk of infection [155]. Catheters placed in the femoral vein are associated with greater risk than those placed in the subclavian or internal jugular veins [156]. To decrease the infection risk, the catheters should be inserted by well-trained providers who adhere to a clinical care bundle that outlines steps for proper catheter insertion and maintenance and removal of the catheter as soon as it is no longer needed [156, 157].

The most common causative pathogens are CoNS, *S. aureus*, enterococci, streptococci, and *Candida* spp., although infections with skin commensals, such as *Bacillus* spp., *Corynebacterium* spp., are also encountered [152, 158]. Gram-negative bacilli do occur but are less frequently encountered. The rapidly growing non-tuberculous mycobacteria, *M. chelonae* and *M. fortuitum*, have been associated with exit site or tunnel infections [153, 159].

Clinical diagnosis of infection can be difficult as local signs and symptoms such as erythema and tenderness are inconsistent and, even if present, can be unreliable indicators of catheter infection even in immunocompromised patients. The evolution of these signs over time, however, is suggestive of infection. Venous access device infections are categorized as entry site infections, tunnel or pocket infections, and catheter-associated bloodstream infections.

Entry site infections can often be treated effectively with appropriate antimicrobial therapy, without the need for catheter removal. Tunnel and pocket

infections necessitate catheter removal as well as immediate initiation of an empirical antimicrobial therapy that includes vancomycin to cover methicillin-resistant *S. aureus* until culture results are available.

It is often especially difficult to determine whether a bloodstream infection is related to the venous access device because frequently, no evidence of local catheter inflammation is seen. Recently, however, the concept of differential time to positivity has been used to distinguish venous-access-device-related infections from other types of infection, as follows: If the times at which blood cultures become positive (by machine detection in the clinical microbiology laboratory) are more than 2 h apart for simultaneously obtained catheter and peripheral vein blood cultures, the catheter is then strongly implicated as the source of the infection. Although this differential may help determine whether a catheter can be retained or must be removed, most indwelling catheter-related infections will respond to antimicrobial therapy alone, without catheter removal; however, some authors suggest that catheter salvage should be attempted cautiously for neutropenic cancer patients with gram-negative bacteremia [160, 161]. Certain exceptions are notable: Catheter removal is advisable for patients with bloodstream infections caused by fungi and non-tuberculous mycobacteria. For other bacteria, the decision concerning the need for catheter removal will depend on the severity of the clinical picture, the degree of immunosuppression, and the availability of an alternative vascular access site in a given patient. *S. aureus* may cause endocarditis, and the value of transesophageal echocardiography in the setting of any *S. aureus* bloodstream infections has been well demonstrated to determine the duration of therapy. In general, if blood cultures remain positive despite appropriate antimicrobial therapy for more than 48 h, or if the patient is clinically unstable, the catheter should be removed independent of etiology [154, 161].

Other Invasive Procedures

Other invasive procedures, such as placement of urinary catheters or tracheostomies, can also alter normal flora. Urinary catheters can become colonized with organisms that track along the catheter and colonize these normally sterile body sites. Patients with tracheostomies generally become colonized with gram-negative bacteria within a few days following placement. If pneumonia develops, it is usually due to these same bacterial pathogens with which the patient is colonized. Indeed, the majority of patients are infected with the organisms with which they are colonized; however, 50 % of these organisms are acquired after hospitalization [162]. Studies have demonstrated that serial axillary surveillance cultures grow primarily *S. epidermidis* and *Corynebacterium* spp. on admission. As illness and hospitalization progress, however, the resident flora shifts toward gram-negative bacteria such as *K. pneumoniae* and *P. aeruginosa*; *E. faecium*; less common organisms such as *Clostridium septicum*; and yeast such as *C. albicans* [145, 163].

Blood Transfusions

Nosocomially acquired infections from blood transfusions occur despite modern blood banking techniques designed to prevent this complication. Cancer patients,

especially those with hematological malignancies or those undergoing HSCT, often require several transfusions during the course of their illness and thus are at increased risk of transfusion-related infection [164–166].

Contamination of blood products can occur during processing and storage, but most commonly occurs through collection of blood from infected donors [166, 167]. For an organism to cause an infection in a transfused patient, it must (1) be present in the donor's blood at the time of collection while producing few or no symptoms; (2) escape detection by current screening methods; (3) remain viable in citrated, refrigerated blood for prolonged periods of time; and (4) be of sufficient virulence and quantity to produce infection in the transfusion recipient [168].

Viruses are the most frequently encountered pathogens associated with blood transfusions. These include hepatitis viruses, HIV, EBV, and CMV. Although most of these are detected by present screening procedures, CMV remains a significant risk for cancer patients [169].

Protozoal diseases, such as leishmaniasis, trypanosomiasis, Chagas' disease, and microfilarial infections, are acquired through transfusion in developing countries. An increased incidence of transfusion-related Chagas' disease has also been reported in the United States. Malaria is uncommon in the United States but does occur, especially in people who have returned from travel in endemic areas. Therefore, transfusion-related malaria remains a potential risk in this country [170–173]. *Babesia microti*, a tick-borne protozoan parasite, has been transmitted through transfusion along coastal regions of the Northeastern United States. It can cause a life-threatening infection in immunocompromised, especially asplenic, patients [171, 174].

The procedure of storing citrated blood at 4 °C for prolonged periods has greatly reduced the risks of transfusion-transmitted bacterial infections. Although up to 6 % of stored blood contains some form of bacterial contamination, most of these organisms are normal skin flora such as *S. epidermidis* and diphtheroids, which do not cause significant infections in transfusion recipients. Conversely, *Pseudomonas fluorescens/putida* and *Yersinia enterocolitica* can survive and multiply in cold storage, and these organisms have been associated with life-threatening sepsis, following blood transfusions [175, 176]. Platelets are often stored at room temperature to enhance their posttransfusion function. Thus, bacterial infections are more likely to occur following platelet transfusions [177].

3 Commonly Encountered Pathogens by Type of Malignancy

The type of malignancy, the status of the malignancy (i.e., active or in remission), and the intensity of the treatments directed against it are all important factors in determining infection risk. Better data exist for incidence and etiology of infections in patients with hematological malignancies, especially those undergoing

treatment for acute leukemia and lymphoma, than for other malignancies. This is especially true for patients who develop neutropenia as a result of their immunosuppressive therapies. This section will outline infections commonly encountered in clinical practice stratified by type of malignancy (Table 3).

3.1 Acute Leukemia and Lymphoma

Patients with acute leukemia and lymphoma who are neutropenic, either due to their underlying disease or due to cytotoxic chemotherapy, are at risk for a different set of infections than those who are not neutropenic. The epidemiology of infection in neutropenic cancer patients undergoes periodic change and is often subject to geographic and institutional factors; however, certain trends are consistent. Approximately half of the episodes of neutropenic fever will have no clinical site or causative pathogen identified, while 20–30 % will have clinical signs of infection such as pneumonia or cellulitis but negative microbiological cultures. Only 25–30 % of episodes will have a microbiologically documented infection, with the most common sites being the bloodstream, urinary tract, respiratory tract, skin and soft tissues, and gastrointestinal tract. A small proportion, generally less than 5 %, will have non-infectious causes of fever, such as tumor or drug fever, identified [40, 178].

Classically, gram-negative bacilli such as *E. coli*, *Klebsiella* spp., and *P. aeruginosa* cause the earliest infections in neutropenic patients. These usually occur within the first 2–3 weeks after the initiation of chemotherapy and are due to the rapid decrease in the neutrophil count. These infections are characterized by acute febrile episodes, which can progress to overwhelming sepsis if not treated promptly [179–184]. However, beginning in the 1980s, investigators noted a relative decrease in the number of gram-negative bacteremia and a significant increase in infections caused by gram-positive aerobic bacteria, namely staphylococci and streptococci. These observations persist in more recent studies, with gram-positive pathogens causing approximately 50 % of microbiologically documented infections, and up to 75 % if only bloodstream infections are considered. Gram-negative organisms now account for 20–25 % of infections, and another 20–25 % are polymicrobial. Isolated anaerobic bacterial infections occur very infrequently. Fungal and viral infections occur much later in the course of neutropenia, and some viral infections occur seasonally, such as respiratory viral infections [178].

Several reasons for the increase in gram-positive infections have been postulated [125]. The use of both prophylactic and empiric antibiotic regimens targeting gram-negative bacteria diminishes recovery of gram-negative pathogens while selecting for gram-positive infections [185, 186]. One example is the emergence of streptococcal infections in populations of patients receiving fluoroquinolones [187]. The use of intravascular catheters also increases the likelihood of infection with gram-positive bacteria, such as staphylococci, that colonize the skin [186].

Table 3 Infections related to underlying malignancy

Malignancy	Immunodeficiency	Common pathogens and syndromes
Acute leukemia and lymphoma	Neutropenia	Bacteria
		Gram positive: <i>S. aureus</i> , <i>S. epidermidis</i> , streptococci, enterococci
		Gram negative: <i>E. coli</i> , <i>Klebsiella</i> spp., <i>P. aeruginosa</i>
		Yeast/fungi
		<i>Candida</i> spp.
		<i>Aspergillus</i> spp.
		Viruses
		HSV
		VZV
		CMV
	Cell mediated (in the non-neutropenic)	Bacteria
		<i>L. monocytogenes</i> , <i>Salmonella</i> spp., <i>N. asteroides</i> , mycobacteria, <i>L. pneumophila</i>
		Yeast/fungi
		<i>C. neoformans</i>
		<i>Aspergillus</i> spp.
		Viruses
		HSV
		VZV
		CMV
		EBV
		Protozoa
		<i>P. jiroveci</i>
		<i>T. gondii</i>
		<i>Cryptosporidium</i>
		Helminth
		<i>S. stercoralis</i>

(continued)

Table 3 (continued)

Malignancy	Immunodeficiency	Common pathogens and syndromes
Chronic lymphocytic leukemia	Hypogammaglobulinemia	Bacteria
		<i>S. pneumoniae</i>
		<i>H. influenzae</i>
		<i>N. meningitidis</i>
Multiple myeloma	Humoral; complement deficiency; neutropenia in late-stage disease	Bacteria
		<i>S. pneumoniae</i>
		<i>H. influenzae</i>
		<i>N. meningitidis</i>
		See pathogens associated with neutropenia above
Hairy cell leukemia	Cell mediated; neutropenia in late-stage disease	Bacteria
		<i>Salmonella</i> spp.
		<i>L. monocytogenes</i>
		<i>M. kansasii</i>
		<i>M. avium</i>
		<i>M. chelonae</i>
		Yeast
		<i>Candida</i> spp.
		<i>C. neoformans</i>
		Viruses
		HSV
		CMV
		See pathogens associated with neutropenia above

(continued)

Table 3 (continued)

Malignancy	Immunodeficiency	Common pathogens and syndromes
Solid tumors	Disruption of anatomical barriers	Skin
		Staphylococci
		Streptococci
		Oral cavity and nasopharynx
		Anaerobic bacteria
		Streptococci
		<i>H. influenzae</i>
		GI tract
		Enterobacteriaceae
		Fungi
		Female genital tract
		Enterobacteriaceae
		Anaerobic gram-negative bacteria
		Enterococci
		<i>Clostridium</i> spp.
	Mechanical obstruction	Biliary, urinary, and respiratory tract infections; vascular obstruction
	Loss of gag reflex	Aspiration pneumonia
	Impaired micturition	Recurrent urinary tract infections
	Impaired mobility	Decubitus ulcers with or without osteomyelitis

Chemotherapeutic regimens that cause oral mucositis predispose to infection with bacteria that ordinarily colonize the oropharynx, namely alpha-hemolytic streptococci. Although the mortality associated with gram-positive infections is less than that of gram-negative infections, the morbidity is significant. For example, alpha-hemolytic streptococci have been associated with cases of acute respiratory distress syndrome (ARDS) in patients receiving cytarabine [187]. Furthermore, patients who remain neutropenic for prolonged periods of time are more likely to develop infections with drug-resistant bacteria such as *Enterococcus* spp., *Corynebacterium jeikeium*, *Serratia* spp., *Enterobacter* spp., *Acinetobacter* spp., *Pseudomonas cepacia*, and *Stenotrophomonas (Xanthomonas) maltophilia*. These emerge as a consequence of protracted courses of broad-spectrum antibiotics [188, 189].

Because neutrophils play a major role in controlling infections due to *Candida* and *Aspergillus*, invasive fungal infections are also frequently encountered in neutropenic patients [188–198]. Autopsy series have documented invasive fungal infections in 10–40 % of patients with underlying hematological malignancies

[45, 191, 199]. Besides prolonged neutropenia, extended hospital stays, previous antibiotics, corticosteroids, central venous catheters, and total parenteral nutrition are also risk factors for fungemia. In addition, many other uncommon fungi have been reported to cause infection in this patient population.

Viruses commonly infect neutropenic hosts. Reactivation of HSV is by far the most common viral infection encountered. VZV, CMV, adenovirus, and the viral hepatitis have also been reported in the neutropenic patient with acute leukemia or lymphoma [200–206]. In the neutropenic patients with leukemia or lymphoma, common sites of infection include the bloodstream; the GI tract, including the mouth, bowel, and perianal region; the respiratory tract; and skin and soft tissues. Bacterial infections predominate, followed by fungal infections and then by viral infections. Parasitic infections are uncommonly encountered.

Fewer data exist on the types of infections encountered in the non-neutropenic host. In one study that included non-neutropenic patients with leukemia and lymphoma, the most common sites of infection were the respiratory tract, secondary bloodstream infections due to gram-negative bacilli, and the GU tract. Primary bloodstream infections were encountered less frequently than in neutropenic hosts; however, when they occurred, they were most often due to gram-positive cocci. Oral infections were also less common in the non-neutropenic host. In this series, no differences were noted in the incidence of fungal, viral, or parasitic infections [207]. Other investigators have demonstrated that polymicrobial bacteremia is more common in the non-neutropenic host [208].

Often, non-neutropenic patients with leukemia or lymphoma have defects in cell-mediated immunity, due either to their underlying disease or to the treatment regimens they receive. This cellular immunodeficiency can predispose to infections with a variety of intracellular organisms after neutrophil recovery. Bacterial infections caused by *L. monocytogenes*, *L. pneumophila*, *Salmonella* spp., *M. tuberculosis*, the non-tuberculous mycobacteria, and *Nocardia* spp. may be encountered. In addition, some patients will have undergone splenectomy, increasing the risk for infection with *S. pneumoniae*, *H. influenza*, and *N. meningitidis* [209]. Fungal infections other than *Cryptococcus* and occasionally *Aspergillus* are uncommon. When aspergillosis occurs in these patients, risk factors such as higher daily doses of corticosteroids, treatment with OKT3, and renal failure often exist [198]. Mucormycosis can rarely occur in the non-neutropenic population but is pathologically associated with less extensive angioinvasion [196]. Protozoal infections, on the other hand, are much more common in the non-neutropenic patient. Infections with *P. jiroveci*, *T. gondii*, *S. stercoralis*, and *Cryptosporidium* have all been reported [57, 61, 64]. Viral infections such as HSV, VZV, and CMV can be encountered in these patients, especially due to reactivation disease [145, 210].

3.2 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) represents a clonal expansion of neoplastic B lymphocytes in more than 95 % of cases. These mature-appearing B lymphocytes are found in the peripheral blood. They also infiltrate the bone marrow, spleen, and lymph nodes. Much of the gamma globulin produced by patients with CLL is non-functional, leading to defects in humoral immunity [211, 212]. The hypogammaglobulinemia may be profound in these patients, worsens as the disease progresses, and does not revert after chemotherapy, increasing the risk for infections with the encapsulated bacteria *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* and with *E. coli* [213]. Additionally, defects in cell-mediated immunity, complement activity, and neutrophil and other phagocytic cell defects exist either due to the disease or as a result of the therapies. Treatment modalities such as alkylating agents with or without corticosteroids predispose to streptococcal, staphylococcal, and enteric gram-negative bacterial infections. In these patients, the infections often occur at mucosal sites, especially the respiratory tract, and recurrent infections are common. Treatments with purine analogs or the monoclonal antibody alemtuzumab predispose to opportunistic infections with *Listeria* spp., *M. tuberculosis*, *Nocardia* spp., *Candida* spp., *Aspergillus* spp., *Pneumocystis jiroveci*, and herpesviruses [211, 212, 214]. More recently, progressive multifocal leukoencephalopathy (PML) caused by JC virus has been described in CLL patients treated with the purine analog fludarabine and with various monoclonal antibodies [215].

3.3 Multiple Myeloma

Like CLL, patients with multiple myeloma (MM) classically present with defects in humoral immunity. MM patients are hypogammaglobulinemic, producing normal immunoglobulins at only 10 % the normal rate. Therefore, they are predisposed to infections with the encapsulated bacteria such as *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* [25, 27, 216–218]. As disease progresses, the malignant plasma cells proliferate within the bone marrow to such an extent that the marrow is unable to produce adequate numbers of neutrophils. Therefore, patients with advanced disease may become neutropenic, increasing their risk of gram-negative bacterial infections [216, 219]. In recent years, however, the advent of new treatment modalities, such as HSCT and the novel antimyeloma agents, bortezomib, thalidomide, and lenalidomide, has improved outcomes for multiple myeloma patients and transformed it into a chronic disease. The resulting cumulative immunosuppression has increased the risk of infection and expanded the spectrum of potential pathogens in this patient population to include infections such as *C. difficile*, CMV, and opportunistic molds [220].

3.4 Hairy Cell Leukemia

This chronic B-cell lymphoproliferative disorder presents with cytopenias in the majority of patients. In particular, patients have monocytopenia, granulocytopenia, and defective T-cell function. This results in a cellular immunodeficiency and predisposes to a variety of infections. In fact, in one study, the major risk factor for the development of severe infection was lymphocytopenia [221]. As with other patients, the neutropenia predisposes to gram-negative bacterial infections. Defects of cell-mediated monocyte/macrophage and T-cell function predispose to other bacterial infections with organisms such as *Salmonella* and *Listeria*; fungal infections with *Candida* and *Cryptococcus*; viral infections with HSV and CMV; and non-tuberculous mycobacterial infections with *M. kansasii*, *M. avium* complex, and *M. chelonae* [222–225]. In one review from the University of Chicago, five of nine hairy cell leukemia patients with non-tuberculous mycobacterial infections had disseminated disease at presentation [226].

3.5 Solid Organ Tumors

Patients with solid organ tumors do not have the same risk of infection as patients with underlying hematological malignancies. This is largely because the standard chemotherapeutic regimens used to treat these malignancies do not usually result in either long-term or profound neutropenia. Exceptions include patients with small cell carcinoma of the lung, testicular carcinoma, and some sarcomas. Aggressive chemotherapeutic regimens used to treat these malignancies may result in periods of neutropenia for 7–10 days or more [72]. Likewise, malignancies such as metastatic carcinoma of the breast, prostate, lung, adrenal, thyroid, and kidney have a propensity to infiltrate the bone marrow and can result in neutropenia in the advanced stages of disease.

Patients with tumors of the central nervous system, either primary or metastatic, are at risk for a unique set of infections based on the associated neurological deficit. Likewise, any solid organ tumor that invades and disrupts anatomical barriers may predispose to infection. These include tumors of the skin, oral cavity, nasopharynx, and gastrointestinal, respiratory, and urogenital tracts. These malignancies and their associated pathogens were discussed previously.

4 Emerging Pathogens and Trends

Many unusual pathogens are known to infect patients with underlying immunodeficiencies, especially patients with hematological malignancies. Some of these pathogens have assumed increasing importance in cancer patients in the last 10 years (Table 4).

Table 4 Emerging pathogens and syndromes**Bacteria and bacterial syndromes**

Viridans streptococci

*Rhodococcus equi**Stenotrophomonas maltophilia**Achromobacter* spp.*Alcaligenes* spp.Hypervirulent strains of *Clostridium difficile**Escherichia coli* pyomyositis**Fungi**Non-albicans *Candida* spp.*Aspergillus flavus**Aspergillus terreus**Trichosporon* spp.*Fusarium* spp.*Rhodotorula* spp.*Saccharomyces cerevisiae* and *S. boulardii*

Phaeohyphomycosis

*Cryptococcus gattii***Viruses**

Respiratory viruses

Influenza, including emerging and pandemic strains

Parainfluenza

Respiratory syncytial virus

Human metapneumovirus

Coronaviruses including SARS CoV and MERS CoV

Adenovirus

Rhinovirus

Bocavirus

KI and WU polyomaviruses

Gastrointestinal viruses

Hepatitis E virus

Noroviruses

Reactivation of hepatitis B and hepatitis C viruses

Global emergence of antimicrobial resistance among bacteria, fungi, and viruses

4.1 Bacteria and Bacterial Syndromes

Viridans streptococci, gram-positive cocci that are part of the normal oral flora, are fast emerging as pathogens causing bacteremia and sepsis in neutropenic patients, especially patients with AML or those who have undergone HSCT [227]. Several species have been implicated with *Streptococcus mitis* predominating. Of all the species, *S. mitis* is also the most likely to be penicillin and fluoroquinolone resistant [228, 229].

Rhodococcus equi, a gram-positive coccobacillus, is an uncommon pathogen that has been reported to cause infection in patients with impaired cellular immunity. HIV infection is the most common predisposing risk factor; however, cancer patients with cellular immunodeficiency are also at increased risk. *R. equi* is most frequently associated with a cavitary pneumonia, which may mimic a fungal infection or tuberculosis. In a study by Harvey and Sunstrum, the survival rate for patients with cavitary pneumonia receiving antibiotics alone was 61 % compared with 75 % for those receiving both antibiotics and surgical resection [230]. More recently, isolated bacteremia has been reported in patients with underlying malignancies, with over 90 % associated with central line infections, likely due to the high percentage of *R. equi* isolates that can form heavy microbial biofilm on catheter surfaces [231].

Gram-negative pathogens of increasing importance in cancer patients include *S. maltophilia*, an emerging pathogen *Burkholderia cenocepacia*, *Achromobacter* spp., and *Alcaligenes* spp. *S. maltophilia*, a gram-negative bacillus, is an organism that is frequently isolated from the environment, particularly from water supplies. Both colonization and infection among immunocompromised patients are increasing, especially in those receiving broad-spectrum antibiotics, particularly carbapenems. *S. maltophilia* causes pneumonia, urinary tract infections, bacteremia, and wound infections in debilitated patients and is notoriously multidrug resistant, making treatment difficult [232]. In a recent retrospective review of *S. maltophilia* infections in HSCT recipients over four years in Israel, 19 of 570 (3 %) had *S. maltophilia* infections. The majority of patients had undergone allogeneic HSCT, had received a carbapenem during the previous month, and had a central venous catheter infection. All isolates remained susceptible to trimethoprim-sulfamethoxazole [233]. *Burkholderia cenocepacia* is a gram-negative pathogen, primarily associated with infections in patients with cystic fibrosis. It has recently been reported to cause an outbreak in cancer patients related to central venous catheters and to cause a vaginal infection in a patient with multiple myeloma [234, 235]. *Achromobacter* spp. and *Alcaligenes* spp. are gram-negative bacteria that are increasingly associated with infections in cancer patients. A review of consecutive bacteremia from 1989 to 2003 at MD Anderson Cancer Center revealed that 67 % of patients had underlying hematological malignancies and 52 % experienced neutropenia. *Achromobacter xylosoxidans* was the most common pathogen (94 %), followed by *Achromobacter denitrificans* (4 %) and *Alcaligenes faecalis* (2 %). The majority of patients had infected intravascular

catheters, followed by pneumonia and urinary tract infections. Of the infections, 52 % were polymicrobial and 7 % had concurrent fungemia. Most isolates were susceptible to carbapenems, antipseudomonal penicillin, and trimethoprim-sulfamethoxazole. Attributable mortality in this series was 15 % [236].

Two emerging bacterial syndromes in patients with underlying malignancies deserve mention. First, appearance of a hypervirulent strain of *C. difficile* in recent years has been associated with rising rates of severe and recurrent infection, and increased morbidity and mortality. Some studies have demonstrated chemotherapeutic agents as an independent risk factor for *C. difficile* infection (CDI) and disease severity [83–86]; however, this was recently disputed in a study by Stewart and colleagues in which they found that patients with CDI with underlying hematological malignancies had longer lengths of hospital stay but no difference in rates of colectomy, ICU admission, or death [89]. A second emerging syndrome, *E. coli* pyomyositis has been increasingly described among patients with hematological malignancies [237–239]. Pyomyositis is typically caused by gram-positive bacteria, primarily *S. aureus*; however, review of cases from 2003 to 2007 at MD Anderson Cancer Center revealed six cases of *E. coli* as the causative agent. Of these patients, all were receiving chemotherapy, five were neutropenic and two (33 %) died despite receiving appropriate antimicrobial therapy with a carbapenem. Of note, all the isolates were resistant to fluoroquinolones and 55 % produced an extended-spectrum beta-lactamase [239].

4.2 Fungi

Infections with *Candida* spp. remain the most common fungal infections in immunocompromised cancer patients; however, several recent trends have been noted. The incidence of nosocomial candidal fungemia rose sharply in the late 1980s and early 1990s. At some institutions, *Candida* fungemia now surpasses that of the Enterobacteriaceae, *Pseudomonas* spp., and *Enterococcus* spp [240]. *Candida albicans* is still the most common species, accounting for approximately half of fungal isolates from cancer patients, although the incidence of non-*albicans* species continues to increase. Among these are *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* [241–243], which tend to be more resistant to the azoles and *C. krusei*, which is inherently azole resistant [244]. Central venous catheters, total parenteral nutrition, and the increasing use of azoles for antifungal prophylaxis are some of the presumed mechanisms thought to account for this rising trend. Oral fungal infections with both *C. albicans* and the non-*albicans* species are very common among patients with cancer of the head and neck, particularly those who have received both chemotherapy and radiation as part of their treatment regimen [245–248].

Infections with *Aspergillus* spp. are still the second most common fungal infections among patients with underlying malignancies. Of the *Aspergillus* spp., *Aspergillus fumigatus* is the most commonly isolated species to cause invasive

disease; however, at some institutions, *A. flavus* has supplanted *A. fumigatus* as the most common cause of aspergillosis [249]. Clinicians caring for cancer patients should also be aware of an emerging pathogen, *A. terreus*, a pathogen closely related to *A. fumigatus*, in patients with underlying leukemia and those who have undergone HSCT, as this pathogen is relatively amphotericin B resistant but may respond better to posaconazole [250].

Many unusual fungi that were once considered commensals are now increasingly recognized as the cause of serious infections in cancer patients. Such organisms include *Trichosporon* spp., *Fusarium* spp., *Rhodotorula* spp., *Saccharomyces* spp., the phaeohyphomycosis, and non-neoformans cryptococci.

Based on the recent reviews, *Trichosporon* spp. are the second most common cause of fungemia in patients with hematological malignancies after candida infections [251]. Although most reported *Trichosporon* infections in the literature are attributed to *T. beigeli* (*T. cutaneum*), newer molecular taxonomic approaches have demonstrated the existence of numerous species of *Trichosporon*, including three species that are commonly isolated from clinical specimens, *T. asahii*, *T. inkin*, and *T. mucoides* [252]. *Trichosporon* spp. are primarily seen in neutropenic patients with hematological malignancies on high-dose corticosteroids. They most often cause central catheter-related infections, pulmonary infections, or soft tissue infections. Treatment for these infections is difficult, and relapse is common [253–255]. Correct identification of the various species requires sequencing of a portion of the rRNA gene; however, this may be important clinically as they have somewhat distinct antifungal susceptibility profiles, particularly *T. asahii* which is highly resistant to fluconazole, the echinocandins, and amphotericin B [252].

Fusarium spp. cause severe, often fatal, infections in neutropenic patients, particularly those who have undergone HSCT, especially those who experience graft versus host disease. Attributable mortality is reported in one recent series to be as high as 50 % and is dependent on prognostic factors such as status of underlying disease, severe lymphopenia, use of steroids, delay in targeted therapy, low albumin levels, fungemia, need for ICU admission, and, most importantly, delay in neutrophil recovery [256]. *Fusarium* is highly resistant to conventional antifungal drugs, and rising neutrophil counts are usually required for a successful response. Voriconazole is the drug of choice for fusariosis, and recent data demonstrate that combination antifungal therapy is no better than voriconazole alone. Subsequent neutropenic episodes are associated with a high incidence of recurrence [257–260].

Rhodotorula mucilaginosa (also known as *R. rubra*) is the most common cause of *Rhodotorula* spp. fungemia, followed by *R. glutinis* and *R. minuta*. Most cases of *Rhodotorula* spp. infections in patients with underlying malignancies are catheter-associated fungemia, followed by endocarditis and meningitis [251]. All *Rhodotorula* spp. must be considered intrinsically resistant to both the azoles and echinocandins. Recently, prophylaxis or treatment with fluconazole has been found to be a risk factor for *Rhodotorula* fungemia, and patients receiving azoles and echinocandins are at risk for breakthrough fungemia. Other risk factors for *Rhodotorula* infections include hyperalimentation, broad-spectrum antimicrobials,

neutropenia, and surgery. The treatment of choice is amphotericin, coupled with catheter removal. Crude mortality of up to 20 % has been observed [252].

Saccharomyces cerevisiae, also known as “baker’s yeast” or “brewer’s yeast,” is widespread in nature and is now included in some diet or health foods. A subtype of *S. cerevisiae*, *S. boulardii*, is also used in probiotic preparations for the prevention and treatment for various diarrheal diseases, such as those associated with *C. difficile* or parenteral nutrition. Invasive infections due to *S. cerevisiae* and *S. boulardii* are rare but have increased among cancer patients since the 1990s [261]. Most cases of *Saccharomyces* fungemia have been associated with central venous catheter use and receipt of antibiotic therapy. Immunocompromised patients are at higher risk of *S. cerevisiae* rather than *S. boulardii* infections which are seen more commonly in patients with underlying GI tract diseases and those in ICUs. Isolates of *S. cerevisiae* in one series demonstrated decreased susceptibility to amphotericin and to azole derivatives, and although break points have not been defined, MIC₉₀ for fluconazole and itraconazole for *S. cerevisiae* are considered to be in the dose-dependent range defined for *C. albicans*. It is hypothesized that the use of these drugs may play a role in the emergence of *S. cerevisiae* infections. Although data are scarce, voriconazole seems to exhibit good efficacy against *S. cerevisiae* (with an MIC₉₀ of <0.25 mg/L). No published series is available for echinocandin treatment, but preliminary data show good efficacy with caspofungin against a limited number of *S. cerevisiae* strains. Despite this spectrum of susceptibility, a favorable outcome has been observed even for amphotericin B or fluconazole therapy coupled with central venous catheter removal. Successful clinical outcome with these agents may be due to the low virulence of this organism [261]. At present, recommendations for treatment include withdrawal of probiotic regimens, if given, administration of an antifungal agent with activity against the organism, and removal of indwelling vascular catheters [252].

A recent review of phaeohyphomycosis by investigators at MD Anderson Cancer Center demonstrates that while rare, infection rates have increased three-fold (from 1.0 to 3.1 cases per 100,000 patient-days) at their institution between 1989 and 2008, primarily among patients with underlying hematological malignancies. The dematiaceous molds that cause phaeohyphomycosis are ubiquitous inhabitants of the soil and encompass more than 100 species and 60 genera, including *Alternaria*, *Bipolaris*, *Curvularia*, *Cladosporium*, *Aureobasidium*, *Exserohilum*, *Fonsecaea*, *Drechslera*, *Phialophora*, and *Hormonema*. The most common sites of infection are the lungs, sinuses, skin, and bloodstream. Risk factors included acute leukemia, receipt of induction chemotherapy, neutropenia, lymphopenia, allogeneic HSCT, and treatment with high-dose corticosteroids. In the isolates available for testing, amphotericin and posaconazole were most active. Most patients in this series received an amphotericin B formulation combined with either an azole or an echinocandin; 33 % had undergone surgery, primarily sinus debridement; and resolution of fungemia was seen in 4 of 5 patients with catheter removal. Mortality was 33 % at 12 weeks after diagnosis and was associated with disseminated infection, bilateral pulmonary disease, treatment with an amphotericin B preparation, breakthrough infection, and coinfection with CMV. Treatment

with granulocyte colony-stimulating factor and recovery from neutropenia within 30 days after diagnosis was associated with improved survival [262].

Cryptococcus gattii, a fungus found in the soil and in association with certain trees, particularly eucalyptus trees, has previously been found throughout tropical and subtropical regions of the world. It received increasing attention as an emerging pathogen when it was found to be the causal agent of outbreaks in Vancouver Island, British Columbia, Canada, in 1999 and in the Pacific Northwest area of the United States between 2004 and 2009 [263, 264]. Although it causes a syndrome of cryptococcosis similar to that of *C. neoformans*, primarily manifesting as pneumonia and meningitis, it is a distinct species. The pathogen *C. gattii* is clinically more virulent than *C. neoformans*, causing multiple lesions in the lungs and brain of infected patients, responding more slowly to therapy, and requiring more diagnostic follow-up evaluations [265]. Although this disease is primarily seen in immunocompetent hosts, disease has been reported in immunocompromised patients, including those with HIV/AIDS, organ transplantation, and underlying malignancies. Preliminary data suggest that severity of *C. gattii* infection is due to defective induction of host immune responses, resulting in low levels of proinflammatory cytokines that are crucial for controlling the spread of infection. Although data are limited, despite antifungal susceptibilities similar to *C. neoformans* in vitro, intracranial infection with *C. gattii* is associated with more neurological complications, a delayed response to therapy, and a higher incidence of neurosurgical intervention [263].

4.3 Viruses

Respiratory viral infections (RVIs) are a significant cause of morbidity and mortality in patients with underlying malignancies. The development of new molecular techniques has improved the detection of established pathogens and the identification of emerging ones and has shaped our understanding of the epidemiology and outcomes of RVIs in immunosuppressed hosts. Clinicians caring for cancer patients must familiarize themselves with respiratory viruses such as influenza, including emerging and pandemic strains; parainfluenza; respiratory syncytial virus; human metapneumovirus; coronaviruses, including SARS CoV and MERS CoV; adenovirus; rhinovirus; bocavirus; and KI and WU polyomaviruses, which have all been associated with upper and lower respiratory tract disease in this population. The incidence of RVIs following HSCT has ranged from 3.5 to 29 %; however, older studies are likely to underestimate the incidence due to less sensitive detection methodologies. Common symptoms include malaise, myalgias, fever, coryza, cough, and sore throat. Dyspnea may signal progression to lower respiratory tract (LRT) disease which is estimated to occur in 35 % of HSCT patients. Some studies suggest that RVIs may be a risk factor for the development of invasive pulmonary aspergillosis in this population. Progression to LRT disease and worse outcome was associated with diagnosis of leukemia, age over 65 years,

severe neutropenia or leukopenia, and myeloablative transplant. Cancer patients with RVIs can have prolonged shedding, creating a risk for transmission and outbreaks in institutional settings [266].

In addition to respiratory viruses, two community-acquired gastrointestinal viruses deserve mention. Hepatitis E virus (HEV) infection, reactivation, prolonged viral shedding, and development of cirrhosis have been increasingly reported in immunocompromised hosts, primarily among patients who have undergone solid organ transplantation. Chronic HEV in HSCT recipients has not been as well studied, given its low endemicity in areas of the world most likely to perform HSCTs. Some case reports in patients with acute leukemia and in those who have undergone HSCT have demonstrated prolonged shedding following chemotherapy, or viral reactivation more than three months following transplantation. Given evidence for prolonged viremia and fecal shedding, the potential exists for nosocomial transmission, and this has been demonstrated in an outbreak in France. In addition to HEV, chronic norovirus infection has emerged as a viral syndrome in patients with underlying malignancies, especially hematological malignancies, and in those who have undergone HSCT. It can cause prolonged shedding and protracted disease in this population, with patients shedding virus and remaining symptomatic for months and, in some cases, for more than a year. Treatment is supportive, and resolution of disease often requires a decrease in immunosuppression and subsequent recovery of T cells. As with hepatitis E virus, prolonged viral shedding poses a risk for norovirus transmission in healthcare settings [267].

Reactivation of hepatitis B virus (HBV) and hepatitis C virus (HCV) can occur in cancer patients. HBV reactivation is a well-known complication in cancer patients who undergo cytotoxic chemotherapy and other immunosuppressive therapies. Rates of reactivation vary from 14 to 72 % in published literature, and variations are associated with underlying malignancy, degree of immunosuppression, and use of prophylaxis. Patients with underlying hematological malignancies are at highest risk, and patients with lymphoma may be at particular risk; however, an increasing number of cases have been described in patients with solid tumors, especially those with breast and hepatocellular carcinomas. Other risk factors include history of high serum viral load, male sex, young age, HBeAg seropositivity, use of corticosteroids, use of certain chemotherapeutic agents such as anthracyclines, cyclophosphamide, and vinca alkaloids, and use of monoclonal antibodies such as rituximab and alemtuzumab. In one series, the use of rituximab was associated with 39 % of reactivation cases. Syndromes associated with reactivation vary widely and range from asymptomatic disease to liver failure and death, with mortality ranging from 5 to 52 %. Prophylactic agents such as lamivudine, adefovir, entecavir, or tenofovir should be started as early as possible before initiating immunosuppressive therapy in HBsAg positive patients. Although HCV infection is more common than HBV infection in cancer patients, HCV reactivation following immunosuppressive therapy is rare. Reactivation of HCV is more common in patients with hematological malignancies but has been reported in patients with solid tumors and in those who have undergone HSCT. No reliable

methods exist to predict an individual patient's risk for reactivation; however, the use of corticosteroids alone or in combination with other immunosuppressive agents has traditionally been associated with reactivation disease. Controversy exists as to whether the use of rituximab is a risk factor for HCV reactivation. The clinical consequences of HCV reactivation seem to be less severe than those of HBV reactivation, with only a few deaths reported. However, if severe hepatitis secondary to viral reactivation develops, mortality rates are similar to those seen with HBV. No prophylaxis is currently approved to prevent HCV reactivation in this patient population [268].

4.4 Antimicrobial Resistance

Antimicrobial resistance is now a global crisis, and patients with underlying malignancies are disproportionately impacted by this emerging trend. Drug-resistant infections cost the United States healthcare system between \$16.6 and \$26 billion in extra costs annually and cost society approximately \$35 billion each year in lost wages and premature deaths [269]. Antibacterial drug resistance is now commonplace among cancer patients. The incidence of penicillin resistance among viridians streptococci is increasing in both adult and pediatric cancer patients [227, 229]. The majority of enterococcal isolates colonizing allogeneic HSCT patients are now vancomycin resistant, and approximately 30 % of VRE-colonized HSCT patients subsequently develop clinical infections. According to one recent study, VRE is now the leading cause of bacteremia in the first 30 days after HSCT and is associated with a fourfold increase in mortality compared to patients without enterococcal bacteremia [270–272]. In addition, daptomycin resistance is also increasing among VRE isolates [273]. Rates of MRSA are increasing among patients with breast cancer and cancers of the head and neck and, in some centers, are common causes of bacteremia in patients with febrile neutropenia [274–279]. Gram-negative bacterial resistance is likewise increasing. In some series, over 80 % of *E. coli* isolates are fluoroquinolone resistant [280]. The presence of extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae and *A. baumannii*, and multidrug-resistant *P. aeruginosa* among cancer patients is now routinely encountered [281–287]. As mentioned above, the increasing use of azoles for antifungal prophylaxis is thought to have played a role in the emergence of azole-resistant non-*albicans* *Candida* spp. such as *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei* that are now commonplace in this patient population. Although less common, antiviral resistance is reported among CMV and HSV, due to the prophylactic use of acyclovir and ganciclovir, which has led to both acyclovir- and ganciclovir-resistant strains among cancer patients. To combat the increasing problem of antimicrobial resistance, clinicians must know and employ the strategies of infection prevention and control and antimicrobial stewardship for these patients who are under their care.

5 Summary

Patients with underlying malignancies are at risk for a wide array of infectious diseases that cause significant morbidity and mortality. To develop a clear etiologic understanding of the infectious agents encountered first requires knowledge of the host- and treatment-associated factors that predispose to infection. The astute clinician must also be aware of new and emerging infections in this patient population. As new pathogens are discovered and established pathogens become increasingly drug resistant, they will continue to present challenges for physicians caring for these patients in the years ahead.

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Infectious Complications in Cancer Patients

Stosor, V.; Zembower, T.R. (Eds.)

2014, X, 511 p. 18 illus., 13 illus. in color., Hardcover

ISBN: 978-3-319-04219-0