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Teresa R. Zembower *Editors*

# Infectious Complications in Cancer Patients

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# Infectious Complications in Cancer Patients

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# Preface

Infectious diseases are leading causes of morbidity and mortality in patients with cancer due to the immunodeficiencies that are inherent to underlying malignancies and acquired as a result of cancer therapies. These infectious complications remain a significant limitation of cancer treatment modalities.

Infections continue to evolve in both predictable and unpredictable ways as a result of new potent immunomodulatory therapies, the resulting host immunodeficiencies, and anti-infective prophylaxis practices. As a result, the spectrum of infections, including the epidemiology of suspected pathogens, new pathogens, and anti-infective resistance, is continually changing. This provides constant diagnostic and therapeutic challenges for clinicians. Our objective for the second edition of this volume in the *Cancer Treatment and Research* series is to provide the reader with an updated review of the epidemiology, diagnosis, and management of infectious diseases that occur in cancer patients and hematopoietic stem cell recipients. This volume is intended for use by infectious diseases physicians, oncologists, medical specialists, and other professionals, in order to assist in the clinical care of this patient population.

The editors wish to thank the authors who generously contributed their time and expertise to this volume and who have dedicated their medical practices to the care of cancer patients.

Valentina Stosor
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# Host Impairments in Patients with Neoplastic Diseases

J. Peter Donnelly, Nicole M. A. Blijlevens and Walter J. F. M. van der Velden

**Abstract**

Healthy individuals possess an immune system comprising physical barriers, innate and acquired immunity as well as the indigenous microflora that populate the body surfaces. The immune system maintains constant vigilance over the body at the cellular level as well as at the interface between the host integument and the resident microflora. However, neoplastic diseases and their treatment often lead to impaired immunity resulting in an increased risk of infections due to viruses, bacteria, fungi, and protozoa. This chapter explores the various aspects of host impairment focusing on the components of immunity and the interplay between them to explain why it is that these patients succumb to infections per se. In so doing, we hope that the reader will be better equipped to understand the risks patients face so as to anticipate potential infectious complications and implement appropriate measures to help attain successful remission of the neoplastic diseases and maintain the best quality of life for the patient.

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**Keywords**
Innate immunity · Commensal flora · Natural antibiotics · Neutropenia · Humoral immunity · Cellular immunity · Host defenses · Mucosal barrier injury · Mucositis · Infectious complications

## Contents



## 1 Introduction

In the course of evolution, nature has provided the normal human individual with an impressive and effective defense system against microbial enemies. On its own, the normal defense system recognizes foreign invaders, alerts the relevant protective mechanisms, launches counterattacks, ceases hostilities as soon as the job is done, and clears up the battlefield, causing only negligible collateral damage. An intact immune system offers protection against most microbial aggressors through a complex interrelationship of protecting surfaces, cells, and soluble factors.

White blood cells (granulocytes, macrophages, dendritic cells, and lymphocytes), platelets, soluble factors of the immunoglobulins, complement, lymphokines, and other cytokines, as well as the physical barriers, have to be considered

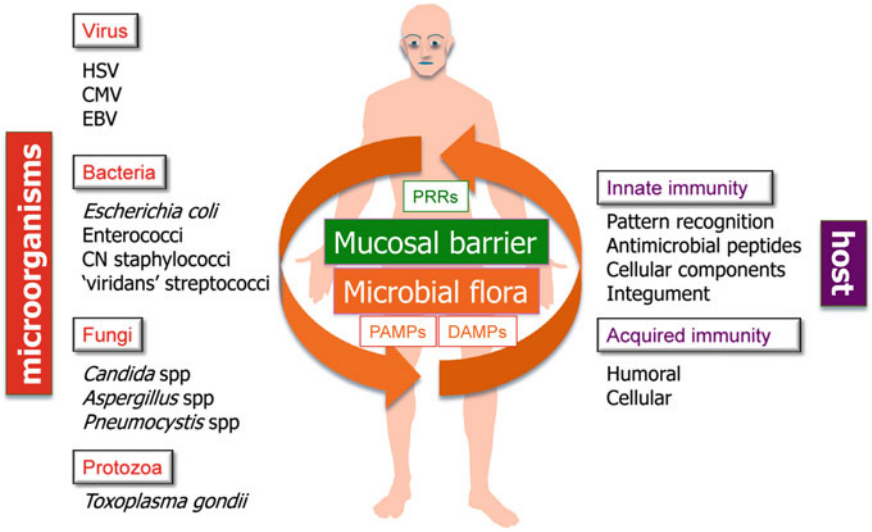


**Fig. 1** The balance between the host and the indigenous microbial flora

as integral and virtually indispensable components of a unitary defense system (Fig. 1). It has also become clear that the interplay between the body surfaces of the alimentary tract, particularly the gut, and its resident commensal microflora presents not a silent landscape but rather a theater in which there is constant movement and chatter between the host cells and a myriad of microbial species. Indeed, from a biologic perspective, we humans comprise a community in which we are outnumbered almost 10 to 1 by our prokaryotic neighbors [1]. Given its complexity, it is not surprising that such a finely tuned system is subject to profound perturbation by hematologic malignancies and their treatment.

The effects of the various noxious events that occur while treating malignancy differ in severity as well as in primary targets. To complicate things further, hazardous events are not static but rather exert their impact dynamically as the degree of disturbance varies with time during or after a course of treatment (Fig. 2). The human defense system is capable of coping with a tremendous number of insults before it finally begins to show the first sign of collapse. Robust as it is, physicians treating malignancies should be aware that their activities put the entire defense system of patients in jeopardy. This complex interaction between host defenses and therapeutic modalities has a profound effect on patient outcome.

## 2 Basic Clinical Condition and Organ Function

### 2.1 Nutritional Status

Weight loss correlates inversely with survival in patients with cancer. This occurs whether or not intensive treatment is given because the integrity of host defenses

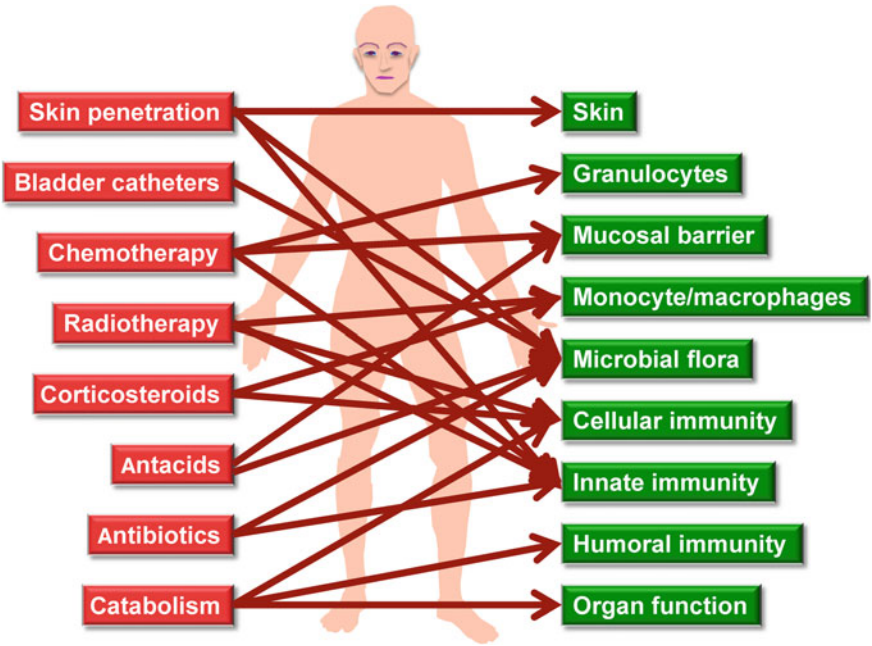


**Fig. 2** Evolution of impairment of defense systems after treatment for malignancy

can be endangered by the catabolic state induced by cachexia and malnutrition, resulting in a quantitatively deficient intake of calories and protein, with insufficient vitamin levels and trace metal concentrations [2, 3]. Cachexia will be exacerbated by anorexia, chemotherapy-induced nausea and vomiting, gastrointestinal obstructions, as well as by metabolic disturbances. These perturbations may result in delayed tissue healing, mucosal atrophy with a decrease in the secretions of lysozyme and secretory IgA, as well as impairment of both the classical and alternative complement pathways. Vitamin A deficiency may also have a detrimental effect on the cellular immune system [4].

Deficiencies in trace elements can further undermine the host defenses on already compromised patients. Zinc deficiency can develop during total parenteral nutrition disturbing the function of phagocytes and T cells but can be overcome by adding the mineral [5]. The microbicidal capacity in vitro of neutrophils and T-lymphocyte function is reduced by iron deficiency though the clinical significance is uncertain. Iron overload occurring in the setting of hematopoietic stem cell transplantation (HSCT) is a risk factor for infection involving a variety of pathogens such as *Yersinia enterocolitica*, *Listeria monocytogenes*, *Vibrio* spp., *Plasmodium falciparum*, *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Candida albicans*, *Aspergillus* spp., and the agents of mucormycosis [6]. A deficit in phosphate, which may occur during episodes of starvation and

insufficient parenteral nutrition, is associated with a decrease in the chemotactic, phagocytic, and microbicidal functions of granulocytes in vitro, and clinically with bacterial and fungal infections [7].

## 2.2 Comorbidity

Concomitant chronic illnesses, such as chronic pulmonary diseases or renal and hepatic failure, enhance the risk of infection. Patients with a preexisting immune disturbance, such as HIV infection or a congenital immunodeficiency syndrome, are placed in double jeopardy. Much more common, however, is the detrimental effects of smoking, particularly in patients with primary lung tumors, due to airway colonization with pathogenic microorganisms and impaired clearance of secretions [8]. Tobacco use is also a risk factor for infection in autologous HSCT recipients [6].

Patients with poorly controlled diabetes mellitus are more likely to develop wound infections after skin penetration injuries, and they frequently suffer from concurrent vascular disease and neuropathy. High concentrations of glucose in the urine, and oral secretions promote colonization by *Candida* spp. and other pathogens [9]. There is a well-known association between diabetes mellitus and notorious infections, such as rhinocerebral mucormycosis and malignant external otitis [10], which is not difficult to explain in view of the immune aberrations that are associated with diabetes, such as impaired opsonization, decreased chemotactic activity of granulocytes and monocytes, iron overload [11], and myeloperoxidase deficiency [12].

## 2.3 Physiologic Status

Tumors themselves may also predispose to infection by local organ dysfunction. In patients with solid tumors, obstruction of natural passages can lead to inadequate drainage of secretory or excretory fluids from nasal sinuses, bronchi, and bile ducts. Furthermore, tissue invasion may create connections between normally sterile spaces and the environment through disruption of epithelial surfaces. Examples include perforation of the esophagus by mediastinal tumors, invasive gynecologic malignancies with local pelvic abscesses, skin ulcerations with cellulitis and deep soft-tissue infections, and invasion of the bowel wall by tumors with the lower gastrointestinal tract, resulting in bacteremia. Localizations in the central nervous system, spinal cord compression, and paraneoplastic neuropathy are associated with an increased risk of infection due to lethargy and, for instance, a diminished ability to cough and swallow, and incomplete emptying of the bladder [8].

Of course, in hematologic malignancies, infectious complications invariably go hand in hand because the neoplasm resides within the immune system itself and interferes directly and indirectly with its function. Patients undergoing splenectomy have a risk of around 1 in 20 of that they will develop overwhelming sepsis

at some time during their life. Encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are usually the culprits, though *Neisseria meningitidis* and staphylococci are occasionally encountered.

Several factors might explain this increased susceptibility to microbial infection. Encapsulated bacteria are able to elude phagocytosis because specific opsonizing antibodies are necessary for efficient phagocytosis. The spleen is also the principal organ for eliminating particles that are not opsonized, and so, it is left to the macrophages within the organ to remove them. The primary immunoglobulin response also takes places in the spleen, and low levels of circulating IgM have been observed after splenectomy and in cases of functional asplenia.

### 2.4 Psychologic Status

Psychologic stress is thought to suppress host defense mechanisms. This general assumption has been corroborated by the observations that psychologic stress has a negative influence on the function of T cells and NK cells. Indeed, stress and the amount of stress appear to be associated with an increased risk of acute viral respiratory illness. This is most likely mediated by endogenous opioids, hormones from the hypothalamic–pituitary–adrenal axis, catecholamines, and cytokines [13].

### 2.5 Aging

In elderly patients, the atrophy and dryness of the skin and mucosal membranes may lead to increased susceptibility to infections. In addition, the primary and secondary humoral responses, as well as the oxidative metabolism of neutrophils and T-cell functions, decline with age, but their exact role in susceptibility to infection is unclear [14].

## 3 Integument and Commensal Microflora

The integument comprises the skin, respiratory tract, (including the nasal cavity, ears, and conjunctiva), the alimentary tract, and the genitourinary tract and provides the first line of defense against microbial invasion. In physical terms, the only difference between the skin and the other parts of the integument is that it is dry, whereas the others are bathed in mucins and therefore continually moist. Thus, while both surfaces are normally colonized with a variety of microorganisms, including many different genera of bacteria and yeasts, the range and number of species and the biomass associated with mucosal surfaces are much greater than those of the skin. However, the resident microbial flora of each surface play an integral role in helping to maintain the function and integrity of these first lines of

defense. Moreover, when intact and healthy, both the mucosa and skin are capable of resisting colonization with foreign or allochthonous organisms, thus maintaining an ecologic balance within the indigenous microbial flora.

## 3.1 Skin

The skin of an adult has an estimated surface area of 1.5–2.3 $m^2$ and possesses features that are inimical to microbial invasion, provided it remains healthy and intact. The cells are composed of keratin and resemble loose paving stones. They are joined together by desmosomes and are continually sloughed off during desquamation so that adherent bacteria are also lost. This rapid cell turnover occurs every 2 weeks and helps to limit opportunities for transient organisms to establish residence.

A number of additional biologic factors contributes to the skin as an effective microbial barrier. Production of sebum establishes an oily, parched environment that is particularly hostile to the establishment of gram-negative bacteria, which are vulnerable to desiccation and require an aqueous environment for survival. Moreover, in this lipid-rich environment, only those microorganisms that elaborate lipases are capable of acquiring carbon from these lipids. The skin is also an effective barrier because it forms an acid mantle, having a pH of 5.0–6.0, and its surface temperature is, on average, about 5 °C lower than that of the core body temperature. Thus, the range of organisms that are able to reside on the skin is strictly limited to a few, mainly gram-positive bacteria, such as various members of the coagulase-negative staphylococci, particularly *Staphylococcus epidermidis, Corynebacterium jeikeium,* and other coryneforms, *Propionibacterium* spp., and certain yeasts (Table 1) that can withstand these hostile conditions and compete successfully for binding sites and nutrients to establish a permanent and intimate attachment to the epidermis [15].

Many of the resident bacteria also elaborate toxins that inhibit closely related microorganisms, allowing individual species to retain their foothold and consolidate their territory. Resident species also grow as biofilms, which consist of microcolonies enmeshed in a glycocalyx, rather than the planktonic growth found in laboratory cultures. Thus, each microbial consortium possesses a boundary and exists as a distinct unit separate from its neighbors.

### 3.1.1 Erosion of the Skin Integument, Including Intravenous Catheters

The effectiveness of the skin as a defense barrier can be eroded in a variety of ways. Topical antibiotics and those secreted in sweat will disturb the balance within the resident commensal flora, leaving the surface vulnerable to colonization by exogenous potential pathogens such as the gram-negative bacteria. Antibiotics will also exert selective pressure on the resident flora, causing resistance to emerge, as has been observed during treatment with ciprofloxacin because the drug

**Table 1** Microbial residents of the normal skin

| Major group | Genus | Opportunistic pathogens |
|---|---|---|
| Gram-positive cocci | *Staphylococcus* spp. | *S. epidermidis* |
| | *Micrococcus* spp. | |
| Gram-positive bacilli | *Corynebacterium* spp. | *C. jeikeium* |
| | *Brevibacterium* spp. | |
| | *Propionibacterium* spp. | |
| | *Acinetobacter* spp. | *A. baumanii* |
| Yeasts | *Pityrosporum* spp. | |
| | *Candida* spp. | *C. parapsilosis* |

is secreted with sweat [16]. Chemotherapy and irradiation can bring about radical changes in the normal skin by interrupting normal cell replacement, resulting in hair loss, dryness, and loss of sweat production. The latter may also lead to lower levels of the antimicrobial peptide, dermcidin, which is secreted in normal sweat and is an effector of innate immunity [17]. In addition, steroids also can exert a profound effect on sebum secretions. When the skin is broken, the release of fibronectin is thought to assist colonization with *Staphylococcus aureus,* and other changes facilitate colonization with gram-negative bacilli such as *Acinetobacter baumanii* and Enterobacteriaceae. Cutaneous infection results from the loss of integrity and reduced local immunity of the skin as well as disturbances within the resident flora. Abraded skin and the associated exudates and minor breaches in the integument can lead to local infection as well as provide a reservoir that assists further spread to other body surfaces, including the oral cavity. When the balance is lost between the host defenses and resident commensal flora around the hair follicles, they can become inflamed and necrotic, forming a potential nidus of infection.

Cutaneous infections in the immunocompromised patient can also develop from needle punctures, but the insertion of catheters provides the single most effective means of breaching the natural protective barrier of the skin and creating access for microorganisms.

## 3.2 Upper Respiratory, Alimentary, and Genitourinary Tracts

The surface area of the upper respiratory, alimentary, and genitourinary tracts available for microbial colonization is greater than that afforded by the skin because of the folds, crypts, and villi. The surfaces of each anatomic region are also very different, ranging from the hard enamel of the teeth to the microvilli of the bowel. Extreme changes in the local environment also occur, ranging from the neutrality of the mouth to the acidity of the stomach. Although the interplay between these environments and their resident microflora is incomplete and poorly

understood, some generalizations are possible and useful in understanding how the mucosal surfaces play their part as a first line of defense.

Two principal physical host factors influence the microbial ecology of the mucosal surfaces. Dilution of the microbial load is achieved by sneezing and coughing of microbes trapped in mucus, flushing of the mouth and esophagus by saliva, micturition, and peristalsis of the intestines. Acidity plays a crucial role both in disinfecting the stomach and in regulating the microbial milieu of the vagina. The upper respiratory, alimentary, and genitourinary tracts are essentially composed of epithelial cells interspersed by cells that produce mucins. These hydrophilic substances perform various functions, including lubrication, waterproofing, and preventing sudden changes in osmotic pressure [18]. They also contain inhibitory substances, such as lactoferrin, lysozyme, defensins, and peroxidase, as well as secretory IgA. Mucins also appear to interfere with adherence of foreign bacteria to epithelial cells and prevent access of antigens to antibodies while allowing the biofilm formed by resident bacteria to blend or fuse so that the bacteria can form a more intimate contact with the epithelial cells.

The resident microbial flora probably plays a crucial role in maintaining the integrity of this part of the integument. The microorganisms compete with one another for sites of attachment and nutrients as they continually modulate the microecology. On the whole, the microflora are harmless commensals exhibiting stable symbiosis. The human host is probably immunologically tolerant to all resident flora because so few of the genera have ever been implicated as opportunistic pathogens, even in the most profoundly immunosuppressed individuals. For example, even when translocation into the bloodstream occurs, the resident bacteria are poorly adapted to the environment within the body proper and only rarely establish an intracorporeal infective process (Table 2).

### 3.2.1 The Lung

The lung appears to be particularly vulnerable to damage by cytotoxic chemotherapy and irradiation and is exquisitely susceptible to infection. Immunopathologic reactions mediated by the pulmonary macrophages that survive chemotherapy can lead to various other syndromes, including respiratory distress. Pulmonary hemorrhage as a result of profound thrombocytopenia further imperils the lung, increasing the risk of infection. However, the risk of invasion and dissemination is high when the integrity of the mucosa is impaired, the ecology of resident flora is disturbed, and exogenous microorganisms such as gram-negative bacilli or other potential pathogens establish colonization. Resident flora such as *Candida* spp. can result in superficial infection, often as a consequence of reactivation of herpes simplex virus [19, 20]. Clinically, the presence of pseudomembranes over the ulcerated tissue can initiate local invasion and progressive spread to the esophagus and gastrointestinal tract, resulting in disseminated candidiasis. Aspiration and inhalation of spores and hyphal elements of *Aspergillus* spp. and other molds permit colonization of the sinuses and bronchial tree, which may extend into the alveolar spaces, resulting in invasive disease that is often fatal.

**Table 2** Resident flora of the upper respiratory tract and oral cavity

| Major group | Genus | Opportunistic pathogens |
|---|---|---|
| Gram-positive cocci | *Micrococcus* spp. | |
| | *Staphylococcus* spp. | *S. epidermidis* |
| | *Stomatococcus* spp. | *S. mucilaginosus* |
| | *Streptococcus* spp. nonhemolytic group | *S. milleri* |
| | *Streptococcus* spp. viridans group | *S. oralis*, *S. mitis* |
| Gram-positive bacilli | *Actinomyces* spp. | *A. israelii* |
| | *Arachnia* spp. | |
| | *Bacillus* spp. | |
| | *Bacterionema* spp. | |
| | *Bifidobacterium* spp. | |
| | *Clostridium* spp. | *C. sporogenes* |
| | *Corynebacterium* spp. | |
| | *Eubacterium* spp. | |
| | *Lactobacillus* spp. | |
| | *Propionibacterium* spp. | |
| | *Rothia* spp. | |
| Gram-negative cocci | *Moraxella* spp. | *M. catarrhalis* |
| | *Neisseria* spp. | |
| | *Veillonella* spp. | |
| Gram-negative bacilli | *Actinobacillus* spp. | *A. actinomycetemcomitans* |
| | *Capnocytophaga* spp. | *C. ochracea* |
| | *Eikonella* spp. | *E. corrodens* |
| | *Fusobacteriurn* spp. | *F. nucleatum* |
| | *Haemophilus* spp. | *H. parainfluenzae* |
| | *Leptotrichia* spp. | *L. buccalis* |
| | *Prevotella* spp. | *P. melanogenicus* |
| | *Selenomonas* spp. | |
| | *Wolinella* spp. | |
| Spirochetes | *Treponema* spp. | |
| Mycoplasma | *Mycoplasma* spp. | *M. salivarium* |
| Yeasts | *Candida* spp. | *C. albicans* |

### 3.2.2 Microflora of the Intestinal Tract

The alimentary tract contains many different bacterial genera, the vast majority of which remain harmless (Table 3). The gut is also the major reservoir of gram-negative bacilli, which are either endogenous (e.g., *Escherichia coli*) or have been acquired by ingestion (e.g., *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) [21–23].

Normally, the alimentary tract flora contains in excess of $10^{14}$ microorganisms, representing between 500 and 1,000 different species [24] and amounting to several grams, but only very few species are capable of establishing infection, even in the most profoundly immunosuppressed patient. Most of the microbial flora is densely distributed around the surfaces of the oral cavity and the large bowel, where scores of different microorganisms, including spirochetes, spore formers, bacilli, and cocci, compete for the available surfaces and nutrients. Anaerobes predominate and play a crucial role in maintaining a healthy commensal flora, preventing the establishment of exogenous or allochthonous organisms, which is known as *colonization resistance* [25, 26]. The integrity of the mucosa, the production of saliva and mucus, peristalsis, gastric pH, bile acids, digestive enzymes, and the levels of secretory IgA also play an important role in maintaining colonization resistance [27].

## 3.3 Impact of Antimicrobial Agents on Colonization Resistance of the Alimentary Tract

Exposure to antimicrobial agents is one of the most effective means for destroying colonization resistance, as is manifest by fungal overgrowth and increases in the enterococcal populations [28–30]. The most likely contributors to colonization resistance, the gram-positive non-spore forming, lactic acid-producing bacilli, particularly bifidobacteria, are particularly susceptible to antibiotics known to impair colonization resistance, including the penicillins, rifamycin, clindamycin, erythromycin, bacitracin, and vancomycin [24, 27, 31–36]. Some cephalosporins are also detrimental to colonization resistance, whereas meropenem and the quinolones have been declared "friendly" [28, 34–39]. Some drugs such as aztreonam and imipenem only appear "friendly" because they are inactivated by feces [30, 40], whereas under the circumstance of diarrhea, parenteral feeding, and gut toxicity, normal stool is no longer produced so these agents may remain sufficiently active to destroy what remains of the colonization resistance. Initially, co-trimoxazole was thought to be neutral [27, 34, 41–45], but other evidence suggests otherwise [46]. Individual antibiotics that appear to spare colonization resistance, such as ceftazidime and piperacillin, might have a marked impact when given in combination, leading to an increase in both *Clostridium difficile* as well as yeasts [47]. *C. difficile* can cause enterocolitis, which responds to treatment with metronidazole or oral vancomycin, but the latter may select for resistant bacteria such as *Enterococcus faecium* and *Lactobacillus rhamnosus* [48]. The widespread

**Table 3** Resident flora of the lower alimentary tract

| Major group | Genus | Opportunistic pathogens |
|---|---|---|
| Gram-negative anaerobic bacilli | *Bacteroide*s spp. | *B. fragilis* |
| | *Desulfomonas* spp. | |
| | *Leptotrichia* spp. | *L. buccalis* |
| | *Fusobacterium* spp. | *F. nucleatum* |
| | *Butyrvibrio* spp. | |
| | *Sucinimonas* spp. | |
| | *Vibrio* spp. | |
| Gram-negative facultatively | *Escherichia* spp. | *E. coli* |
| Anaerobic bacilli | *Citrobacter* spp. | *C. freundii* |
| | *Klebsiella* spp. | *K. pneumoniae* |
| | *Enterobacter* spp. | *E. cloacae* |
| | *Morganella* spp. | *M. morganii* |
| | *Proteus* spp. | *P. mirabilis* |
| Gram-positive facultatively | *Lactobacillus* spp. | *L. rhamnosus* |
| Anaerobic bacilli | | |
| Gram-positive anaerobic bacilli | *Bifidobacterium* spp. | |
| | *Clostridium* spp. | *C. tertium*, *C. difficile*, *C. sporogenes* |
| | *Eubacterium* spp. | |
| | *Lachnospira* spp. | |
| | *Propionibacterium* spp. | *P. acne* |
| Gram-positive facultatively | *Enterococcus* spp. | *E. faecalis*, *E. faecium* |
| Anaerobic cocci | *Staphylococcus* spp. | *S. epidermidis* |
| | *Streptococcus* spp. | *S. milleri*, *S. mitis*, *S. oralis*, |
| | | *S. bovis* |
| Gram-positive anaerobic cocci | *Peptococcus s*pp. | |
| | *Peptostreptococcus* spp. | |
| | *Acidaminococcus* spp. | |
| | *Megasphaera* spp. | |

(continued)

**Table 3** (continued)

| Major group | Genus | Opportunistic pathogens |
|---|---|---|
| Gram-positive anaerobic cocci | *Ruminococcus* spp. | |
| | *Sarcina* spp. | |
| | *Veillonella* spp. | |
| | *Coprococcus* spp. | |
| | *Gemella* spp. | |
| Yeasts | *Candida* spp. | *C. albicans*, *C. glabrata*, *C. krusei*, *C. lusitania* |

use of fluoroquinolones for prophylaxis has led to the emergence of resistance among the *E. coli,* which are indigenous to the bowel [49–52].

## 4 Innate Immunity

The immune system has historically been divided into the innate ("natural") and adaptive ("acquired") immune system to highlight the difference in primary primitive versus secondary more sophisticated responses. Current knowledge, however, challenges this dichotomy because the innate and adaptive immune systems have considerable overlap and are highly interlinked. For instance, the composition of the "cytokine cocktail" released after stimulation of pattern recognition receptors (PRRs) by pathogen-associated molecular patterns (PAMP) directs the adaptive immune response toward T-helper 1 (Th1), Th2, Th17, or regulatory T-cell activity [1]. In other words, the innate immune system orchestrates the adaptive immune system [53, 54]. Nevertheless, for the sake of clarity, the dichotomy has been maintained so far.

The innate immune system is a primary highly conserved immune system that can been found in most living organisms, from plants to insects to mammals [55]. This is essentially all there is to the immune system of plants and insects unlike more evolved creatures such as mammals that also possess an adaptive immune response. Being the first point of contact with microorganisms and foreign molecules, the innate immune system mobilizes a primary response to external threats. This is characterized by being rapid, crude, lacking in specificity and without any development of "memory" so that when re-challenged the same response ensues. By contrast, the adaptive immune system is highly specific in recognizing foreign molecules and reacts with increased magnitude with every re-challenge.

The innate immune system consists of a variety of humoral and cellular components [55] as well as the epithelial cell network that creates a direct physical barrier. Humoral factors consist of the complement systems (classical, alternative, and lectin pathway), antimicrobial peptides (AMPs), acute phase proteins (e.g., C-reactive protein), and mucosal secretions (mucins and saliva). Cellular components consist of natural killer cells (NK) and phagocytic cells such as

monoyctes, macrophages, polymorphonuclear neutrophils (PMN), and dendritic cells (DC). Endothelial cells and fibroblasts are also being increasingly recognized as essential cellular components of the innate immune system. For instance, intestinal epithelial cells (IECs) recognize microbes, produce cytokines and AMPs, phagocytize and present antigens [56].

## 4.1 Pattern Recognition Receptors: Key Players of the Innate Immune System

The discovery of a pattern recognition receptor (PRR, the so-called Toll receptor) in the fruit fly helped reveal just how innate immune cells recognize foreign molecules. It also boosted research into innate immunity, which lead to the discovery of many different PRRs in humans, including the Toll-like receptors (TLRs), the NOD-like receptors (NLRs), and the family of C-type lectin receptors (CLRs) [57–59].

PRRs recognize conserved molecular patterns of the cell wall of bacteria, or the so-called PAMPs, including lipids, proteins, and nucleic acids. PRRs are expressed on nearly every human cell ranging from blood cells to epithelial and endothelial cells. They are present on the cell surface though some reside in the cytosol. The expression is highly regulated with an increase in expression during infection and other inflammatory conditions. These receptors are capable of recognizing PAMPs with a degree of specificity. Because microbes contain different motifs that are recognized by different PRRs, the system is redundant, thereby reducing the risk of infection when there is any dysfunction of certain PRRs.

Although originally PRRs were thought to discriminate self from nonself, they also recognize endogenous ligands, such as heparin sulfate, fibrinogen, heat shock proteins, and $\beta$-defensin-2, so-called danger-associated molecular patterns (DAMPs), released mostly in case of tissue damage [60, 61]. This enables the innate immune system to respond to danger, whether or not resulting from infection [62].

During infection and tissue damage, the ensemble of activated PRRs and subsequently activated intracellular signaling pathways results in the release of a mixture of cytokines and activation of diverse signaling pathways. The cytokine profile then defines the inflammatory response and orchestrates the development of the adaptive immune response, adequately controlling the infection while preventing uncontrolled inflammation and tissue damage [63, 64]. The simultaneous activation of multiple PRRs provides virtually an infinite range of possibilities for tailoring an effective response to a wide range of microbes. However, overwhelming infection, deregulated expression or activation of PRRs, and failing negative feedback mechanisms can result in disruption of this finely tuned immune system, resulting in infections or uncontrolled inflammatory responses manifesting as autoimmune diseases and sometimes systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS) [63, 65].

## 4.2 Antimicrobial Peptides: Nature's Antibiotics

Antimicrobial peptides are evolutionarily conserved elements of innate immunity and probably originated because of the coevolution of host and pathogens, necessitating a strict control of pathogenic microbes while preserving beneficial commensal bacteria. More than 700 AMPs have been identified, and they are widely distributed in nature [14]. In general, AMPs are small (12–50 amino acids), and amphipatic, and they contain two positive charges. AMPs are produced mainly by epithelial cells and PMNs. They can be constitutively expressed or inducible by microbial cell wall constituents, tissue damage, and pro-inflammatory cytokines.

AMPs possess pleiotropic functions in the context of host immunity, although not all AMPs share the same set of activities [66, 67]. Direct antimicrobial activity is related to the charge and amphipatic nature of the peptides, hydrophilic at one end and hydrophobic at the other end, facilitating interaction with the microbial cell membrane and ultimately resulting in pore formation and subsequent cell death [68]. Other mechanisms of action have been described for these peptides including increased microbial clearance by opsonization and increased chemotaxis and activation of phagocytic cells. Other immunomodulatory activities have been described such as increased production of cytokines by stimulating PRRs, increased chemotaxis, reduced apoptosis in PMNs, and increased differentiation, maturation, and antigen presentation of DCs [66–68].

## 4.3 Cellular Components

### 4.3.1 Epithelial Cells: A Physical and Immunologic Barrier

The best-known defense function of epithelial cells is the creation of physical barriers. However, these cells are, in fact, "non-classical" immune cells as they are equipped with receptors that sense their surroundings and direct immune activity. Epithelial cells produce a wide array of mediators including antimicrobial peptides, growth factors, chemokines, and cytokines (IL-1 alpha, IL-7, IL-8, and IL-18). In addition, these cells can act as antigen-presenting cells. Moreover, they have immune regulatory functions as they communicate with B-lymphocytes, $\gamma\delta$-T lymphocytes, and dendritic cells. For instance, through the release of TGF-$\beta$, TSLP, and retinoic acid, epithelial cells contribute to the induction of tolerogenic dentritic cells and down-regulation of inflammation in environments that are constantly exposed to foreign antigens and the commensal flora.

### 4.3.2 Thrombocytes

The protective role of platelets [69] in normal individuals is often underestimated but becomes obvious during treatment for a malignant disease. Thrombocytopenia is an almost inevitable repercussion of intensive chemotherapy and irradiation, but a decreased function of thrombocytes is a similar matter of concern. Such a thrombocytopathy is either disease-related or caused by concurrent medication (Table 4). The consequences for both an increased susceptibility to infection and a

**Table 4** Causes and sequelae of thrombocytopenia and thrombocytopathy

| | |
|---|---|
| *Causes of thrombocytopenia* | |
| Disease related | Leukemia and lymphoma, bone marrow metastasis |
| Treatment related | Chemotherapy, radiotherapy |
| *Causes of thrombocytopathy* | |
| Disease related | Leukemia and myeloma, renal insufficiency |
| Treatment related | Chemotherapy, $\beta$-lactam antibiotics, anti-inflammatory drugs, antihistamines, heparin |
| Hazardous sequelae | Hemorrhagic lesions facilitate growth of microorganisms and interfere with organ function |
| | Decrease of platelet-derived growth factor, epidermal cell growth factor, endothelial cell growth factor, fibronectin (diminished adhesion), P-selectin (diminished transmigration) |

decreased capacity to repair damaged tissues can be considerable and may have an impact on the eventual outcome of a treatment episode. Thrombocytopenia also appears to be an independent risk factor for bacteremia [70], and the incidence of major hemorrhages at autopsy of patients who die with or from an infection is striking.

### 4.3.3 Granulocytes

Under normal circumstances, the proliferation of neutrophil precursors is regulated by hematopoietic growth factors such as interleukin-3, granulocyte macrophage-colony stimulating factor (GM-CSF), and granulocyte-colony stimulating factor (G-CSF). Starting from a pluripotent stem cell, it takes approximately 6 days to form metamyelocytes by sequential divisions and another 6 days to mature into polymorphonuclear granulocytes [71]. Approximately 90 % of the total population of neutrophils resides in the bone marrow, only to be released into the circulation upon an inflammatory stimulus. Neutrophils that enter the bloodstream are distributed over two compartments of equal size in dynamic equilibrium: a free circulating pool of neutrophils and the marginating pool, consisting of neutrophils that adhere loosely to the vascular endothelium. The size of these respective pools is under the influence of several factors.

Adherence of neutrophils to endothelial cells is mediated by a number of adhesion molecules on neutrophils, which are induced by factors such as complement factor C5a, which acts as a ligand. Likewise, there is a whole series of adhesion molecules on the endothelial cells themselves, with cytokines such as interleukin-1 and tumor necrosis factor-$\alpha$ being important inducers of these molecules [72]. Other inflammatory impulses and glucocorticosteroids are also potent inhibitors of margination. Circulating neutrophils disappear after approximately 6 h in blood, whereas they survive 1–3 days in tissues.

During an acute inflammatory reaction, an increase in neutrophils, sometimes accompanied by eosinophils and followed by macrophages, can be seen at the site of inflammation. The formation of this inflammatory exudate is the result of activation of several humoral factors, such as cytokines, prostaglandins, and complement, which enhance the blood flow and increase vascular permeability. This occurs in conjunction with chemotactic activity, which results from other soluble factors, especially C5a, leukotriene B, interleukin-8, and bacterial products. In the peripheral blood, granulocytosis evolves as a consequence of the release of the marrow reserve and increased granulocytopoiesis on stimulation by factors such as interleukin-1. However, the mere presence of granulocytes at the site of an infection is meaningless if they are not able to execute their normal functions. Phagocytosis, an Fc- and C3b receptor-mediated process with IgG1, IgG3, and C3b as ligands or opsonins, results in the uptake of particles larger than one micron via pseudopods until they enclose in a vacuole (phagosome). The rate of ingestion by neutrophils is impressive in comparison with that of other phagocytes.

As soon as the particles, with or without opsonins, make contact with the cell membrane of a granulocyte, oxidases in the membrane are triggered to activate oxygen-dependent microbicidal mechanisms, and superoxide, hydrogen peroxide, and hydroxyl radicals are formed. During and after ingestion, the lysosomes, which are microscopically visible as azurophilic granules, fuse with the phagosome and pour their digestive enzymes into the vacuole, a process known as *degranulation.* One of these lysosomal enzymes, myeloperoxidase, triggers the reaction of $H_2O_2$ with chloride, which results in the formation of hypochlorite, a potent microbicidal product. Usually, this operation of phagocytosis and intracellular killing of microorganisms is a suicidal act for the neutrophils, leaving the remainder for consumption and enzymatic digestion by the more powerful macrophages. However, even macrophages may require cooperation with products from activated T lymphocytes for the optimal killing of some microorganisms.

The proliferation and maturation of eosinophilic precursors are under the control of interleukin-3, GM-CSF, and interleukin-5 and have a time span similar to that of neutrophils [73], whereas survival in the tissues appears to be considerably longer. Eosinophils are able to kill several parasites, largely by means of an extracellular process mediated by IgE and, probably, complement.

### 4.3.4 Monocytes and Macrophages

#### Monocytes (blood) and macrophages (tissue)

Monocytes and macrophages are cells of the myeloid lineage derived from the pluripotent myeloid progenitors under the influence of growth factors IL-3 and GM-CSF. Monocytes circulate in the peripheral blood, but enter peripheral tissues where they transform to more adapted macrophages, which patrol the barriers for invaders. Monocytes and macrophages are preeminently equipped in phagocytosis of microbial invaders, but also of cell debris, apoptotic cells, and foreign materials. Additionally, they can act as antigen-presenting cells, although less efficiently as

DCs, and produce pro-inflammatory cytokines (M1-type macrophages). However, some macrophages (M2 type) also exhibit regulatory functions by releasing anti-inflammatory cytokines, such as IL-10.

### 4.3.5 NK Cells

NK cells were originally defined as immune cells naturally capable of killing specific tumor cell lines. They belong to the innate immune system, for they do not need aid with DCs and priming to be effective. These cells have been shown to be indispensible in inducing anti-viral and anti-tumor responses. NK cells are equipped with a complex set of surface molecules and receptors that are either activating (KARs) or inhibiting (KIRs) [74]. The KIRS are very important because with these receptors NK cells can differentiate normal host cells from foreign or infected cells by differentiating between host cell expression of normal or altered MHC class I expression. Effector functions consist of direct cytotoxicity resulting from the release of perforin and granzyme, antibody-dependent cellular cytotoxicity, and release of cytokines, especially IFN$\gamma$. In addition, NK cells possess regulatory functions. At one side, they support DC maturation, Th1 cell activation, and release of pro-inflammatory cytokines, but at the other side, they kill activated T lymphocytes, hyper-activated macrophages, and immature DCs, dampening inflammation and shutting down immune response [75].

## 4.4 Innate Immunity and the Integument

The integument is normally in a state of immunologic tolerance and homeostasis despite being exposed to billions of microorganisms and other foreign substances such as food, beverages, and drugs. This clearly demands comprehensive and careful regulation of the immune system [76, 77]. There is a steady balance between tolerance to non-pathogenic commensal bacteria and intolerance to their pathogenic cousins, necessitating the generation of an effective immune response. Constant interaction and "cross talk" between IECs, immune cells (monocytes, macrophages, and DCs), and microbes are necessary to determine exactly what is going on at the epithelial surface and direct immune actions for maintaining the status quo [76, 78, 79]. Commensal and pathogenic bacteria are also kept in check, as are immune responses, to prevent damage and uncontrolled inflammation.

The innate immune system plays a central role in keeping this delicate balance and even small defects therein can result in disease as a result of infection or uncontrolled inflammation. Both PRRs and AMPs are of great significance here. During homeostasis, activation of PRRs such as TLR2 and TLR9, by commensal flora, helps to maintain barrier function and immune quiescence [80–82], whereas sensing of even commensal flora can elicit pro-inflammatory responses and contribute to the pathogenesis of diseases that compromise barrier functions, such as inflammatory bowel diseases [83–86] AMPs like $\beta$-defensins are widely expressed in the skin and gastrointestinal tract and regulate the composition and burden of the microbial flora at these epithelial barriers.

# 5 Acquired Immunity

## 5.1 Humoral Immunity

The humoral branch of the immune system involves interaction of B cells with antigen and their subsequent proliferation and differentiation into antibody-secreting plasma cells. An important difference in antigen recognition by T cells and B cells is that the latter can recognize an antigen, whereas T cells can only do so once the antigen has been phagocytosed and is presented on the surface of an antigen-presenting cell. In this way, the immune system is able to cope with invaders under a variety of different circumstances. The humoral system recognizes a plethora of bacterial or viral microorganisms as well as the soluble proteins they release. The cell-mediated system is suited to recognizing altered cells belonging to the "self," that is, infected phagocytes as well as cancer cells.

### 5.1.1 Immunoglobulins

Immunoglobulins are produced by the humoral branch of the system when challenged by an antigen and bound to it. IgM is secreted early and during differentiation. Plasma cells then become committed to produce the other classes of immunoglobulin, such as IgG, IgA, IgE, and IgD [72]. The specific functions of IgG and IgM include not only neutralization of the antigen, but also complement activation and opsonization. Secretory IgA, which is found on mucosal surfaces, is not an opsonin but it inhibits the motility of bacteria, neutralizes their toxins, and prevents their adherence to epithelial cells. Circulating IgA probably plays only a minor role in host defense.

The spleen plays an important role in the humoral immune response as the primary immunoglobulin response takes place there, as shown by the low concentrations of IgM found after splenectomy. Reduced concentrations of the complement factor properdin have also been found, leading to suboptimal opsonization. Functional asplenia develops in a large proportion of patients after allogeneic HSCT and is also associated with increased risk for bacterial infections.

## 5.2 Acquired Cellular Immunity

Whereas humoral immunity is primarily responsible for clearing extracellular bacteria, the cellular immune system serves also to eliminate intracellular pathogens and virus-infected cells.

### 5.2.1 Dendritic Cells

Dendritic cells have a specific role in immunity as they function at the crossroads of innate and acquired immunity. They arouse a keen interest because of their unique capacity to efficiently process antigens, present them, and sensitize naive T cells. By releasing different cocktails of cytokines, they shape T lymphocyte,

and also B-lymphocyte and NK cell responses, functioning as orchestrators of acquired immunity. A wide range of dendritic cells have been discovered with even more specific functions [87]. There is now strong evidence that cells of the dendritic family not only control immunity but also regulate responses to self and non-self, thereby avoiding immunopathology. These two complementary functions are critical to ensure the integrity of the organism in an environment full of microbes and foreign antigens. These cells are also important in the intestinal tract for maintaining the immunologic homeostasis. For instance, CD103+ dendritic cells express indoleamine 2,3-dioxygenase that influences T regulatory/T effector cell balance and oral tolerance induction [88].

### 5.2.2 B-Lymphocytes

B-lymphocytes produce immunoglobulins but also possess antibody-independent functions. They act as antigen-presenting cells and interact with T lymphocytes optimizing cellular immune responses, although some controversies still exist about these B–T-cell interactions [89].

### 5.2.3 T Lymphocytes

T lymphocytes are classically categorized as T-cytotoxic CD8+ (Tc), T-helper CD4+ (Th), and regulatory T cells (Treg), including naturally occurring Foxp3+ CD4+ Tregs. Naïve T lymphocytes are sensitized by antigen-presenting cells and the differentiation and activation status depends on multiple conditions including contact between the T-cell receptor (TCR) with MCH molecules, contact between co-stimulatory receptors and an optimal cytokine environment. Tc plays an important role in viral infections and anti-tumor immunity. On activation after contact between the TCR and MCH class I molecules expressing antigens, cytotoxins such as perforin, granzyme, and granulysin are released. Perforin forms pores in the target cell's plasma membrane allowing granzymes to enter the target cell, which eventually leads to apoptosis. A second way to induce apoptosis is via cell-surface interactions between the Tc and the infected cell through Fas–Fas ligand interactions. Th aid other immune and non-immune cells, such as epithelial cells, in their defensive actions. Several phenotypes have been defined based on cytokine signatures. However, new variants are still discovered and T-cell plasticity is increasingly recognized showing T cells capable of changing their phenotype, for instance, transition of Tregs into Th17 and vice versa has been reported [90]. Traditionally, Th1 and Th2 were recognized as functionally different Th subtypes [91]. Th1 cells (T bet) are generated from naïve T cells under the influence of IL-12, and IFN$\gamma$ and Th2 (GATA-3) under the influence of IL-4 and IL-5. Recently, a third subset was discovered, named Th17 (ROR$\gamma$t) generated by IL-1, IL-6, TGF-$\beta$, and IL-23 [92]. In their effector functions, these Th subsets also differ. Th1 cells release IL-2, IFN$\gamma$, and TNF$\alpha$ and increase the phagocytic and killing capacity of normal macrophages helping them to eliminate intracellular organisms (e.g., *Toxoplasma gondii*, *L. monocytogenes*, and *Aspergillus* spp.). IFN$\gamma$ also induced anti-viral defenses. Th2 release IL-4, IL-5, and IL-13 and are

more specifically involved in extracellular parasitic and worm infections as they boost eosinophilic infiltration and activation. In addition, Th2 contributes to effective B-lymphocyte activation and immunoglobulin production. Th17 have largely been implicated in the defense against extracellular pathogens, both bacteria and fungi, residing at the host barriers of skin and mucosa. Th17 cells release IL-17A, IL-17F, IL-21, and IL-22 contributing to chemotaxis of neutrophils and the increased release of antimicrobial proteins from epithelial cells.

## 6 Altered Defenses in Cancer

### 6.1 Physiologic Changes in Cancer

Tumors themselves also predispose to infection by local organ dysfunction. In patients with solid tumors, obstruction of natural passages can lead to inadequate drainage of secretory or excretory fluids from nasal sinuses, bronchi, and bile ducts. Furthermore, tissue invasion may create connections between normally sterile spaces and the environment through disruption of epithelial surfaces. Examples include skin ulcerations with cellulitis and deep soft-tissue infections, and invasion of the bowel wall by tumors of the lower gastrointestinal tract, resulting in bacteremia. Localizations in the central nervous system, spinal cord compression, and paraneoplastic neuropathy are associated with an increased risk of infection due to lethargy and, for instance, a diminished ability to cough and swallow, and incomplete emptying of the bladder [8].

### 6.2 Dysfunctional Innate Immunity

Chemotherapy and radiotherapy inflict severe damage upon the different components of the immune system. Physiologic barriers are breached, immune cells decreased in number resulting in neutropenia, monocytopenia, and various degrees of lymphopenia, often accompanied by functional impairment, and the production of humoral factors such as antimicrobial peptides is decreased. In the setting of SCT, extensive immunodeficiencies result from myeloablative conditioning and immunosuppression for graft-versus-host disease (GVHD) prophylaxis. The residual components of the immune system, especially those comprising innate immunity, are of the utmost importance in defending patients against infection [93], although little is known about which components of the innate immune system remain relatively intact. In general, immune cells such as tissue-residing macrophages, APCs, and NK-cells as well as stromal and epithelial cells and humoral factors such as complement remain [94]. Specialized Paneth cells of the small intestine are also spared from [95] chemotherapy-induced damage, although the impact on their capacity to produce AMPs is not known. Most of these cells are effective by swiftly recognizing bacterial motifs capable of eliciting immune responses.

Although innate immune components aid in the protection of patients treated with chemotherapy, they also contribute to the inflammatory complications related to the resultant damage that consists of oral and gastrointestinal mucositis [96], SIRS as well as ARDS and, in the HSCT setting, GVHD and immune-mediated pulmonary complications [97, 98]. The common denominator is an uncontrolled inflammatory response resulting from excessive release of pro-inflammatory cytokines. Central in the pathogenesis of most of these inflammatory conditions is the occurrence of conditioning-induced tissue damage and disturbance of the normal host bacterial homeostasis in these tissues. Chemotherapy and radiotherapy initiate an inflammatory cascade by activating nuclear factor-$\kappa$B [99], resulting in the production and release of pro-inflammatory cytokines and chemokines (IL-1, IL-6, IL-8, TNF$\alpha$, IFN$\gamma$) by macrophages, IECs, and endothelial cells [99–101]. This inflammatory response is subsequently aggravated by the loss of barriers facilitating the translocation of microbes or microbial wall components stimulating PRRs [102–104] finally, resulting in clinical disorders. In GVHD, the alloreactive T-cell responses are initiated and during the effector phase sustained by innate immune responses.

Besides the loss of adequate barrier function, epithelial cells under "stress" change their attitude toward bacteria and label all microbes as a threat resulting in uncontrolled immune responses [105]. Treatment-related factors mentioned earlier also change the microbial composition, overall with an inversion of the ratio of opportunistic pathogens versus commensals. At the same time, microbes sense the immune status and "stress" of the host and change their behavior by up-regulating virulence factors and becoming genuine pathogens [106].

The role of the innate immunity in cancer patients has been emphasized by the impact of single nucleotide polymorphisms (SNPs) in innate immune genes, which result in enhanced or attenuated expression and/or function, on treatment complications including infections. This has been based on the concept "environmentally determined genetic expression" (EDGE), which states that the effects of normally silent genetic polymorphisms are unmasked when normal homeostasis is severely disrupted such as occurs after exposure to high-dose chemotherapy and/or radiotherapy (Fig. 3) [107]. Several studies have shown SNPs in complement components (mannose-binding lectin), NK receptors, and PRRs resulting in increased risk of bacterial and fungal infections [108–110]. These and other polymorphisms have also been related to other complications of cancer therapy and have been studied especially in the HSCT setting [111, 112]. Polymorphisms in PRRs is of importance in host–microbe interactions such as NOD2, originally described in Crohn's disease, and TLRs have been implicated in the occurrence of GVHD, bronchiolitis obliterans, and treatment-related mortality [113, 114]. Although contradictory results and lack of consistency do not permit firm conclusions, these polymorphisms have provided an insight into the pathogenesis of complex immunologic processes that occur following intensive anti-cancer treatment. Future studies are designed to address the applicability of this information in the prevention or treatment of infections and other complications in patients receiving chemotherapy or undergoing HSCT. Modulating the innate immune

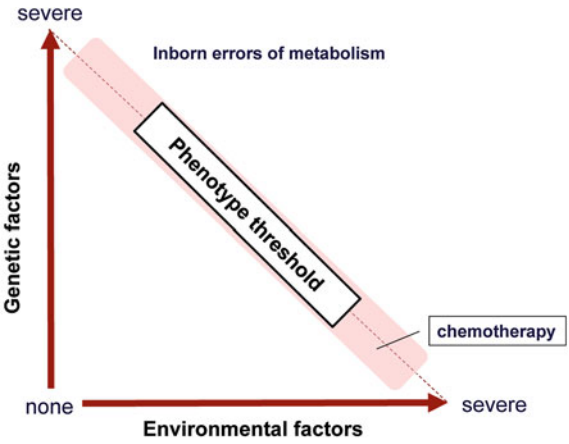


**Fig. 3** EDGE concept. The concept "environmentally determined genetic expression" (*EDGE*) states that the effects of normally silent genetic polymorphisms are unmasked when normal homeostasis is severely disrupted such as occurs after exposure to high-dose chemotherapy or radiotherapy (Adapted from [107]. With permission from Nature Publishing Group)

system with the use of selective agonists and antagonists of TLRs and other PRRs could be a future therapeutic strategy ameliorating complications in cancer therapy [115, 116].

## 6.3 Impairment of Granulocyte Function

Most cytotoxic drugs used in the treatment of malignant diseases have a dose-dependent deleterious effect on the proliferation of normal hematopoietic progenitor cells, including those of the myeloid series. After destruction of the mitotic pool by one or more cytotoxic compounds and depletion of the marrow pool reserve, granulocytopenia lasting days or weeks will ensue, particularly in the treatment of hematologic malignancies and following HSCT-conditioning regimens. Likewise, therapeutic radiation may induce a clinically significant granulocytopenia, depending on dose rate, total dose, irradiated area, and field size. Total body irradiation, as used in HSCT procedures, is the most illustrative of the potential deleterious effects of irradiation. However, both chemotherapeutic drugs and irradiation do not only inhibit the proliferating cell pool, they also interfere with nonproliferating cells and their function. In granulocytes, this may result in decreased chemotaxis, diminished phagocytotic capacity, and defective intracellular killing. Glucocorticosteroids seem to enhance granulocytopoiesis and mobilize the marginal as well as marrow pool reserve, but these supposedly positive effects on the granulocytes are counterbalanced by numerous disadvantages. Indeed, these drugs restrain the accumulation of neutrophils at the site of inflammation through impaired migration, probably due to reduced adherent capacity of the granulocytes, and diminished chemotactic activity. Furthermore, they negatively influence phagocytosis and intracellular killing by neutrophils in a dose-dependent fashion and are associated with a reduction in the number of eosinophils in the blood. Finally, many other drugs, including antibiotics, that are

regularly used in cancer patients are known to interfere with the production and function of granulocytes, which also may lead to an increased susceptibility to infection.

Although they usually occur simultaneously, any substantial reduction in the number of granulocytes or qualitative defect in the phagocytic process can, in fact, make the patient prone to recurrent bacterial and fungal infections. It has been shown that an inverse correlation exists between the number of circulating neutrophils and lymphocytes, and the frequency of infection. Depending on the duration of neutropenia, the risk of a febrile episode varies between 30 and 80 %. In a study by Bodey et al. [117], all patients with a neutrophil count of less than 100/μL for more than 3 weeks developed an infectious complication, and the risk for secondary infections increased proportionally with the duration of granulocytopenia. Moreover, infection-related mortality increased with the duration of hospitalization and the number of days of granulocytopenia.

It may be difficult to establish an unequivocal diagnosis of infection because the inflammatory response in patients without properly functioning granulocytes is muted, thereby obscuring the classic signs and symptoms of infection [118]. Of the episodes of fever associated with granulocytopenia, a definite microbiologic etiology can be established in about a quarter of cases. Local infections, if detected at all, are frequently complicated by bacteremia, which accounts for more than 90 % of culture-documented infections in cancer patients [119, 120].

After bacteria, fungi are the next most common pathogens, especially in immunosuppressed patients who have prolonged and profound granulocytopenia. Autopsy evidence of significant fungal infections can be found in one half of these patients. Most of these infections are not diagnosed or treated antemortem, but they account for 20–30 % of fatal infections in patients with acute leukemia [121–123]. Besides granulocytopenia, the use of pharmacologic doses of corticosteroids and indwelling catheters may also foster the development of systemic fungal infection [124].

## 6.4 Dysfunctional Acquired Immunity

### 6.4.1 Impaired Humoral Immunity

Humoral immunity is impaired in patients with malignancies, leading to decreased production of immunoglobulins, such as in chronic lymphocytic leukemia (CLL), multiple myeloma, and other lymphoproliferative disorders. Humoral immunity is generally well preserved in patients with acute lymphocytic or myelogenous leukemia. However, with intensive chemotherapy and/or progression of the disease, the capacity to produce immunoglobulins decreases. This may lead to defective opsonization of bacteria and subsequent impairment of phagocytosis by neutrophils and macrophages, adding to the quantitative effect of chemotherapy-induced neutropenia.

Although the humoral response in patients with malignant lymphomas is unimpaired, subsequent radiotherapy and chemotherapy, particularly if both treatment modalities are combined, lead to reduced antibody titers and increased susceptibility to infections with pneumococci and *H. influenzae*. Splenectomy potentiates the reduction in immunoglobulins by chemotherapy in these patients. Therefore, combined therapy may increase the risk of post-splenectomy bacteremia in patients with lymphoma, and even after curing Hodgkin's disease, patients are left with a potentially life-threatening humoral immunodeficiency, due to the effects of treatment rather than to the underlying disease itself.

Thus, the advent of more aggressive chemotherapy has changed the classic concept of specific defects of host defense mechanisms in the various types of leukemia and lymphoma. The effects of chemotherapy and radiation are now the primary factor determining the nature and depth of the defect in host defense. Likewise, the increased susceptibility to pneumococci and *H. influenzae* in patients with CLL or multiple myeloma may be replaced by a defect in cellular immunity and neutrophil function when these patients are being treated with glucocorticosteroids or other agents. Whether patients with hypogammaglobulinemia due to CLL should routinely receive intravenous immunoglobulins has been a matter of considerable debate. A cost-effectiveness analysis has suggested that indiscriminate replacement may not improve quality or length of life in this patient group, and that it is extraordinarily expensive [125]. However, such a decision analysis model cannot be applied to the individual patient who actually has suffered from recurrent bacterial infections. Therefore, it seems reasonable to institute immunoglobulin replacement in those patients who have had a documented infection with pneumococcus or *H. influenzae* and have decreased serum IgG concentrations.

### 6.4.2 Impaired Cellular Immunity

The importance of cell-mediated immunity in protecting the host against various intra- and extracellular pathogens is evident from the opportunistic infections occurring in various groups of patients with cancer. Those treated with prednisone or other immunosuppressive agents that affect specific cellular immune responses may be unable to cope with pathogens such as *L. monocytogenes, T. gondii,* herpesviruses, and fungi. The introduction of monoclonal antibodies including rituximab and alemtuzumab to treat hematologic malignancies has resulted in an increase in opportunistic infections due to the induction of lymphopenia, impaired T lymphocyte responses, and phagocyte dysfunction.

Stem cell transplantation (SCT) results in long-lasting dysfunction of T, B, and NK cells hence opportunistic infections may only become manifest long after transplantation and recovery from neutropenia. The most prominent example is VZV infection, which occurred in up to 50 % of SCT recipients in earlier series, but now significantly less because of the use of prophylaxis with acyclovir during the first year after transplant. Additional viral threats include CMV and EBV reactivation and disease as well as infections due to respiratory viruses. Other opportunistic infections consist of fungal infections as invasive aspergillosis, systemic candidiasis, and *Pneumocystis jirovecii* infections. The occurrence of

these infections after SCT is even more pronounced when acute and chronic GVHD occur as these conditions result in organ damage and require prolonged use of immunosuppressants.

Lymphoproliferative diseases, including Hodgkin's lymphoma, T-cell non-Hodgkin lymphoma, and CLL themselves can also elicit impaired cellular immune responses. Hodgkin's lymphoma is a disease that is associated with impaired cellular immunity, although delayed hypersensitivity responses are intact in the majority of untreated patients [126]. The particular defect in T-cell-mediated immunity is probably due to an excess of T-suppressor cells. CLL has also been associated with opportunistic infections, due to a varying degree of defective T-lymphocyte responses, but these defects are most pronounced with an increased duration of the disease and the number of therapies received to treat CLL [127].

## 6.5 Mucosal Barrier Injury

The pathobiology of cytotoxic therapy-induced mucositis has been depicted as consisting of five phases that are not necessarily sequential [128]. First, there is an initiation phase in which free radicals are generated and apoptotic cell death is induced by damage to DNA and other structures. Next, the master transcription factor, NF-$\kappa$B, is involved in the production of the pro-inflammatory cytokines, TNF-$\alpha$ IL-1 and IL-6, which is followed by the amplification and signaling phase of these pro-inflammatory cytokines. Then, there is ulceration, crypt hypoplasia, villous atrophy, and cleavage of extracellular-matrix substrates such as collagen and fibronectin by activated matrix metalloproteinases. This is the phase when bacteria and their cell wall products such as peptidoglycan and lipopolysaccharide are thought to breach the impaired physical barrier more easily and activate tissue macrophages to produce more pro-inflammatory cytokines. The last phase is the healing phase when various factors down-regulate inflammation and restore the integrity of the mucosal barrier. The paracrine mediator of mesenchymal–epithelial communication, keratinocyte growth factor, plays a key role in maintaining the barrier function of epithelial tissues and the healing process after injury [129].

### 6.5.1 Effect of Chemotherapy and Irradiation on the Oral Cavity

Cytotoxic chemotherapy and irradiation interrupt cell division, leading to breakdown in the integrity of the oral mucosa. The production of saliva may also be impaired, leading to a dry mouth and, if mucin is produced may be extremely viscous and difficult to either swallow or expectorate. Periodontal disease may be exacerbated and minor oral cuts and abrasions may become inflamed or ulcerated. The nonkeratinized surfaces of the mouth, including the dorsal surface of the tongue, the roof of the mouth, and the buccal mucosa, may become erythematous, inflamed, and edematous, limiting the intake of both solids and liquids [130]. This phenomenon is now generally referred to as *mucositis,* although some prefer the older term, *stomatitis.* Thus, when mucositis is present, the mouth loses its normal

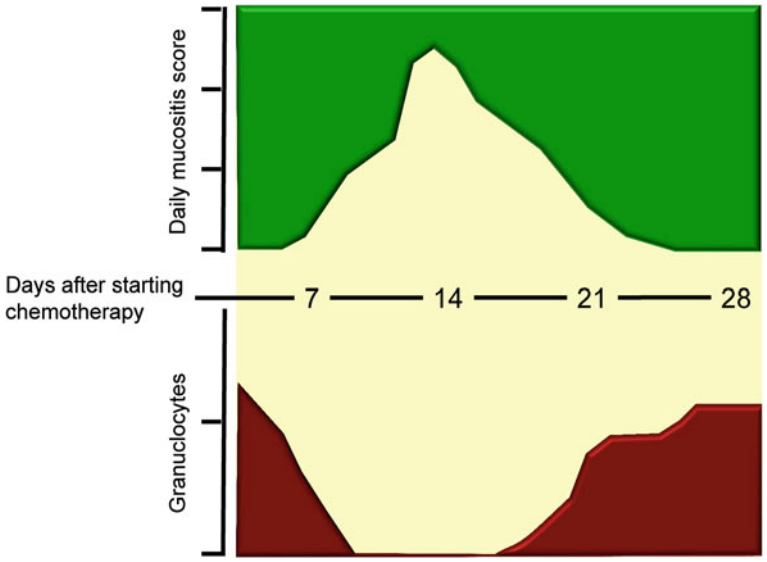


**Fig. 4** Oral mucositis and its relationship to neutropenia. Mucositis and bone marrow aplasia, leading to profound neutropenia, are both manifestations of toxicity frequently occurring together with gut toxicity manifested by nausea, vomiting, and diarrhea. As with neutropenia, mucosal changes normally progress to a peak severity, which coincides with the nadir of bone marrow aplasia and then begins to recover as hematopoiesis returns

ability to dilute foreign bacteria. Mucositis also occurs at the same time as other manifestations of toxicity, particularly bone marrow depletion and gut toxicity, manifested by nausea, vomiting, and diarrhea. Moreover, mucosal changes normally progress to a peak severity and coincide with the nadir of bone marrow aplasia and then begin to recover as hematopoiesis returns (Fig. 4) [130–133].

Because myeloablative regimens deplete the pool of myeloid cells, the patient becomes further dependent on the vestiges of the innate immune system and especially epithelial cells of the digestive tract and skin for protection against potentially lethal infectious complications. These epithelia form an anatomic and immunologic barrier often referred to as the integument that serves as the front line against microbial invasion. Although these epithelia are highly organized and sophisticated structures, the barrier they create is not invincible to microorganisms especially after it is damaged by anti-cancer therapy.

### 6.5.2 Oral Mucositis

Mucositis is essentially the clinical manifestation of mucosal barrier injury and is characterized by functional complaints such as dysphagia and odynophagia, anatomic changes such as edema, erythema, ulceration, pseudomembrane formation, and alterations in mucus consistency with changes in saliva production (xerostomia). Mucositis results in significant morbidity and markedly lowers the quality of life for several weeks following cytotoxic chemotherapy and irradiation. Modern

remission-induction cytostatic chemotherapy and conditioning regimens for HSCT often induce substantial injury to the mucosa. Combinations containing melphalan, etoposide, methotrexate, cytarabine, and idarubicin have all been shown to induce mucositis [134, 135]. Mucositis can be particularly severe when anthracyclines are combined with total body irradiation and cyclophosphamide to condition patients for an allogeneic HSCT [136]. The duration and incidence of fever, parenteral narcotic use, total parenteral nutrition, antibiotic therapy, and the length of stay in a hospital are all correlated with the severity of mucositis, as is the risk of significant infections and mortality [134, 137, 138]. Oral viridans streptococcal infections are related to mucosal barrier injury of the upper part of the digestive tract, particularly the oral cavity, whereas enteric gram-negative bacillary infections and neutropenic enterocolitis are related to the lower part of the digestive tract.

Extensive mucosal damage is often accompanied by a decline in saliva production leading to a dry mouth. Any mucus produced may be extremely viscous and difficult to either swallow or cough up [136, 139]. Periodontal disease may be exacerbated, and minor oral cuts and abrasions may become inflamed and ulcerated. The nonkeratinized surfaces of the mouth, including the underside of the tongue, the roof of the mouth, and the cheeks, may become red, inflamed, and swollen, and thus limit the intake of both food and drink with the risk of malnutrition and catabolism [130]. Moreover, mucosal changes normally progress to a peak severity coinciding independently with the nadir of bone marrow aplasia, and then begin to recover as hematopoiesis returns [130, 140, 141].

Exposing oral commensal flora to the antimicrobial agents used for prophylaxis and local antisepsis will inevitably select for more resistant species. Very susceptible bacteria, such as the oral *Neisseria* spp., will be suppressed by a wide range of antimicrobials. Others that are marginally susceptible to frequently used agents such as co-trimoxazole, penicillin, and fluoroquinolones, will thrive. This partly explains why the viridans streptococci have become one of the most frequent causes of bacteremia in neutropenic patients who have undergone myelosuppressive chemotherapy or HSCT [142], although the chemotherapeutic agents may be a more important factor, especially when it induces severe mucosal damage [143]. *S. mitis*, many of which are actually *S. oralis* (formerly *S. sanguis* II) [144], is causing concern because its appearance in the bloodstream following treatment with high-dose cytarabine is associated with sepsis syndrome and the adult respiratory distress syndrome (ARDS).

Bacteremia due to other unusual oral commensals, such as *Stomatococcus, Rothia mucilaginosa, Capnocytophaga* spp., and *Leptotrichia buccalis,* are likely to be selected by quinolone use. In addition, gingivitis as the source of *S. epidermidis* bacteremia has been reported [145]. Similar risk factors are associated with bacteremia due to members of the *S. milleri* group [146]. The chlorhexidine mouthwashes used to minimize infective complications arising from the oral toxicity induced by chemotherapy also influence the microflora [133, 147, 148]. The oral flora may also change as a direct result of chemotherapy [149], and it is likely that more intensive conditioning regimens will aggravate mucositis, leading to a commensurate increase in the number of unusual bacteria.

Use of the growth factors, G-CSF and GM-CSF [150, 151] does not appear to have any influence on mucositis [152].

### 6.5.3 Gut Mucositis

Besides damage to the oropharyngeal, esophageal, and gastric mucosa, chemotherapy and irradiation impair gut function and lead to rapid alterations in permeability. The increased absorption of sugars such as rhamnose, mannose, and lactulose and the decreased uptake of xylose after chemotherapy, irradiation, or a combination of both indicate a loss of integrity and damage to tight junctions [135, 153, 154]. Impaired gut function and integrity may also facilitate translocation, and blood stream infections of patients colonized with bacteria and fungi [155]. Gut toxicity has also been shown to be responsible for the reduced absorption of quinolones [156, 157] and has been implicated in the erratic bioavailability of the antifungal agent itraconazole and posaconazole [158, 159]. A dysfunctional gut will also have a marked effect on the nutritional status of the patient not least by the diminished release of citrulline by the lower number of functioning enterocytes [160]. This amino acid can be detected in blood and used to determine the extent of gut injury in stem cell transplant recipients [160].

The gastrointestinal tract has long been implicated as the principal origin of infections caused by the enteric gram-negative bacilli, including *E. coli, K. pneumoniae,* and *Enterobacter* spp. [161], providing the motivation for adopting prophylaxis with fluoroquinolones [162–164]. More recently, the role of neutropenic enterocolitis or typhlitis, a severe form of mucosal damage of the gut induced by cytotoxic therapy, has also become clearer in providing a portal of entry for various toxin-producing bacteria, including *S. aureus, P. aeruginosa,* various *Clostridium* spp. and even *Bacillus cereus* [165–168]. This illustrates how the delicate balance between the host and the resident microflora can be disturbed in the setting of mucosal barrier injury and prolonged exposure to antibiotics. Colonization by *Candida* species of the mucosal surfaces appears to be a prerequisite for local mucosal infection and subsequent invasive disease [169]. Mucosal barrier injury, including neutropenic enterocolitis, is also an independent risk factor for invasive candidiasis among patients receiving cytotoxic chemotherapy [135, 153].

One of the most important consequences of the loss of colonization resistance is that cell surfaces become vacant, allowing some exogenous bacteria such as *P. aeruginosa* to establish residence, leading to chronic colonization, with the attendant risks of invasion and systemic dissemination. The ecology of the bowel flora is also altered markedly by diarrhea induced by treatment with certain chemotherapy [170], GVHD [171], and total body irradiation [170, 172]. When severe chemotherapy-induced mucositis extends to the cecum, typhlitis, or neutropenic enterocolitis can occur and the recovery of *Clostridium septicum* from the blood confirms the diagnosis [173] (Fig. 5) [174]. Gut permeability also increases following conditioning therapy for bone marrow transplant [175]. Agents used either for the treatment of neoplasms or supportive care may even exert an influence on gut and oral flora, either alone or in combination.

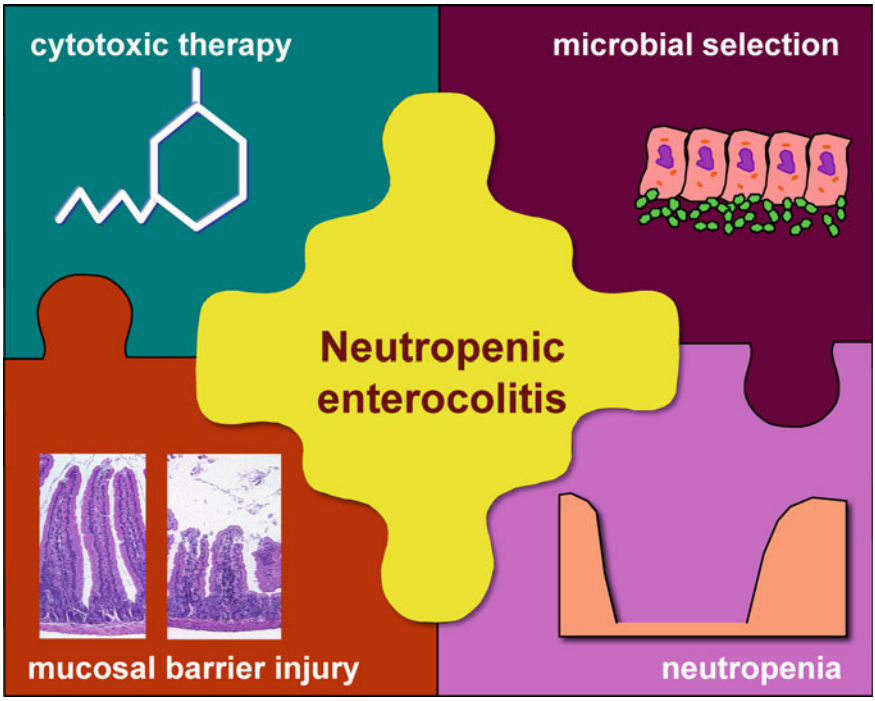


**Fig. 5** Neutropenic enterocolitis—an example of MBI-related infection. Neutropenic enterocolitis (also known as typhlitis) is an example of the interplay between the nature of the chemotherapeutic regimen, the mucosal barrier injury it induces, the indigenous microbial flora that remains after exposure to broad-spectrum antimicrobial therapy, and the absence of neutrophils. Certain cytotoxic drugs e.g., cytarabine can disrupt the mucosal barrier of the gut as well as causing protracted neutropenia and hemorrhage due to thrombocytopenia. Necrosis of the gastrointestinal mucosa particularly of the terminal ileum or cecum manifests as enterocolitis and predisposes the patient to infection with any organism capable of invasion. Antimicrobial treatment, first with selective antimicrobial prophylaxis e.g., with a fluoroquinolone and later with broad-spectrum antibiotics e.g., ceftazidime, will profoundly disturb the normal resident flora and may provide a selective advantage to a resistant bacterium such as *Clostridium septicum*. The stage is set for neutropenic enterocolitis associated with infection. Neutropenic enterocolitis is not only a paradigm for MBI but is also the most severe clinical manifestation of MBI

Some chemotherapeutic agents have been shown to have antibacterial activity and even to enhance the effects of antimicrobial agents [176–181]. The antifungal, miconazole, is also inhibitory to gram-positive bacteria [182]. Gut motility is reduced during parenteral nutrition due to the low amounts of fiber and reduced microbial biomass, which result in dilute feces. When the gut fails to function normally, the protective "anaerobic wallpaper" may still be intact but will be unusually fragile to the effect of antimicrobial agents. Thus, unless placed in a degree of isolation and supplied with low-microbial content diets, patients will be vulnerable to acquiring other gram-negative bacilli from the environment [21–23].

### 6.5.4 Mucosal Barrier Injury and Infection

The systemic inflammatory response as measured by CRP appears directly related to the course and extent of mucosal damage reflected by low-citrulline levels rather than infection per se [183]. Also, the risk of infection is significantly higher during chemotherapy cycles that are complicated by mucositis than during those without mucositis. This has been shown for bacteremia due to oral viridans streptococci mainly *S. mitis* and *S. oralis* [184]. Drug-induced achlorhydria and the use of antimicrobial prophylaxis with typically but not exclusively fluoroquinolones also contributes toward the development of bacteremia [142].

*Candida* spp. normally reside on the mucosal surfaces of the digestive tract of many adults. Adherence to these surfaces appears to be a prerequisite for local infection and subsequent invasive disease since regular surveillance cultures of hematologic patients have shown that colonization invariably precedes infection [52]. Patients treated for AML with either high-dose cytarabine or an anthracycline have low serum D-xylose levels indicating malabsorption and are at higher risk of developing invasive candidiasis. SCT recipients prepared with regimens composed of TBI and patients treated with remission-induction regimens have an increased risk of developing invasive *Candida* disease.

## 7 Conclusions

It is clear from the foregoing that patients with neoplastic diseases seldom suffer impairment of a single defense mechanism. Rather, the risk of infection is the product of the interplay between the many lines of defense, all of which can be breached simultaneously. Moreover, any attempt to confine the damage inflicted upon the host defenses by protecting only one specific line of defense such as the use of growth factors to stimulate hematopoiesis is likely to offer only limited benefit. What is required is a two-pronged approach involving more selective cancer treatment, to avoid damaging healthy tissue combined with strategies that prevent, or at least ameliorate, any unavoidable toxicity. This requires a holistic approach involving both the laboratory and the clinician in continuing to refine therapeutic regimens that are effective and in designing others to cope with the morbidity associated with impaired host defenses. Both are essential to successfully achieve remission of neoplastic disease and to maintain the best quality of life for the patient.

## References

1. Johnson CL, Versalovic J (2012) The human microbiome and its potential importance to pediatrics. Pediatrics 129(5):950–960 (PubMed PMID: 22473366. Pubmed Central PMCID: 3340594)
2. Chandra RK (1983) Nutrition, immunity, and infection: present knowledge and future directions. Lancet 1(8326 Pt 1):688–691 (PubMed PMID: 6132048. Epub 1983/03/26, Eng)
3. Louria DB (1984) Symposium on infectious complications of neoplastic disease (part I). Introduction and epidemiology. Am J Med 76(3):414–420

4. Salimonu LS, Ojo-Amaize E, Williams AI, Johnson AO, Cooke AR, Adekunle FA, et al (1982) Depressed natural killer cell activity in children with protein-calorie malnutrition. Clin Immunol Immunopathol 24(1):1–7 (PubMed PMID: 6179671. Epub 1982/07/01, Eng)
5. Sugarman B (1983) Zinc and infection. Rev Infect. Dis 5(1):137–147 (PubMed PMID: 6338570. Epub 1983/01/01, Eng)
6. Miceli MH, Dong L, Grazziutti ML, Fassas A, Thertulien R, Van Rhee F, et al (2006) Iron overload is a major risk factor for severe infection after autologous stem cell transplantation: a study of 367 myeloma patients. Bone Marrow Transplant 7(9):857–864 (PubMed PMID: 16532017. Eng)
7. Craddock PR, Yawata Y, VanSanten L, Gilberstadt S, Silvis S, Jacob HS (1974) Acquired phagocyte dysfunction. A complication of the hypophosphatemia of parenteral hyperalimentation. N Engl J Med 290(25):1403–1407 (PubMed PMID: 4208370. Epub 1974/06/20. Eng)
8. McGeer A, Feld R (1994) Epidemiology of infection in immunocompromised oncological patients. Baillikre's Clin Infect Dis 1:415–438
9. Allen J (1981) The diabetic as a compromised host. In: Allen J (ed) Infection and the compromised host: clinical correlations and therapeutic approaches. Williams&Wilkins, Baltimore, pp 229–270
10. Rubin J, Yu VL (1988) Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis, and therapy. Am J Med 85(3):391–398 (PubMed PMID: 3046354. Epub 1988/09/01. Eng)
11. Chayakulkeeree M, Ghannoum MA, Perfect JR (2006) Zygomycosis: the re-emerging fungal infection. Eur J Clin Microbiol Infect Dis 25(4):215–229 (PubMed PMID: 16568297. Eng)
12. Cech P, Stalder H, Widmann JJ, Rohner A, Miescher PA (1979) Leukocyte myeloperoxidase deficiency and diabetes mellitus associated with *Candida albicans* liver abscess. Am J Med 66(1):149–153 (PubMed PMID: 217268. Epub 1979/01/01. Eng)
13. Swartz MN (1991) Stress and the common cold. N Engl J Med 325(9):654–656 (PubMed PMID: 1861700. Epub 1991/08/29. Eng)
14. Saltzman RL, Peterson PK (1987) Immunodeficiency of the elderly. Rev Infect Dis 9(6):1127–1139 (PubMed PMID: 3321363. Epub 1987/11/01. Eng)
15. Roth RR, James WD (1988) Microbial ecology of the skin. Ann Rev Microbiol 42:441–464
16. Kotilainen P, Nikoskelainen J, Huovinen P (1990) Emergence of ciprofloxacin-resistant coagulase-negative staphylococcal skin flora in immunocompromised patients receiving ciprofloxacin. J Infect Dis 161:41–44
17. Schittek B, Hipfel R, Sauer B, Bauer J, Kalbacher H, Stevanovic S, et al (2001) Dermcidin: a novel human antibiotic peptide secreted by sweat glands. Nat Immunol 2(12):1133–1137 (PubMed PMID: 11694882. Epub 2001/11/06. Eng)
18. McNab PC, Tomasi TB (1981) Host defense mechanisms at mucosal surfaces. Ann Rev Microbiol 35:477–496
19. Beattie G, Whelan J, Cassidy J, Milne L, Burns S, Leonard R (1989) Herpes simplex virus, *Candida albicans* and mouth ulcers in neutropenic patients with non-haematological malignancy. Cancer Chemother Pharmacol 25:75–76
20. Bergmann OJ (1992) Oral infections in haematological patients—pathogenesis and clinical significance. Dan Med Bull 39(1):15–29
21. Schimpff SC (1980) Infection prevention during profound granulocytopenia: new approaches to alimentary canal microbial suppression. Ann Intern Med 93:358–361
22. Van Der Waaij D (1979) The colonization resistance of the digestive tract of man and animals. Gustav Fischer Verlag, New York
23. Young LS (1988) Antimicrobial prophylaxis in the neutropenic host: lessons of the past and perspectives for the future. Eur J Clin Microbiol Infect Dis 1988 7(1):93–97 (PubMed PMID: 3132393. Epub 1988/02/01. Eng)

24. Van der Waaij D (1989) The ecology of the human intestine and its consequences for overgrowth by pathogens such as *Clostridium difficile*. Ann Rev Microbiol 43:69–87
25. Vollaard EJ, Clasener HAL (1994) Colonization resistance. Antimicrob Agents Chemother 38(3):409–414
26. Van der Waaij D (1984) Effect of antibiotics on colonization resistance. In: Easmon CS (ed) Medical microbiology, 4th edn. Academic Press Inc, London, pp 227–237
27. Louie TJ, Chubb H, Bow EJ, Conly JM, Harding GKM, Rayner E et al (1985) Preservation of colonization resistance parameters during empiric therapy with aztreonam in febrile neutropenic patient. Rev Infect Dis 7:S747–S761
28. Meijer-Severs GJ, van Santen E (1987) Short-chain fatty acids and succinate in feces of healthy human volunteers and their correlation with anaerobe cultural counts. Scand J Gastroenterol 22(6):672–676 (PubMed PMID: 3659829. Epub 1987/08/01. Eng)
29. Welling GW, Groen G (1989) Inactivation of aztreonam by faecal supernatants of healthy volunteers as determined by HPLC. J Antimicrob Chemother 24:805–810
30. Dietrich M, Rasche H, Rommel K, Hochapfel G (1973) Antimicrobial therapy as a part of the decontamination procedures for patients with acute leukemia. Eur J Cancer 9:443–447
31. Bender JF, Schimpff SC, Young VM, Fortner CL, Brouillet MD, Love LJ et al (1979) Role of vancomycin as a component of oral nonabsorbable antibiotics for microbial suppression in leukemic patient. Antimicrob Agents Chemother 15:455–460
32. Pizzo PA, Robichaud KJ, Edwards BK, Schumaker C, Kramer BS, Johnson A (1983) Oral antibiotic prophylaxis in patients with cancer: a double-blind randomized placebo-controlled trial. J Pediatr 102(1):125–133 (PubMed PMID: 6336781. Epub 1983/01/01. Eng)
33. Walsh TJ, Schimpff SC (1983) Prevention of infection among patients with cancer. Eur J Cancer Clin Oncol 19(10):1333–1344 (PubMed PMID: 6416846. Epub 1983/10/01. Eng)
34. Nord CE, Kager L, Heimdahl A (1984) Impact of antimicrobial agents on the gastrointestinal microflora and the risk of infections. Am J Med 15:99–106
35. Rozenberg-Arska M, Dekker AW (1987) Ciprofloxacin for infection prevention in patients with acute leukemia. Pharm Weekbl Sci 9:S45–S47
36. Jones PG, Bodey GP, Swabb EA, Rosenbaum B (1984) Effect of aztreonam on throat and stool flora of cancer patients. Antimicrob Agents Chemother 26:941–943
37. Jones RN, Barry AL, Thornsberry C (1989) In-vitro studies of meropenem. J Antimicrob Chemother 24(suppl A):9–29
38. Vollaard EJ, Clasener HAL, Janssen AJHM (1990) Decontamination of the bowel by intravenous administration of pefloxacin. J Antimicrob Chemother 26:847–852
39. Vollaard EJ, Clasener HAL, Janssen AJHM (1990) The contribution of *Escherichia coli* to microbial colonization resistance. J Antimicrob Chemother 26:411–418
40. Welling GW, Slootmakervandermeulen C, Jansen GJ (1993) Inactivation of imipenem by faecal fractions from human volunteers and the effect of clavulanate and cilastatin. J Antimicrob Chemother 31(4):617–619
41. Clasener HA, Vollaard EJ, van Saene HK (1987) Long-term prophylaxis of infection by selective decontamination in leukopenia and in mechanical ventilation. Rev Infect Dis 9(2):295–328 (PubMed PMID: 3296099. Epub 1987/03/01. Eng)
42. Van der Leur JJ, Thunnissen PL, Clasener HA, Muller NF, Dofferhoff AS (1993) Effects of imipenem, cefotaxime and cotrimoxazole on aerobic microbial colonization of the digestive tract. Scand J Infect Dis 25(4):473–478 (PubMed PMID: 8248747. Epub 1993/01/01. Eng)
43. Van Der Waaij D, Hofstra H, Wiegersma N (1982) Effect of ß-lactam antibiotics on the resistance of the digestive tract of mice to colonization. J Infect Dis 146:417–422
44. Vollaard EJ, Clasener HAL, Van Griethuysen AJA, Janssen AJHM, Sanders-Reimers AHJ, Muller NF et al (1988) Influence of cefaclor, phenethicillin, co-trimoxazole and doxycycline on colonization resistance in healthy volunteers. J Antimicrob Chemother 22:747–758

45. Wiegersma N, Jansen G, Van Der Waaij D (1982) Effect of twelve antimicrobial drugs on the colonization resistance of the digestive tract of mice and on endogenous potentially pathogenic bacteria. J Hyg Camb 88:221–230
46. Vollaard EJ, Clasener HAL, Janssen AJHM (1992) Co-trimoxazole impairs colonization resistance in healthy volunteers. J Antimicrob Chemother 30:685–691
47. Meijer-Severs GJ, Joshi JH (1989) The effect of new broad-spectrum antibiotics on faecal flora of cancer patients. J Antimicrob Chemother 24:605–613
48. Chomarat M, Espinouse D (1991) *Lactobacillus rhamnosus* septicemia in patients with prolonged aplasia receiving ceftazidime-vancomycin. Eur J Clin Microbiol Infect Dis 10(1):44 (PubMed PMID: 2009881. Epub 1991/01/01. Eng)
49. Cometta A, Calandra T, Bille J, Glauser MP (1994) *Escherichia coli* resistant to fluoroquinolones in patients with cancer and neutropenia. N Engl J Med 330(17):1240–1241
50. Kern WV, Markus A, Andriof E (1994) Bacteremia due to fluoroquinolone resistant *Escherichia coli* in two immunocompromised patients. Eur J Clin Microbiol Infect Dis 13:161–165
51. Kern WV, Andriof E, Oethinger M, Kern P, Hacker J, Marre R (1994) Emergence of fluoroquinolone-resistant *Escherichia coli* at a cancer center. Antimicrob Agents Chemother 38(4):681–687 (PubMed PMID: 8031031. Pubmed Central PMCID: 284525. Epub 1994/04/01. Eng)
52. Zinner SH, Calandra T, Meunier F, Gaya H, Viscoli C, Klastersky J et al (1994) Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer—a trial of oral penicillin v or placebo combined with pefloxacin. JAMA 272(15):1183–1189
53. Iwasaki A, Medzhitov R (2004) Toll-like receptor control of the adaptive immune responses. Nat Immunol 5(10):987–995 (PubMed PMID: 15454922. Epub 2004/09/30. Eng)
54. Medzhitov R, Janeway CA Jr (1998) Innate immune recognition and control of adaptive immune responses. Semin Immunol 10(5):351–353 (PubMed PMID: 9799709. Epub 1998/11/04. Eng)
55. Medzhitov R, Janeway C Jr (2000) Innate immunity. N Engl J Med 343(5):338–344 (PubMed PMID: 10922424. Epub 2000/08/03. Eng)
56. Pitman RS, Blumberg RS (2000) First line of defense: the role of the intestinal epithelium as an active component of the mucosal immune system. J Gastroenterol 35(11):805–814 (PubMed PMID: 11085489. Epub 2000/11/21. Eng)
57. Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124(4):783–801 (PubMed PMID: 16497588. Epub 2006/02/25. Eng)
58. Robinson MJ, Sancho D, Slack EC, LeibundGut-Landmann S, Reis e Sousa C (2006) Myeloid C-type lectins in innate immunity. Nat Immunol 7(12):1258–1265 (PubMed PMID: 17110942. Epub 2006/11/18. Eng)
59. Strober W, Murray PJ, Kitani A, Watanabe T (2006) Signalling pathways and molecular interactions of NOD1 and NOD2. Nat Rev Immunol 6(1):9–20 (PubMed PMID: 16493424. Epub 2006/02/24. Eng)
60. Bianchi ME (2007) DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 81(1):1–5 (PubMed PMID: 17032697. Epub 2006/10/13. Eng)
61. Medzhitov R, Janeway CA Jr (2002) Decoding the patterns of self and nonself by the innate immune system. Science 296(5566):298–300 (PubMed PMID: 11951031. Epub 2002/04/16. Eng)
62. Matzinger P (2002) The danger model: a renewed sense of self. Science 296(5566):301–305 (PubMed PMID: 11951032. Epub 2002/04/16. Eng)
63. Barton GM (2008) A calculated response: control of inflammation by the innate immune system. J Clin Invest 118(2):413–420 (PubMed PMID: 18246191. Pubmed Central PMCID: 2214713. Epub 2008/02/05. Eng)
64. Underhill DM (2003) Toll-like receptors: networking for success. Eur J Immunol 33(7):1767–1775 (PubMed PMID: 12811836. Epub 2003/06/18. Eng)
65. Han J, Ulevitch RJ (2005) Limiting inflammatory responses during activation of innate immunity. Nat Immunol 6(12):1198–1205 (PubMed PMID: 16369559. Epub 2005/12/22. Eng)

66. Mookherjee N, Hancock RE (20007) Cationic host defence peptides: innate immune regulatory peptides as a novel approach for treating infections. Cell Mol Life Sci 64(7–8):922–933 (PubMed PMID: 17310278. Epub 2007/02/21. Eng)
67. Scott MG, Hancock RE (2000) Cationic antimicrobial peptides and their multifunctional role in the immune system. Crit Rev Immunol 20(5):407–431 (PubMed PMID: 11145218. Epub 2001/01/06. Eng)
68. Zasloff M (2002) Antimicrobial peptides of multicellular organisms. Nature 415(6870):389–395 (PubMed PMID: 11807545. Epub 2002/01/25. Eng)
69. Ware AJ, Coller BS (1995) Platelet morphology, biochemistry, and function. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ (eds) Williams hematology. McGraw-Hill, New York, pp 1161–1201
70. Viscoli C, Bruzzi P, Castagnola E, Boni L, Calandra T, Gaya H, et al (1994) Factors associated with bacteraemia in febrile, granulocytopenic cancer patients. The International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 30A(4):430–437 (PubMed PMID: 8018397. Eng)
71. Cronkite EP, Fliedner TM (1964) Granulocytopoiesis. N Engl J Med 270:1347–1352 CONTD (PubMed PMID: 14140268. Epub 1964/06/18. Eng)
72. Van der Meer JWM (1994) Defects in host defense mechanisms. In: Rubin RH, Young LS (eds) Current approach to infection in the compromised host. Plenum Medical, New York, pp 33–66
73. Weller PF (1991) The immunobiology of eosinophils. N Engl J Med 324(16):1110–1118 (PubMed PMID: 2008184. Epub 1991/04/18. Eng)
74. Lanier LL (2008) Up on the tightrope: natural killer cell activation and inhibition. Nat Immunol 9(5):495–502 (PubMed PMID: 18425106. Pubmed Central PMCID: 2669298)
75. Vivier E, Malissen B (2005) Innate and adaptive immunity: specificities and signaling hierarchies revisited. Nat Immunol 6(1):17–21
76. Artis D (2008) Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut. Nat Rev Immunol 8(6):411–420 (PubMed PMID: 18469830. Epub 2008/05/13. Eng)
77. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI (2005) Host-bacterial mutualism in the human intestine. Science 307(5717):1915–1920 (PubMed PMID: 15790844. Epub 2005/03/26. Eng)
78. Rescigno M, Lopatin U, Chieppa M (2008) Interactions among dendritic cells, macrophages, and epithelial cells in the gut: implications for immune tolerance. Curr Opin Immunol 20(6):669–675 (PubMed PMID: 18852045. Epub 2008/10/15. Eng)
79. Rimoldi M, Chieppa M, Salucci V, Avogadri F, Sonzogni A, Sampietro GM, et al (2005) Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. Nat Immunol 6(5):507–514 (PubMed PMID: 15821737. Epub 2005/04/12. Eng)
80. Cario E (2008) Barrier-protective function of intestinal epithelial Toll-like receptor 2. Mucosal Immunol 1(1):S62–S66 (PubMed PMID: 19079234. Epub 2008/12/23. Eng)
81. Lee J, Mo JH, Katakura K, Alkalay I, Rucker AN, Liu YT, et al. Maintenance of colonic homeostasis by distinctive apical TLR9 signalling in intestinal epithelial cells. Nat Cell Biol 8(12):1327–1336 (PubMed PMID: 17128265. Epub 2006/11/28. Eng)
82. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R (2004) Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 118(2):229–241 (PubMed PMID: 15260992. Epub 2004/07/21. Eng)
83. McGuckin MA, Eri R, Simms LA, Florin TH, Radford-Smith G (2009) Intestinal barrier dysfunction in inflammatory bowel diseases. Inflamm Bowel Dis 15(1):100–113 (PubMed PMID: 18623167. Epub 2008/07/16. Eng)
84. McInturff JE, Modlin RL, Kim J. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease (2005) J Invest Dermatol 125(1):1–8 (PubMed PMID: 15982296. Epub 2005/06/29. Eng)

85. Rogler G (2004) Update in inflammatory bowel disease pathogenesis. Curr Opin Gastroenterol 20(4):311–317 (PubMed PMID: 15703658. Epub 2005/02/11. Eng)
86. Sansonetti PJ (2008) Host-bacteria homeostasis in the healthy and inflamed gut. Curr Opin Gastroenterol 24(4):435–439 (PubMed PMID: 18622156. Epub 2008/07/16. Eng)
87. Coquerelle C, Moser M (2010) DC subsets in positive and negative regulation of immunity. Immunol Rev 234(1):317–334
88. Matteoli G, Mazzini E, Iliev ID, Mileti E, Fallarino F, Puccetti P et al (2010) Gut CD103+ dendritic cells express indoleamine 2,3-dioxygenase which influences T regulatory/T effector cell balance and oral tolerance induction. Gut 59(5):595–604
89. Lund FE, Randall TD (2010) Effector and regulatory B cells: modulators of CD4(+) T cell immunity. Nat Rev Immunol 10(4):236–247 (PubMed PMID: 20224569. Pubmed Central PMCID: 3038334)
90. Zhou L, Chong MM, Littman DR (2009) Plasticity of CD4+ T cell lineage differentiation. Immunity 30(5):646–655
91. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 136(7):2348–2357
92. Weaver CT, Harrington LE, Mangan PR, Gavrieli M, Murphy KM (2006) Th17: an effector CD4 T cell lineage with regulatory T cell ties. Immunity 24(6):677–688
93. Neth OW, Bajaj-Elliott M, Turner MW, Klein NJ (2005) Susceptibility to infection in patients with neutropenia: the role of the innate immune system. Br J Haematol 129(6):713–722 (PubMed PMID: 15952996. Epub 2005/06/15. Eng)
94. Geddes M, Storek J (2007) Immune reconstitution following hematopoietic stem-cell transplantation. Best Pract Res Clin Haematol 20(2):329–348 (PubMed PMID: 17448965. Epub 2007/04/24. Eng)
95. Verburg M, Renes IB, Meijer HP, Taminiau JA, Buller HA, Einerhand AW, et al (2000) Selective sparing of goblet cells and paneth cells in the intestine of methotrexate-treated rats. Am J Physiol Gastrointest Liver Physiol 2000 279(5):G1037–G1047 (PubMed PMID: 11053002. Epub 2000/10/29. Eng)
96. Blijlevens NM, Donnelly JP, DePauw BE (2005) Inflammatory response to mucosal barrier injury after myeloablative therapy in allogeneic stem cell transplant recipients. Bone Marrow Transplant 36(8):703–707 (PubMed PMID: 16062174. Epub 2005/08/03. Eng)
97. Cooke KR (2005) Acute lung injury after allogeneic stem cell transplantation: from the clinic, to the bench and back again. Pediatr Transplant 9(7):25–36 (PubMed PMID: 16305615. Epub 2005/11/25. Eng)
98. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease (2009) Lancet 373(9674):1550–1561 (PubMed PMID: 19282026. Pubmed Central PMCID: 2735047. Epub 2009/03/14. Eng)
99. Sonis ST (2002) The biologic role for nuclear factor-kappaB in disease and its potential involvement in mucosal injury associated with anti-neoplastic therapy. Crit Rev Oral Biol Med 13(5):380–389 (PubMed PMID: 12393757. Epub 2002/10/24. Eng)
100. Logan RM, Stringer AM, Bowen JM, Yeoh AS, Gibson RJ, Sonis ST, et al (2007) The role of pro-inflammatory cytokines in cancer treatment-induced alimentary tract mucositis: pathobiology, animal models and cytotoxic drugs. Cancer Treat Rev 33(5):448–460 (PubMed PMID: 17507164. Epub 2007/05/18. Eng)
101. Xun CQ, Thompson JS, Jennings CD, Brown SA, Widmer MB (1994) Effect of total body irradiation, busulfan-cyclophosphamide, or cyclophosphamide conditioning on inflammatory cytokine release and development of acute and chronic graft-versus-host disease in H-2-incompatible transplanted SCID mice. Blood 83(8):2360–2367 (PubMed PMID: 8161803. Epub 1994/04/15. Eng)
102. Levy O, Teixeira-Pinto A, White ML, Carroll SF, Lehmann L, Wypij D, et al (2003) Endotoxemia and elevation of lipopolysaccharide-binding protein after hematopoietic stem

cell transplantation. Pediatr Infect Dis J 22(11):978–981 (PubMed PMID: 14614371. Epub 2003/11/14. Eng)
103. Song D, Shi B, Xue H, Li Y, Yang X, Yu B, et al (2006) Confirmation and prevention of intestinal barrier dysfunction and bacterial translocation caused by methotrexate. Dig Dis Sci 51(9):1549–1556 (PubMed PMID: 16927144. Epub 2006/08/24. Eng)
104. Tsuji E, Hiki N, Nomura S, Fukushima R, Kojima J, Ogawa T, et al (2003) Simultaneous onset of acute inflammatory response, sepsis-like symptoms and intestinal mucosal injury after cancer chemotherapy. Int J Cancer 107(2):303–308 (PubMed PMID: 12949812. Epub 2003/09/02. Eng)
105. Nazli A, Yang PC, Jury J, Howe K, Watson JL, Soderholm JD, et al (2004) Epithelia under metabolic stress perceive commensal bacteria as a threat. Am J Pathol 164(3):947–957 (PubMed PMID: 14982848. Pubmed Central PMCID: 1614709. Epub 2004/02/26. Eng)
106. Alverdy J, Zaborina O, Wu L (2005) The impact of stress and nutrition on bacterial-host interactions at the intestinal epithelial surface. Curr Opin Clin Nutr Metab Care 8(2):205–209 (PubMed PMID: 15716801. Epub 2005/02/18. Eng)
107. Kallianpur AR (2005) Genomic screening and complications of hematopoietic stem cell transplantation: has the time come? Bone Marrow Transplant 35(1):1–16 (PubMed PMID: 15489868. Epub 2004/10/19. Eng)
108. Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, et al (2008) Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med 359(17):1766–1777 (PubMed PMID: 18946062. Pubmed Central PMCID: 2656610. Epub 2008/10/24. Eng)
109. Cook M, Briggs D, Craddock C, Mahendra P, Milligan D, Fegan C, et al (2006) Donor KIR genotype has a major influence on the rate of cytomegalovirus reactivation following T-cell replete stem cell transplantation. Blood 107(3):1230–1232 (PubMed PMID: 16239436. Epub 2005/10/22. Eng)
110. Mullighan CG, Heatley S, Doherty K, Szabo F, Grigg A, Hughes TP, et al (2002) Mannose-binding lectin gene polymorphisms are associated with major infection following allogeneic hemopoietic stem cell transplantation. Blood 99(10):3524–3529 (PubMed PMID: 11986203. Epub 2002/05/03. Eng)
111. Dickinson AM, Holler E (2008) Polymorphisms of cytokine and innate immunity genes and GVHD. Best Pract Res Clin Haematol 21(2):149–164 (PubMed PMID: 18503983. Epub 2008/05/28. Eng)
112. Mullally A, Ritz J (2007) Beyond HLA: the significance of genomic variation for allogeneic hematopoietic stem cell transplantation. Blood 109(4):1355–1362 (PubMed PMID: 17008540. Epub 2006/09/30. Eng)
113. Hildebrandt GC, Granell M, Urbano-Ispizua A, Wolff D, Hertenstein B, Greinix HT, et al (2008) Recipient NOD2/CARD15 variants: a novel independent risk factor for the development of bronchiolitis obliterans after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 14(1):67–74 (PubMed PMID: 18158963. Epub 2007/12/27. Eng)
114. Holler E, Rogler G, Herfarth H, Brenmoehl J, Wild PJ, Hahn J, et al (2004) Both donor and recipient NOD2/CARD15 mutations associate with transplant-related mortality and GvHD following allogeneic stem cell transplantation. Blood 104(3):889–894 (PubMed PMID: 15090455. Epub 2004/04/20. Eng)
115. Kanzler H, Barrat FJ, Hessel EM, Coffman RL (2007) Therapeutic targeting of innate immunity with Toll-like receptor agonists and antagonists. Nat Med 13(5):552–529 (PubMed PMID: 17479101. Epub 2007/05/05. Eng)
116. O'Neill LA (2003) Therapeutic targeting of Toll-like receptors for inflammatory and infectious diseases. Curr Opin Pharmacol 3(4):396–403 (PubMed PMID: 12901949. Epub 2003/08/07. Eng)
117. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64(2):328–340

118. Sickles EA, Greene WH, Wiernik PH (1975) Clinical presentation of infection in granulocytopenic patients. Arch Intern Med 135:715–719
119. Pizzo PA, Robichaud KJ, Wesley R, Commers JR (1982) Fever in the pediatric and young adult patients with cancer. Medicine 61(3):153–165
120. The EORTC International Antimicrobial Therapy Project Group (1978) Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. J Infect Dis 137:14–29
121. Anaissie E, Bodey GP, Kantarjian H, Ro J, Vartivarian SE, Hopfer R et al (1989) New spectrum of fungal infections in patients with cancer. Rev Infect Dis 11(3):369–378
122. Bodey G, Bueltmann B, Duguid W, Gibbs D, Hanak H, Hotchi M et al (1992) Fungal infections in cancer patients—an international autopsy survey. Eur J Clin Microbiol Infect Dis 11(2):99–109
123. DeGregorio MW, Lee WM, Ries CA (1982) *Candida* infections in patients with acute leukemia: ineffectiveness of nystatin prophylaxis and relationship between oropharyngeal and systemic candidiasis. Cancer 50(12):2780–2784
124. Gerson S, Talbot G, Huwitz S, Strom B, Lusk E, Cassileth P (1984) Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Int Med 100:345–351
125. Weeks JC, Tierney MR, Weinstein MC (1991) Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia (see comments). N Engl J Med 325(2):81–86
126. Young RC, Corder MP, Haynes HA, DeVita VT (1972) Delayed hypersensitivity in Hodgkin's disease. A study of 103 untreated patients. Am J Med 52(1):63–72 (PubMed PMID: 5058359. Epub 1972/01/01. Eng)
127. Deardon C (2008) Chronic lymphocytic leukemia. ASH Education, Hematology, pp 450–456
128. Sonis ST (2004) The pathobiology of mucositis. Nat Rev 4(4):277–284 (PubMed PMID: 15057287. Eng)
129. Blijlevens NM, Logan RM, Netea MG (2009) The changing face of febrile neutropenia—from monotherapy to moulds to mucositis. Mucositis: from febrile neutropenia to febrile mucositis. J Antimicrob Chemother 63(1):i36–i40 (PubMed PMID: 19372181. Epub 2009/04/23. Eng)
130. Kolbinson DA, Schubert MM, Fluornoy N, Truelove EL (1988) Early oral changes following bone marrow transplantation. Oral Surg Oral Med Oral Pathol 66:130–138
131. Donnelly JP, Muus P, Schattenberg A, De Witte T, Horrevorts A, DePauw BE (1992) A scheme for daily monitoring of oral mucositis in allogeneic BMT recipients. Bone Marrow Transplant 9(6):409–413
132. Rocke LK, Loprinzi CL, Lee JK, Kunselman SJ, Iverson RK, Finck G, et al (1993) A randomized clinical trial of two different durations of oral cryotherapy for prevention of 5-fluorouracil-related stomatitis. Cancer 72(7):2234–2238 (PubMed PMID: 8374882. Eng)
133. Weisdorf DJ, Bostrom B, Raether D, Mattingly M, Walker P, Pihlstrom B, et al (1989) Oropharyngeal mucositis complicating bone marrow transplantation: prognostic factors and the effect of chlorhexidine mouth rinse. Bone Marrow Transplant 4(1):89–95 (PubMed PMID: 2647192. Eng)
134. Blijlevens N, Schwenkglenks M, Bacon P, D'Addio A, Einsele H, Maertens J, et al (2008) Prospective oral mucositis audit: oral mucositis in patients receiving high-dose melphalan or BEAM conditioning chemotherapy—European Blood and Marrow Transplantation Mucositis Advisory Group. J Clin Oncol 26(9):1519–1525 (PubMed PMID: 18268357. Eng)
135. Bow EJ, Loewen R, Cheang MS, Shore TB, Rubinger M, Schacter B (1997) Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. J Clin Oncol 15(6):2254–2261
136. Raemaekers J, De Witte T, Schattenberg A, Van der Lely N (1989) Prevention of leukemic relapse after transplantation with lymphocyte depleted marrow by intensification of the

conditioning regimen with a 6-day continuous infusion of anthracyclines. Bone Marrow Transplant 4(2):167–171 (PubMed PMID: 2650787. Epub 1989/03/01. Eng)
137. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al (2001) Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 19(8):2201–2205 (PubMed PMID: 11304772. Eng)
138. Fanning SR, Rybicki L, Kalaycio M, Andresen S, Kuczkowski E, Pohlman B, et al (2006) Severe mucositis is associated with reduced survival after autologous stem cell transplantation for lymphoid malignancies. Br J Haematol 135(3):374–381 (PubMed PMID: 16995885. Eng)
139. McGuire DB, Altomonte V, Peterson DE, Wingard JR, Jones RJ, Grochow LB (1993) Patterns of mucositis and pain in patients receiving preparative chemotherapy and bone marrow transplantation. Oncol Nurs Forum 20(10):1493–1502 (PubMed PMID: 8278277. Eng)
140. Donnelly JP, Maschmeyer G, Daenen S (1992) Selective oral antimicrobial prophylaxis for the prevention of infection in acute leukaemia—ciprofloxacin versus co-trimoxazole plus colistin. The EORTC-Gnotobiotic Project Group. Eur J Cancer 959–8049
141. Morrison VA, Haake RJ, Weisdorf DJ (1993) The spectrum of non-*Candida* fungal infections following bone marrow transplantation. Medicine (Baltimore) 72(2):78–89 (PubMed PMID: 8479326. Epub 1993/03/01. Eng)
142. Bochud PY, Eggiman P, Calandra T, Van Melle G, Saghafi L, Francioli P (1994) Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical spectrum and risk factors (see comments). Clin Infect Dis 18(1):25–31
143. Donnelly JP, Dompeling EC, Meis JF, de Pauw BE (1995) Bacteremia due to oral viridans streptococci in neutropenic patients with cancer: cytostatics are a more important risk factor than antibacterial prophylaxis. Clin Infect Dis 20(2):469–470
144. Beighton D, Carr AD, Oppenheim BA (1994) Identification of viridans streptococci associated with bacteraemia in neutropenic cancer patients. J Med Microbiol 40(3):202–204
145. Lina B, Forey F, Troncy J, Greenland T, Fleurette J, Etienne J (1994) Oral source of *Staphylococcus epidermidis* septicemia in a neutropenic patient. Eur J Clin Microbiol Infect Dis 13:773–774
146. Jacobs JA, Pietersen HG, Stobberingh EE, Soeters PB (1994) Bacteremia involving the *Streptococcus milleri* group: analysis of 19 cases. Clin Infect Dis 19(4):704–713
147. Ferretti GA, Ash RC, Brown AT, Largent BM, Kaplan A, Lillich TT (1987) Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. J Am Dent Assoc 114:461–467
148. Meurman JH, Laine P, Murtomaa H, Lindqvist C, Torkko H, Teerenhovi L et al (1991) Effect of antiseptic mouthwashes on some clinical and microbiological findings in the mouths of lymphoma patients receiving cytostatic drugs. J Clin Periodontol 18(8):587–591
149. Bergmann OJ (1991) Alterations in oral microflora and pathogenesis of acute oral infections during remission-induction therapy in patients with acute myeloid leukaemia. Scand J Infect Dis 23(3):355–366
150. Bronchud M (1993) Can hematopoietic growth factors be used to improve the success of cytotoxic chemotherapy? Anticancer Drugs 4(2):127–139 (PubMed PMID: 8490192. Epub 1993/04/01. Eng)
151. Schuster MW (1992) Granulocyte-macrophage colony-stimulating factor (GM-CSF)—what role in bone marrow transplantation. Infection 20(2):S95–S99
152. De Witte T, Van Der Lely N, Muus P, Donnelly JP, Schattenberg T (1993) Recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF) accelerates bone marrow recovery after allogeneic T-cell depleted bone marrow transplantation. L'Ospedale Maggiore 87(1):42–46
153. Bow EJ, Loewen R, Cheang MS, Schacter B (1995) Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. Clin Infect Dis 21(2):361–369

154. Keefe DM, Cummins AG, Dale BM, Kotasek D, Robb TA, Sage RE (1997) Effect of high-dose chemotherapy on intestinal permeability in humans. Clin Sci 92(4):385–389
155. Tancrede CH, Andremont AO (1985) Bacterial translocation and gram-negative bacteremia in patients with hematological malignancies. J Infect Dis 152:99–103
156. Brown NM, White LO, Blundell EL, Chown SR, Slade RR, Macgowan AP et al (1993) Absorption of oral ofloxacin after cytotoxic chemotherapy for haematological malignancy. J Antimicrob Chemother 32(1):117–122
157. Johnson EJ, MacGowan AP, Potter MN, Stockley RJ, White LO, Slade RR et al (1990) Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. J Antimicrob Chemother 25(5):837–842
158. Prentice AG, Warnock DW, Johnson SA, Phillips MJ, Oliver DA (1994) Multiple dose pharmacokinetics of an oral solution of itraconazole in autologous bone marrow transplant recipients. J Antimicrob Chemother 34(2):247–252
159. Gubbins PO, Krishna G, Sansone-Parsons A, Penzak SR, Dong L, Martinho M, et al (2006) Pharmacokinetics and safety of oral posaconazole in neutropenic stem cell transplant recipients. Antimicrob Agents Chemother 50(6):1993–1999 (PubMed PMID: 16723557. Eng)
160. Blijlevens NM, Lutgens LC, Schattenberg AV, Donnelly JP (2004) Citrulline: a potentially simple quantitative marker of intestinal epithelial damage following myeloablative therapy. Bone Marrow Transplant 34(3):193–196 (PubMed PMID: 15170165. Eng)
161. Schimpff SC (1993) Gram-negative bacteremia. Support Care Cancer 1(1):5–18
162. Cruciani M, Rampazzo R, Malena M, Lazzarini L, Todeschini G, Messori A et al (1996) Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. Clin Infect Dis 23(4):795–805
163. Engels EA, Lau J, Barza M (1998) Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 16(3):1179–1187 (PubMed PMID: 9508206. Eng)
164. Gafter-Gvili A, Paul M, Fraser A, Leibovici L (2007) Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. J Antimicrob Chemother 59(1):5–22 (PubMed PMID: 17077101. Eng)
165. Coleman N, Speirs G, Khan J, Broadbent V, Wight DG, Warren RE (1993) Neutropenic enterocolitis associated with Clostridium tertium. J Clin Pathol 46(2):180–183 (PubMed PMID: 8459041. Eng)
166. Gomez L, Martino R, Rolston KV (1998) Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. Clin Infect Dis 27(4):695–699 (PubMed PMID: 9798018. Eng)
167. Pouwels MJ, Donnelly JP, Raemaekers JM, Verweij PE, de Pauw BE (1997) Clostridium septicum sepsis and neutropenic enterocolitis in a patient treated with intensive chemotherapy for acute myeloid leukemia. Ann Hematol 74(3):143–147
168. Ginsburg AS, Salazar LG, True LD, Disis ML (2003) Fatal Bacillus cereus sepsis following resolving neutropenic enterocolitis during the treatment of acute leukemia. Am J Hematol 72(3):204–208 (PubMed PMID: 12605393. Eng)
169. Nucci M, Anaissie E (2001) Revisiting the source of candidemia: skin or gut? Clin Infect Dis 33(12):1959–1967 (PubMed PMID: 11702290. Eng)
170. Peters WG, Willemze R, Colly LP, Guiot HFL (1987) Side effects of intermediate- and high-dose cytosine arabinoside in the treatment of refractory or relapsed acute leukaemia and on-Hodgkins lymphoma. Neth J Med 30:64–74
171. Guiot HF, Biemond J, Klasen E, Gratama JW, Kramps JA, Zwaan FE (1987) Protein loss during acute graft-versus-host disease: diagnostic and clinical significance. Eur J Haematol 38(2):187–196
172. Callum JL, Brandwein JM, Sutcliffe SB, Scott JG, Keating A (1991) Influence of total body irradiation on infections after autologous bone marrow transplantation. Bone Marrow Transplant 8(4):245–251 (PubMed PMID: 1756321. Epub 1991/10/01. Eng)
173. Johnson S, Driks MR, Tweten RK, Ballard J, Stevens DL, Anderson DJ, et al (1994) Clinical courses of seven survivors of Clostridium septicum infection and their

immunologic responses to alpha toxin. Clin Infect Dis 19(4):761–764 (PubMed PMID: 7803645. Epub 1994/10/01. Eng)
174. Blijlevens NM, Donnelly JP, De Pauw BE (2000) Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. Bone Marrow Transplant 25(12):1269–1278 (PubMed PMID: 10871732. Eng)
175. Fegan C, Poynton CH, Whittaker JA (1990) The gut mucosal barrier in bone marrow transplantation. Bone Marrow Transplant 5(6):373–377
176. Bergström P, Grankvist K, Henriksson R (1994) Interaction between antibiotics and antineoplastic drugs on antibacterial activity in vitro: estramustine phosphate sensitizes pneumococci to amikacin. Int J Oncol 4:43–439
177. Jacobs JY, Michel J, Sacks T (1979) Bactericidal effect of combinations of antimicrobial drugs and antineoplastic antibiotics against *Staphylococcus aureus*. Antimicrob Agents Chemother 15:580–586
178. Michel J, Jacobs JY, Sacks T (1979) Bactericidal effect of combinations of antimicrobial drugs and antineoplastic antibiotics against gram-negative bacilli. Antimicrob Agents Chemother 16:761–766
179. Moody MR, Morris MJ, Young VM, Moye LA III, Schimpff SC, Wiernik PH (1978) Effect of two cancer chemotherapeutic agents on the antibacterial activity of three antimicrobial agents. Antimicrob Agents Chemother 14:737–742
180. Neuman M (1992) The antimicrobial activity of non-antibiotics—interactions with antibiotics. APMIS 100(30):15–23
181. Bodet CA 3rd, Jorgensen JH, Drutz DJ (1985) Antibacterial activities of antineoplastic agents. Antimicrob Agents Chemother 28(3):437–439 (PubMed PMID: 2416271. Pubmed Central PMCID: 180269. Epub 1985/09/01. Eng)
182. Van Cutsem JM, Thienpont D (1972) Miconazole, a broad-spectrum antimycotic agent with antibacterial activity. Chemotherapy 17:392–404
183. van der Velden WJ, Blijlevens NM, Feuth T, Donnelly JP (2009) Febrile mucositis in haematopoietic SCT recipients. Bone Marrow Transplant 43(1):55–60 (PubMed PMID: 18762766. Epub 2008/09/03. Eng)
184. Marron A, Carratala J, Gonzalez-Barca E, Fernandez-Sevilla A, Alcaide F, Gudiol F (2000) Serious complications of bacteremia caused by Viridans streptococci in neutropenic patients with cancer. Clin Infect Dis 31(5):1126–1130 (PubMed PMID: 11073739. Epub 2000/11/14. Eng)

# 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

## Contents



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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<br>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 |
|---|---|---|
| *Characteristics* | 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 |
| *Components* | | |
| 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 microorganisms. 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/mm$^3$, 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/mm$^3$ during therapy were successfully treated, whereas 88 % of those whose count rose by at least 100 cells/mm$^3$ 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-albic*ans 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. chelonei* 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: *S. aureus, S. epidermidis*, streptococci, enterococci |
| | | Gram negative: *E. coli, Klebsiella* spp., *P. aeruginosa* |
| | | Yeast/fungi |
| | | *Candida* spp. |
| | | *Aspergillus* spp. |
| | | Viruses |
| | | HSV |
| | | VZV |
| | | CMV |
| | Cell mediated (in the non-neutropenic) | Bacteria |
| | | *L. monocytogenes*, *Salmonella* spp., *N. asteroides*, mycobacteria, *L. pneumophila* |
| | | Yeast/fungi |
| | | *C. neoformans* |
| | | *Aspergillus* spp. |
| | | Viruses |
| | | HSV |
| | | VZV |
| | | CMV |
| | | EBV |
| | | Protozoa |
| | | *P. jeroveci* |
| | | *T. gondii* |
| | | *Cryptosporidium* |
| | | Helminth |
| | | *S. stercoralis* |

(continued)

**Table 3** (continued)

| Malignancy | Immunodeficiency | Common pathogens and syndromes |
|---|---|---|
| Chronic lymphocytic leukemia | Hypogammaglobulinemia | Bacteria |
| | | *S. pneumoniae* |
| | | *H. influenzae* |
| | | *N. meningitidis* |
| Multiple myeloma | Humoral; complement deficiency; neutropenia in late-stage disease | Bacteria |
| | | *S. pneumoniae* |
| | | *H. influenzae* |
| | | *N. meningitidis* |
| | | See pathogens associated with neutropenia above |
| Hairy cell leukemia | Cell mediated; neutropenia in late-stage disease | Bacteria |
| | | *Salmonella* spp. |
| | | *L. monocytogenes* |
| | | *M. kansasii* |
| | | *M. avium* |
| | | *M. chelonei* |
| | | Yeast |
| | | *Candida* spp. |
| | | *C. neoformans* |
| | | 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 |
| | | *H. influenzae* |
| | | GI tract |
| | | Enterobacteriaceae |
| | | Fungi |
| | | Female genital tract |
| | | Enterobacteriaceae |
| | | Anaerobic gram-negative bacteria |
| | | Enterococci |
| | | *Clostridium* 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 hepatitides 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. pneumophilia, 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. chelonei* [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 A*lcaligenes 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, $MIC_{90}$ 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 $MIC_{90}$ 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 threefold (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, Exserohilium, Fonsacea, 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 disproportionally 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.

## References

1. Chang HY et al (1976) Causes of death in adults with acute leukemia. Medicine 55(3):259–268 (Baltimore)
2. Hersh EM et al (1965) Causes of death in acute leukemia: a ten-year study of 414 patients from 1954–1963. JAMA 193:105–109
3. Homsi J et al (2000) Infectious complications of advanced cancer. Support Care Cancer 8(6):487–492
4. Hughes WT (1971) Fatal infections in childhood leukemia. Am J Dis Child 122(4):283–287
5. Inagaki J, Rodriguez V, Bodey GP (1974) Proceedings: causes of death in cancer patients. Cancer 33(2):568–573
6. Mayo JW, Wenzel RP (1982) Rates of hospital-acquired bloodstream infections in patients with specific malignancy. Cancer 50(1):187–190
7. Nosari A et al (1991) Infections in haematologic neoplasms: autopsy findings. Haematologica 76(2):135–140
8. Viscoli C, Castagnola E (1995) Factors predisposing cancer patients to infection. In: Klastersky K (ed) Infectious complications of cancer. Kluwer Academic, Boston, pp 1–30
9. Morittu L et al (1989) Patients at risk of chemotherapy-associated toxicity in small cell lung cancer. Br J Cancer 59(5):801–804
10. Freifeld AG, Kaul DR (2008) Infection in the patient with cancer, in Abeloff's clinical oncology. In: Abeloff MD et al (eds) Churchill Livingstone, Philadelphia, pp 717–738
11. Viscoli C, Castagnola E (2009) Prophylaxis and empirical therapy of infection in cancer patients. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Doublas, and Bennett's principle and practice of infectious diseases. Churchill Livingstone, Philadelphia, pp 3793-3808
12. Donnelly JP, Blijlevens NMA, De Pauw BE (2009) Infections in the immunocompromised host: general principles. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Churchill Livingstone, Philadelphia, pp 3781–3792
13. Vusirikala M (2009) Supportive care in hematologic malignancies, in Wintrobe's clinical hematology. In: Greer JP et al (ed) Lippincott Williams and Wilkins, Philadelphia, pp 1747–1790
14. Maschmeyer G, Haas A (2008) The epidemiology and treatment of infections in cancer patients. Int J Antimicrob Agents 31(3):193–197
15. Todar K (2008) Immune defense against bacterial pathogens: innate immunity. In: Todar K (ed) Todar's online textbook of bacteriology
16. Todar K (2008) Immune defense against bacterial pathogens: adaptive or acquired immunity. In Todar K (ed) Todar's online textbook of bacteriology

17. Donnelly JP (1995) Chemoprophylaxis for the prevention of bacterial and fungal infections. Cancer Treat Res 79:45–81
18. Roth RR, James WD (1988) Microbial ecology of the skin. Annu Rev Microbiol 42:441–464
19. Schroder JM (2010) The role of keratinocytes in defense against infection. Curr Opin Infect Dis 23(2):106–110
20. Awada A et al (1992) Streptococcal and enterococcal bacteremia in patients with cancer. Clin Infect Dis 15(1):33–48
21. Axelrod PI, Lorber B, Vonderheid EC (1992) Infections complicating mycosis fungoides and Sezary syndrome. JAMA 267(10):1354–1358
22. Glauser MP, Zinner SH (1982) Mechanisms of acquisition and development of bacterial infections in cancer patients. In: Klastersky J (ed) Infections in cancer patients. Raven Press, New York, pp 13–30
23. Hall VC et al (2003) Dermatologic side effects of thalidomide in patients with multiple myeloma. J Am Acad Dermatol 48(4):548–552
24. Dorman SE et al (1999) Viral infections in interferon-gamma receptor deficiency. J Pediatr 135(5):640–643
25. Fahey JL et al (1963) Infection, antibody response and gamma globulin components in multiple myeloma and macroglobulinemia. Am J Med 35:698–707
26. Favoreel HW et al (2003) Virus complement evasion strategies. J Gen Virol 84(Pt 1):1–15
27. Salmon SE (1973) Immunoglobulin synthesis and tumor kinetics of multiple myeloma. Semin Hematol 10(2):135–144
28. Sheridan JF et al (1990) Immunoglobulin G subclass deficiency and pneumococcal infection after allogeneic bone marrow transplantation. Blood 75(7):1583–1586
29. Wagner RR (1963) Cellular resistance to viral infection, with particular reference to endogenous interferon. Bacteriol Rev 27:72–86
30. Johnston RB Jr (1988) Current concepts: immunology. Monocytes and macrophages. N Engl J Med 318(12):747–752
31. Barbuto S et al (2013) Induction of innate and adaptive immunity by delivery of poly dA:dT to dendritic cells. Nat Chem Biol 9(4):250–256
32. Steinman RM, Inaba K (1988) The binding of antigen presenting cells to T lymphocytes. Adv Exp Med Biol 237:31–41
33. Urb M, Sheppard DC (2012) The role of mast cells in the defence against pathogens. PLoS Pathog 8(4):e1002619
34. Hall LJ et al (2013) Natural killer cells protect against mucosal and systemic infection with the enteric pathogen Citrobacter rodentium. Infect Immun 81(2):460–469
35. Horowitz A, Stegmann KA, Riley EM (2011) Activation of natural killer cells during microbial infections. Front Immunol 2:88
36. Marras F, Bozzano F, De Maria A (2011) Involvement of activating NK cell receptors and their modulation in pathogen immunity. J Biomed Biotechnol 2011:152430
37. Steinhauer EH et al (1985) Natural killer cytotoxic factor induction by K562 cells in patients with advanced cancer: correlation with production of interferon. J Natl Cancer Inst 75(6):1017–1023
38. Bodey GP et al (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64(2):328–340
39. Feld R, Bodey GP (1977) Infections in patients with malignant lymphoma treated with combination chemotherapy. Cancer 39(3):1018–1025
40. Freifeld AG et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52(4):e56–e93
41. Valdez JM et al (2009) Infections in patients with aplastic anemia. Semin Hematol 46(3):269–276

42. Schimpff SC et al (1978) Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. The EORTC international antimicrobial therapy project group. J Infect Dis 137(1):14–29
43. Brooks WH et al (1972) Depressed cell-mediated immunity in patients with primary intracranial tumors. Characterization of a humoral immunosuppressive factor. J Exp Med 136(6):1631–1647
44. Han T, Takita H (1972) Immunologic impairment in bronchogenic carcinoma: a study of lymphocyte response to phytohemagglutinin. Cancer 30(3):616–620
45. Krick JA, Remington JS (1976) Opportunistic invasive fungal infections in patients with leukaemia lymphoma. Clin Haematol 5(2):249–310
46. Lum LG (1990) Immune recovery after bone marrow transplantation. Hematol Oncol Clin North Am 4(3):659–675
47. Orita K et al (1976) Preoperative cell-mediated immune status of gastric cancer patients. Cancer 38(6):2343–2348
48. Schellhammer PF et al (1976) Immune evaluation with skin testing. A study of testicular, prostatic, and bladder neoplasms. Cancer 38(1):149–156
49. Seligmann M et al (1984) AIDS–an immunologic reevaluation. N Engl J Med 311(20): 1286–1292
50. Whittaker MG, Rees K, Clark CG (1971) Reduced lymphocyte transformation in breast cancer. Lancet 1(7705):892–893
51. Young RC et al (1972) Delayed hypersensitivity in Hodgkin's disease. A study of 103 untreated patients. Am J Med 52(1):63–72
52. Kim JH, Perfect JR (1989) Infection and cyclosporine. Rev Infect Dis 11(5):677–690
53. Mackall CL et al (1995) Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy. N Engl J Med 332(3):143–149
54. Mackall CL et al (1994) Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood 84(7):2221–2228
55. Bishop JF et al (1981) Infections during intensive chemotherapy for non-Hodgkin's lymphoma. Ann Intern Med 95(5):549–555
56. Bookman MA, Longo DL (1986) Concomitant illness in patients treated for Hodgkin's disease. Cancer Treat Rev 13(2):77–111
57. Chan JC, Hensley GT, Moskowitz LB (1984) Toxoplasmosis in the central nervous system. Ann Intern Med 100(4):615–616
58. Hardy I et al (1991) The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. Varicella Vaccine Collaborative Study Group. N Engl J Med 325(22):1545–1550
59. Hughes WT et al (1975) Intensity of immunosuppressive therapy and the incidence of Pneumocystis carinii pneumonitis. Cancer 36(6):2004–2009
60. Hughes WT, Townsend TR (1981) Nosocomial infections in immunocompromised children. Am J Med 70(2):412–416
61. Keiser PB, Nutman TB (2004) Strongyloides stercoralis in the immunocompromised population. Clin Microbiol Rev 17(1):208–217
62. Sepkowitz KA (1993) Pneumocystis carinii pneumonia in patients without AIDS. Clin Infect Dis 17(Suppl 2):S416–S422
63. Sepkowitz KA et al (1992) Pneumocystis carinii pneumonia among patients without AIDS at a cancer hospital. JAMA 267(6):832–837
64. Varthalitis I, Meunier F (1993) Pneumocystis carinii pneumonia in cancer patients. Cancer Treat Rev 19(4):387–413
65. Hosea SW et al (1981) Opsonic requirements for intravascular clearance after splenectomy. N Engl J Med 304(5):245–450
66. Van Der Meer JWM (1988) Defects in host-defense mechanisms. In: Rubin RH, Young LS (eds) Clinical approach to infection in the compromised host. Plenum Medical, New York, pp 41–63

67. Gaston MH et al (1986) Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 314(25):1593–1599
68. Jugenburg M et al (1999) The morbidity and mortality of pediatric splenectomy: does prophylaxis make a difference? J Pediatr Surg 34(7):1064–1067
69. Keenan RD, Boswell T, Milligan DW (1999) Do post-splenectomy patients take prophylactic penicillin? Br J Haematol 105(2):509–510
70. Group, A.A.I.W. et al (2013) Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 years and older—United States, 2013. MMWR Surveill Summ 62(1):9–19
71. Group A.C.A.I.W. et al (2013) Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for persons aged 0 through 18 years–United States. MMWR Surveill Summ 62(l):2–8
72. Schimpff SC (1995) Infection in the cancer patient–diagnosis, prevention, and treatment. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Churchill Livingstone, New York, pp 2666–2675
73. Rammaert B et al (2012) Diabetes and mucormycosis: a complex interplay. Diabetes Metab 38(3):193–204
74. Renehan AG et al (2012) Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia 55(6):1619–1632
75. Barone BB et al (2008) Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 300(23):2754–2764
76. Barone BB et al (2010) Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. Diabetes Care 33(4):931–939
77. Daly AL et al (1989) Mucormycosis: association with deferoxamine therapy. Am J Med 87(4):468–471
78. Pagano L et al (2004) Mucormycosis in hematologic patients. Haematologica 89(2): 207–214
79. Balentine CJ et al (2010) Obese patients benefit from minimally invasive colorectal cancer surgery. J Surg Res 163(1):29–34
80. Merkow RP et al (2009) Effect of body mass index on short-term outcomes after colectomy for cancer. J Am Coll Surg 208(1):53–61
81. Tsujinaka S et al (2008) Visceral obesity predicts surgical outcomes after laparoscopic colectomy for sigmoid colon cancer. Dis Colon Rectum 51(12):1757–1765; discussion 1765–1767
82. Safdar A, Bodey G, Armstrong D (2011) Infections in patients with cancer: overview. In: S. A (ed) Principles and practice of cancer infectious diseases. Springer, New York, pp 3–16
83. Anand A, Glatt AE (1993) *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis 17(1):109–113
84. Blot E et al (2003) Outbreak of *Clostridium difficile*-related diarrhoea in an adult oncology unit: risk factors and microbiological characteristics. J Hosp Infect 53(3):187–192
85. Chopra T, Alangaden GJ, Chandrasekar P (2010) *Clostridium difficile* infection in cancer patients and hematopoietic stem cell transplant recipients. Expert Rev Anti Infect Ther 8(10):1113–1119
86. Palmore TN et al (2005) Risk factors for acquisition of *Clostridium difficile*-associated diarrhea among outpatients at a cancer hospital. Infect Control Hosp Epidemiol 26(8):680–684
87. Raza S et al (2010) *Clostridium difficile* infection following chemotherapy. Recent Pat Antiinfect Drug Discov 5(1):1–9
88. Resnik E, Lefevre CA (1999) Fulminant *Clostridium difficile* colitis associated with paclitaxel and carboplatin chemotherapy. Int J Gynecol Cancer 9(6):512–514
89. Stewart DB, Yacoub E, Zhu J (2012) Chemotherapy patients with C. difficile colitis have outcomes similar to immunocompetent C. difficile patients. J Gastrointest Surg 16(8):1566–1572

90. National Cancer Institute (2009) Nutrition in cancer care (PDQ) health professional version. 30 Dec 2009. Available from http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition/HealthProfessional/page1. Last accessed 18 Aug 2013
91. Marin Caro MM, Laviano A, Pichard C (2007) Impact of nutrition on quality of life during cancer. Curr Opin Clin Nutr Metab Care 10(4):480–487
92. Pressoir M et al (2010) Prevalence, risk factors and clinical implications of malnutrition in French comprehensive cancer centres. Br J Cancer 102(6):966–971
93. Wong PW, Enriquez A, Barrera R (2001) Nutritional support in critically ill patients with cancer. Crit Care Clin 17(3):743–767
94. Horie H et al (2006) Favorable effects of preoperative enteral immunonutrition on a surgical site infection in patients with colorectal cancer without malnutrition. Surg Today 36(12):1063–1068
95. Heyland DK et al (2001) Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA 286(8):944–953
96. Celik JB et al (2009) The role of immunonutrition in gynecologic oncologic surgery. Eur J Gynaecol Oncol 30(4):418–421
97. Weisdorf SA et al (1987) Positive effect of prophylactic total parenteral nutrition on long-term outcome of bone marrow transplantation. Transplantation 43(6):833–838
98. Irwin J, Livnat S (1987) Behavioral influences on the immune system: stress and conditioning. Prog Neuropsychopharmacol Biol Psychiatry 11(2–3):137–143
99. Marsland AL et al (2002) Stress, immune reactivity and susceptibility to infectious disease. Physiol Behav 77(4–5):711–716
100. Falagas ME et al (2010) Psychosocial factors and susceptibility to or outcome of acute respiratory tract infections. Int J Tuberc Lung Dis 14(2):141–148
101. Kemeny ME, Schedlowski M (2007) Understanding the interaction between psychosocial stress and immune-related diseases: a stepwise progression. Brain Behav Immun 21(8):1009–1018
102. Aubert A (2008) Psychosocial stress, emotions and cytokine-related disorders. Recent Pat Inflamm Allergy Drug Discov 2(2):139–148
103. Reiche EM, Nunes SO, Morimoto HK (2004) Stress, depression, the immune system, and cancer. Lancet Oncol 5(10):617–625
104. Paun BC et al (2010) Postoperative complications following surgery for rectal cancer. Ann Surg 251(5):807–818
105. Wilson BD, Surgalla MJ, Yates JW (1974) Aerobic and anaerobic surgical wound contamination in patients with cancer. Surg Gynecol Obstet 139(3):329–332
106. Morris CD et al (2003) Prospective identification of risk factors for wound infection after lower extremity oncologic surgery. Ann Surg Oncol 10(7):778–782
107. Gongaware RD, Slanetz CA Jr (1973) Hartmann procedure for carcinoma of the sigmoid and rectum. Ann Surg 178(1):28–30
108. Naito H et al (1973) High incidence of acute postoperative meningitis and septicemia in patients undergoing craniotomy with ventriculoatrial shunt. Surg Gynecol Obstet 137(5):810–812
109. Geelhoed GW, Ketcham AS (1973) Pseudomonas meningitis complicating radical resection for radiorecurrent cancer of the paranasal sinuses: report of two patients successfully treated with intrathecal polymyxin. J Surg Oncol 5(4):365–374
110. Lefebvre D et al (2000) Incidence and surgical wound infection risk factors in breast cancer surgery. Presse Med 29(35):1927–1932
111. Vilar-Compte D et al (2004) Surgical site infections in breast surgery: case-control study. World J Surg 28(3):242–246
112. Accolla RS (2006) Host defense mechanisms against pathogens. Surg Infect 7(Suppl 2):S5–S7 (Larchmt)

113. Nakamura T et al (2009) Retrospective, matched case-control study comparing the oncologic outcomes between laparoscopic surgery and open surgery in patients with right-sided colon cancer. Surg Today 39(12):1040–1045
114. Villar HV et al (1987) Role of surgical treatment in the management of complications of the gastrointestinal tract in patients with leukemia. Surg Gynecol Obstet 165(3):217–222
115. Wade DS, Nava HR, Douglass HO Jr (1992) Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer 69(1):17–23
116. Ullery BW et al (2009) Neutropenic enterocolitis. Surg Infect 10(3):307–314 (Larchmt)
117. Say CC, Donegan W (1974) A biostatistical evaluation of complications from mastectomy. Surg Gynecol Obstet 138(3):370–376
118. Smith MG et al (1972) Cell-mediated immune responses in chronic liver diseases. Br Med J 1(5799):527–530
119. Lowell DM, LiVolsi VA, Ludwig ME (1983) Genital condyloma virus infection following pelvic radiation therapy: report of seven cases. Int J Gynecol Pathol 2(3):294–302
120. Caloglu M et al (2007) An ambiguous phenomenon of radiation and drugs: recall reactions. Onkologie 30(4):209–214
121. Camidge R, Price A (2001) Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 59(3):237–245
122. Greco FA et al (1976) Adriamycin and enhanced radiation reaction in normal esophagus and skin. Ann Intern Med 85(3):294–298
123. Smith KJ, Germain M, Skelton H (2002) Histopathologic features seen with radiation recall or enhancement eruptions. J Cutan Med Surg 6(6):535–540
124. Spirig C et al (2009) Radiation recall dermatitis with soft tissue necrosis following pemetrexed therapy: a case report. J Med Case Rep 3:93
125. Viscoli C, Van der Auwera P, Meunier F (1988) Gram-positive infections in granulocytopenic patients: an important issue? J Antimicrob Chemother 21(lC):149–56
126. Baxevanis CN, Perez SA, Papamichail M (2009) Combinatorial treatments including vaccines, chemotherapy and monoclonal antibodies for cancer therapy. Cancer Immunol Immunother 58(3):317–324
127. Cersosimo RJ (2003) Monoclonal antibodies in the treatment of cancer. Part 1 Am J Health Syst Pharm 60(15):1531–1548
128. Reang P, Gupta M, Kohli K (2006) Biological response modifiers in cancer. Med Gen Med 8(4):33
129. Worth LL, Jeha SS, Kleinerman ES (2001), Biologic response modifiers in pediatric cancer. Hematol Oncol Clin North Am 15(4):723–740, 9
130. Zhang T, Herlyn D (2009) Combination of active specific immunotherapy or adoptive antibody or lymphocyte immunotherapy with chemotherapy in the treatment of cancer. Cancer Immunol Immunother 58(4):475–492
131. Ponce R (2008) Adverse consequences of immunostimulation. J Immunotoxicol 5(1):33–41
132. Rafailidis PI et al (2007) Infectious complications of monoclonal antibodies used in cancer therapy: a systematic review of the evidence from randomized controlled trials. Cancer 109(11):2182–2189
133. Aksoy S et al (2009) Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. Leuk Lymphoma 50(3):357–365
134. Schwartz RN, Stover L, Dutcher J (2002) Managing toxicities of high-dose interleukin-2. Oncology 16(11(13)):11–20 (Williston Park)
135. van der Waaij D, Berghuis JM (1974) Determination of the colonization resistance of the digestive tract of individual mice. J Hyg (Lond) 72(3):379–387
136. Johanson WG, Pierce AK, Sanford JP (1969) Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. N Engl J Med 281(21):1137–1140
137. Kelly CP, Pothoulakis C, LaMont JT (1994) *Clostridium difficile* colitis. N Engl J Med 330(4):257–262

138. Gaskins HR et al (2008) Impact of the intestinal microbiota on the development of mucosal defense. Clin Infect Dis 46(2): S80–S86; discussion S144–S151
139. Lampe JW (2008) The Human Microbiome Project: getting to the guts of the matter in cancer epidemiology. Cancer Epidemiol Biomarkers Prev 17(10):2523–2524
140. Mans JJ et al (2009) The degree of microbiome complexity influences the epithelial response to infection. BMC Genom 10:380
141. Rabizadeh S, Sears C (2008) New horizons for the infectious diseases specialist: how gut microflora promote health and disease. Curr Infect Dis Rep 10(2):92–98
142. Tancrede C (1992) Role of human microflora in health and disease. Eur J Clin Microbiol Infect Dis 11(11):1012–1015
143. Raum E et al (2008) Changes in Escherichia coli resistance patterns during and after antibiotic therapy: a longitudinal study among outpatients in Germany. Clin Microbiol Infect 14(1):41–48
144. van Vliet MJ et al (2009) Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. Clin Infect Dis 49(2):262–270
145. Wade JC, Schimpff SC (1988) Epidemiology and prevention of infection in the compromised host. In: Rubin RH, Young LS (eds) Clinical approach to infection in the compromised host. Plenum Medical, New York, pp 5–40
146. Aisner J et al (1976) Torulopsis glabrata infections in patients with cancer. Increasing incidence and relationship to colonization. Am J Med 61(1):23–28
147. Boken DJ, Swindells S, Rinaldi MG (1993) Fluconazole-resistant Candida albicans. Clin Infect Dis 17(6):1018–1021
148. Fan-Havard P et al (1991) Development of resistance in candida isolates from patients receiving prolonged antifungal therapy. Antimicrob Agents Chemother 35(11):2302–2305
149. Meunier F, Aoun M, Bitar N (1992) Candidemia in immunocompromised patients. Clin Infect Dis 14(Suppl 1):S120–S125
150. Merz WG et al (1986) Increased incidence of fungemia caused by Candida krusei. J Clin Microbiol 24(4):581–584
151. Wingard JR et al (1991) Increase in Candida krusei infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 325(18):1274–1277
152. Groeger JS et al (1993) Infectious morbidity associated with long-term use of venous access devices in patients with cancer. Ann Intern Med 119(12):1168–1174
153. Al Wohoush I, Chaftari AM, Raad I (2011) Catheter-related infections in cancer patients. In: Safdar A (ed) Principles and practice of cancer infectious diseases. Springer, New York, pp 113–122
154. Beekmann SE, Henderson DK (2010) Infections caused by percutaneous intravascular devices. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Doublas, and Bennett's principles and practice of infectious diseases. Churchill Livingstone, Philadelphia, pp 3697–3716
155. Segreti J et al (2009) Consensus conference on prevention of central line-associated bloodstream infections. J Infus Nurs 34(2):126–133
156. Schiffer CA et al (2013) Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 31(10):1357–1370
157. O'Grady NP et al (2011) Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 52(9):e162–e193
158. Tenney JH et al (1986) Adherent microorganisms on lumenal surfaces of long-term intravenous catheters. Importance of Staphylococcus epidermidis in patients with cancer. Arch Intern Med 146(10):1949–1954
159. Pizzo PA (1993) Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 328(18):1323–1332

160. Joo EJ et al (2011) Clinical outcome of catheter salvage in neutropenic cancer patients with catheter-related infection. Scand J Infect Dis 43(4):258–263
161. Mermel LA et al (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 49(1):1–45
162. Schimpff SC et al (1972) Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. Ann Intern Med 77(5):707–714
163. Schwartz SN et al (1978) Sources of gram-negative bacilli colonizing the tracheae of intubated patients. J Infect Dis 138(2):227–331
164. Allain JP et al (2009) Transfusion-transmitted infectious diseases. Biologicals 37(2):71–77
165. Alter HJ, Stramer SL, Dodd RY (2007) Emerging infectious diseases that threaten the blood supply. Semin Hematol 44(1):32–41
166. Rachoin JS et al (2009) Microbiology, time course and clinical characteristics of infection in critically ill patients receiving packed red blood cell transfusion. Vox Sang 97(4):294–302
167. Gottesdiener KM (1989) Transplanted infections: donor-to-host transmission with the allograft. Ann Intern Med 110(12):1001–1016
168. Barbara JA, Contreras M (1990) ABC of transfusion. Infectious complications of blood transfusion: viruses. BMJ 300(6722):450–453
169. Nichols WG et al (2003) Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. Blood 101(10):4195–4200
170. Alter HJ et al (1989) Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 321(22):1494–1500
171. Mayer KH, Opal SM (1989) Unusual nosocomial pathogens. Infect Dis Clin North Am 3(4):883–899
172. Sayers MH et al (1992) Reducing the risk for transfusion-transmitted cytomegalovirus infection. Ann Intern Med 116(1):55–62
173. Soulier JP (1984) Diseases transmissible by blood transfusion. Vox Sang 47(1):1–6
174. Wittner M et al (1982) Successful chemotherapy of transfusion babesiosis. Ann Intern Med 96(5):601–604
175. Tabor E, Gerety RJ (1984) Five cases of Pseudomonas sepsis transmitted by blood transfusions. Lancet 1(8391):1403
176. Wright DC et al (1985) Fatal Yersinia enterocolitica sepsis after blood transfusion. Arch Pathol Lab Med 109(11):1040–1042
177. Yomtovian R et al (1993) A prospective microbiologic surveillance program to detect and prevent the transfusion of bacterially contaminated platelets. Transfusion 33(11):902–909
178. Rolston KV (2009) Risk assessment and the management of neutropenic fever. In: Yeung SJ, Escalante CP, Gagel RF (eds) Medical care of cancer patients. People's Medical Publishing House, Shelton, pp 133–138
179. Bodey GP et al (1978) Fever and infection in leukemic patients: a study of 494 consecutive patients. Cancer 41(4):1610–1622
180. Gupta A et al (2010) Infections in acute myeloid leukemia: an analysis of 382 febrile episodes. Med Oncol 27(4):1037–1045
181. Jagarlamudi R et al (2000) Infections in acute leukemia: an analysis of 240 febrile episodes. Med Oncol 17(2):111–116
182. Menichetti F (2010) Infectious complications in neutropenic cancer patients. Intern Emerg Med 5(Suppl 1):S21–S25
183. Rolston KV (2005) Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis 40(Suppl 4):S246–S252
184. Schimpff SC (1977) Therapy of infection in patients with granulocytopenia. Med Clin North Am 61(5):1101–1118

185. Karp JE et al (1986) Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. Am J Med 81(2):237–242
186. Winston DJ et al (1983) Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 143(1):32–36
187. Arning M et al (1990) Septicemia due to *Streptococcus mitis* in neutropenic patients with acute leukemia. Blut 61(6):364–368
188. Neu HC (1992) The crisis in antibiotic resistance. Science 257(5073):1064–1073
189. Sanders JW, Powe NR, Moore RD (1991) Ceftazidime monotherapy for empiric treatment of febrile neutropenic patients: a meta-analysis. J Infect Dis 164(5):907–916
190. Anaissie E (1992) Opportunistic mycoses in the immunocompromised host: experience at a cancer center and review. Clin Infect Dis 14(Suppl 1):S43–S53
191. DeGregorio MW et al (1982) Fungal infections in patients with acute leukemia. Am J Med 73(4):543–548
192. Fisher BD et al (1981) Invasive aspergillosis. Progress in early diagnosis and treatment. Am J Med 71(4):571–577
193. Gerson SL et al (1984) Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 100(3):345–351
194. Lecciones JA et al (1992) Vascular catheter-associated fungemia in patients with cancer: analysis of 155 episodes. Clin Infect Dis 14(4):875–883
195. Meunier-Carpentier F, Kiehn TE, Armstrong D (1981) Fungemia in the immunocompromised host. Changing patterns, antigenemia, high mortality. Am J Med 71(3):363–370
196. Ben-Ami R et al (2009) A clinicopathological study of pulmonary mucormycosis in cancer patients: extensive angioinvasion but limited inflammatory response. J Infect 59(2):134–138
197. Eggimann P, Pittet D (2001) Candidiasis among non-neutropenic patients: from colonization to infection. Ann Fr Anesth Reanim 20(4):382–388
198. Shaukat A et al (2005) Invasive filamentous fungal infections in allogeneic hematopoietic stem cell transplant recipients after recovery from neutropenia: clinical, radiologic, and pathologic characteristics. Mycopathologia 159(2):181–188
199. Bodey G et al (1992) Fungal infections in cancer patients: an international autopsy survey. Eur J Clin Microbiol Infect Dis 11(2):99–109
200. Corey L, Spear PG (1986) Infections with herpes simplex viruses (2). N Engl J Med 314(12):749–757
201. Corey L, Spear PG (1986) Infections with herpes simplex viruses (1). N Engl J Med 314(11):686–691
202. Kaplan LJ et al (1992) Severe measles in immunocompromised patients. JAMA 267(9):1237–1241
203. Meyers JD, Flournoy N, Thomas ED (1986) Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis 153(3):478–488
204. Rand KH, Kramer B, Johnson AC (1982) Cancer chemotherapy associated symptomatic stomatitis: role of Herpes simplex virus (HSV). Cancer 50(7):1262–1265
205. Straus SE et al (1988) NIH conference. Varicella-zoster virus infections. Biology, natural history, treatment, and prevention. Ann Intern Med 108(2):221–237
206. Zahradnik JM, Spencer MJ, Porter DD (1980) Adenovirus infection in the immunocompromised patient. Am J Med 68(5):725–732
207. Toussaint E et al (2006) Causes of fever in cancer patients (prospective study over 477 episodes). Support Care Cancer 14(7):763–769
208. Velasco E et al (2000) Epidemiology of bloodstream infections at a cancer center. Sao Paulo Med J 118(5):131–138
209. Schimpff SC et al (1975) Infections in 92 splenectomized patients with Hodgkin's disease. A clinical review. Am J Med 59(5):695–701

210. Fassas AB et al (2001) Cytomegalovirus infection and non-neutropenic fever after autologous stem cell transplantation: high rates of reactivation in patients with multiple myeloma and lymphoma. Br J Haematol 112(1):237–241
211. Tsiodras S et al (2000) Infection and immunity in chronic lymphocytic leukemia. Mayo Clin Proc 75(10):1039–1054
212. Wadhwa PD, Morrison VA (2006) Infectious complications of chronic lymphocytic leukemia. Semin Oncol 33(2):240–249
213. Morrison VA (1998) The infectious complications of chronic lymphocytic leukemia. Semin Oncol 25(1):98–106
214. Morrison VA (2009) Infectious complications in patients with chronic lymphocytic leukemia: pathogenesis, spectrum of infection, and approaches to prophylaxis. Clin Lymphoma Myeloma 9(5):365–370
215. D'Souza A et al (2010) Progressive multifocal leukoencephalopathy in chronic lymphocytic leukemia: a report of three cases and review of the literature. Clin Lymphoma Myeloma Leuk 10(1):E1–E9
216. Jacobson DR, Zolla-Pazner S (1986) Immunosuppression and infection in multiple myeloma. Semin Oncol 13(3):282–290
217. Miller MI, Hoppmann RA, Pisko EJ (1987) Multiple myeloma presenting with primary meningococcal arthritis. Am J Med 82(6):1257–1258
218. Wachter E et al (1985) Neisseria meningitidis serogroup 29E (Z′) septicemia in a patient with far advanced multiple myeloma (plasma cell leukemia). J Clin Microbiol 21(3):464–466
219. Paradisi F, Corti G, Cinelli R (2001) Infections in multiple myeloma. Infect Dis Clin North Am 15(2):373–384, 7–8
220. Nucci M, Anaissie E (2009) Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 49(8):1211–1225
221. Damaj G et al (2009) Risk factors for severe infection in patients with hairy cell leukemia: a long-term study of 73 patients. Eur J Haematol 83(3):246–250
222. Audeh YM et al (2003) Hairy cell leukemia with concurrent cryptococcus infection. Am J Hematol 72(3):223–224
223. Goyal R et al (1995) Hairy cell leukemia–an unusual presentation. Leuk Res 19(7):485–487
224. Mackowiak PA et al (1980) Infections of hairy cell leukemia. Clinical evidence of a pronounced defect in cell-mediated immunity. Am J Med 68(5):718–724
225. Savoie L, Johnston JB (2001) Hairy cell leukemia. Curr Treat Options Oncol 2(3):217–224
226. Bennett C, Vardiman J, Golomb H (1986) Disseminated atypical mycobacterial infection in patients with hairy cell leukemia. Am J Med 80(5):891–896
227. Huang WT et al (2007) Clinical features and complications of viridans streptococci bloodstream infection in pediatric hemato-oncology patients. J Microbiol Immunol Infect 40(4):349–354
228. Elting LS, Bodey GP, Keefe BH (1992) Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis 14(6):1201–1207
229. Han XY, Kamana M, Rolston KV (2006) Viridans streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. J Clin Microbiol 44(1):160–165
230. Harvey RL, Sunstrum JC (1991) Rhodococcus equi infection in patients with and without human immunodeficiency virus infection. Rev Infect Dis 13(1):139–145
231. Al Akhrass F et al (2012) Rhodococcus bacteremia in cancer patients is mostly catheter related and associated with biofilm formation. PLoS One 7(3):e32945
232. Khardori N et al (1990) Nosocomial infections due to Xanthomonas maltophilia (Pseudomonas maltophilia) in patients with cancer. Rev Infect Dis 12(6):997–1003
233. Yeshurun M et al (2010) Clinical characteristics of Stenotrophomonas maltophilia infection in hematopoietic stem cell transplantation recipients: a single center experience. Infection 38(3):211–215

234. Mann T et al (2010) An outbreak of Burkholderia cenocepacia bacteremia in immunocompromised oncology patients. Infection 38(3):187–194
235. Petrucca A et al (2004) Burkholderia cenocepacia vaginal infection in patient with smoldering myeloma and chronic hepatitis C. Emerg Infect Dis 10(11):1957–1959
236. Aisenberg G, Rolston KV, Safdar A (2004) Bacteremia caused by Achromobacter and Alcaligenes species in 46 patients with cancer (1989–2003). Cancer 101(9):2134–2140
237. Chiu SK, Chang FY (2009) Pyomyositis caused by extended-spectrum beta-lactamase-producing Escherichia coli in a patient with acute myeloid leukemia. Int J Infect Dis 13(3):e85–e87
238. Sharma U, Schwan WR, Agger WA (2011) Escherichia coli pyomyositis in an immunocompromised host. WMJ 110(4):182–184
239. Vigil KJ et al (2010) Escherichia coli Pyomyositis: an emerging infectious disease among patients with hematologic malignancies. Clin Infect Dis 50(3):374–380
240. Pfaller M, Wenzel R (1992) Impact of the changing epidemiology of fungal infections in the 1990s. Eur J Clin Microbiol Infect Dis 11(4):287–291
241. Walsh TJ et al (1991) Empiric therapy with amphotericin B in febrile granulocytopenic patients. Rev Infect Dis 13(3):496–503
242. Wingard JR, Merz WG, Saral R (1979) Candida tropicalis: a major pathogen in immunocompromised patients. Ann Intern Med 91(4):539–543
243. Sipsas NV et al (2009) Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001–2007): stable incidence but changing epidemiology of a still frequently lethal infection. Cancer 115(20):4745–4752
244. Hachem R et al (2008) The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. Cancer 112(11):2493–2499
245. Dahiya MC et al (2003) Oropharyngeal candidiasis caused by non-albicans yeast in patients receiving external beam radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 57(1):79–83
246. Lalla RV et al (2010) A systematic review of oral fungal infections in patients receiving cancer therapy. Support Care Cancer 18(8):985–992
247. Redding SW et al (2004) Candida glabrata is an emerging cause of oropharyngeal candidiasis in patients receiving radiation for head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 97(1):47–52
248. Schelenz S et al (2011) Epidemiology of oral yeast colonization and infection in patients with hematological malignancies, head neck and solid tumors. J Oral Pathol Med 40(1):83–89
249. Anaissie E, Bodey GP (1989) Nosocomial fungal infections. Old problems and new challenges. Infect Dis Clin North Am 3(4):867–882
250. Hachem RY et al (2004) Aspergillus terreus: an emerging amphotericin B-resistant opportunistic mold in patients with hematologic malignancies. Cancer 101(7):1594–1600
251. Miceli MH, Diaz JA, Lee SA (2011) Emerging opportunistic yeast infections. Lancet Infect Dis 11(2):142–151
252. Pfaller MA et al (2009) Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: 10.5-year analysis of susceptibilities of noncandidal yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J Clin Microbiol 47(1):117–123
253. Kalter DC et al (1986) Genital white piedra: epidemiology, microbiology, and therapy. J Am Acad Dermatol 14(6):982–993
254. Nahass GT et al (1993) Disseminated infection with Trichosporon beigelii. Report of a case and review of the cutaneous and histologic manifestations. Arch Dermatol 129(8):1020–1023
255. Walsh TJ et al (1986) Trichosporonosis in patients with neoplastic disease. Medicine 65(4):268–279 (Baltimore)

256. Pagano L et al (2011) Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. J Antimicrob Chemother 66(Suppl 1):i5–14
257. Campo M, Lewis RE, Kontoyiannis DP (2010) Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998–2009. J Infect 60(5):331–337
258. Gamis AS et al (1991) Disseminated infection with Fusarium in recipients of bone marrow transplants. Rev Infect Dis 13(6):1077–1088
259. Lortholary O et al (2010) International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. Antimicrob Agents Chemother 54(10):4446–4450
260. Nucci M et al (1992) Three cases of infection with Fusarium species in neutropenic patients. Eur J Clin Microbiol Infect Dis 11(12):1160–1162
261. Enache-Angoulvant A, Hennequin C (2005) Invasive Saccharomyces infection: a comprehensive review. Clin Infect Dis 41(11):1559–1568
262. Ben-Ami R et al (2009) Phaeohyphomycosis in a tertiary care cancer center. Clin Infect Dis 48(8):1033–1041
263. Chaturvedi V, Chaturvedi S (2011) Cryptococcus gattii: a resurgent fungal pathogen. Trends Microbiol 19(11):564–571
264. MacDougall L et al (2011) Risk factors for Cryptococcus gattii infection, British Columbia, Canada. Emerg Infect Dis 17(2):193–199
265. Perfect JR et al (2010) Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 50(3):291–322
266. Kumar D, Humar A (2010) Respiratory viral infections in transplant and oncology patients. Infect Dis Clin North Am 24(2):395–412
267. Kaltsas A, Sepkowitz K (2012) Community acquired respiratory and gastrointestinal viral infections: challenges in the immunocompromised host. Curr Opin Infect Dis 25(4): 423–430
268. Torres HA, Davila M (2012) Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. Nat Rev Clin Oncol 9(3):156–166
269. Roberts RR et al (2009) Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis 49(8):1175–1184
270. Kamboj M et al (2010) The changing epidemiology of vancomycin-resistant Enterococcus (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Biol Blood Marrow Transplant 16(11):1576–1581
271. Vydra J et al (2012) Enterococcal bacteremia is associated with increased risk of mortality in recipients of allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 55(6):764–770
272. Ghanem G et al (2007) Outcomes for and risk factors associated with vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant Enterococcus faecium bacteremia in cancer patients. Infect Control Hosp Epidemiol 28(9):1054–1059
273. Wudhikarn K, Gingrich RD, de Magalhaes M (2013) Silverman, Daptomycin nonsusceptible enterococci in hematologic malignancy and hematopoietic stem cell transplant patients: an emerging threat. Ann Hematol 92(1):129–131
274. Morris PG et al (2008) Emergence of MRSA in positive blood cultures from patients with febrile neutropenia–a cause for concern. Support Care Cancer 16(9):1085–1088
275. Chemaly RF et al (2010) Characteristics and outcomes of methicillin-resistant Staphylococcus aureus surgical-site infections in patients with cancer: a case-control study. Ann Surg Oncol 17(6):1499–1506
276. Reish RG et al (2013) Infection following implant-based reconstruction in 1952 consecutive breast reconstructions: salvage rates and predictors of success. Plast Reconstr Surg 131(6):1223–1230

277. Rogers SN et al (2008) Which patients are most at risk of methicillin resistant *Staphylococcus aureus*: a review of admissions to a regional maxillofacial ward between 2001 and 2005. Br J Oral Maxillofac Surg 46(6):439–444
278. Shiomori T et al (2007) Clinical features of head and neck cancer patients with methicillin-resistant *Staphylococcus aureus*. Acta Otolaryngol 127(2):180–185
279. Watters K, O'Dwyer TP, Rowley H (2004) Cost and morbidity of MRSA in head and neck cancer patients: what are the consequences? J Laryngol Otol 118(9):694–699
280. Cattaneo C et al (2008) Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother 61(3):721–728
281. Arnan M et al (2011) Risk factors for, and clinical relevance of, faecal extended-spectrum beta-lactamase producing Escherichia coli (ESBL-EC) carriage in neutropenic patients with haematological malignancies. Eur J Clin Microbiol Infect Dis 30(3):355–360
282. Gudiol C et al (2010) Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 65(2):333–341
283. Irfan S et al (2008) Emergence of Carbapenem resistant Gram negative and vancomycin resistant Gram positive organisms in bacteremic isolates of febrile neutropenic patients: a descriptive study. BMC Infect Dis 8:80
284. Kunz AN, Brook I (2010) Emerging resistant Gram-negative aerobic bacilli in hospital-acquired infections. Chemotherapy 56(6):492–500
285. Ortega M et al (2009) Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother 63(3):568–574
286. Sood P et al (2012) Emergence of multidrug resistant acinetobacter blood stream infections in febrile neutropenia patients with haematological cancers and bone marrow failure syndromes. J Indian Med Assoc 110(7):439–444
287. Vigil KJ et al (2009) Multidrug-resistant Escherichia coli bacteremia in cancer patients. Am J Infect Control 37(9):741–745

# Bacterial Pathogens

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**Abstract**

Bacterial infections are frequent complications among patients treated for cancer. The type, severity, and treatment of bacterial infections vary and depend upon the specific malignancy, associated chemotherapies, and transplantation. This chapter discusses commonly encountered bacterial pathogens as well as *Nocardia* and mycobacteria in patients with cancer and addresses the clinical syndromes and management. Drug-resistant bacteria are becoming an increasingly recognized problem in patients with cancer. Antimicrobial resistance in select gram-positive and gram-negative bacteria are discussed along with the mechanisms of resistance and recommended therapies.

**Keywords**

Bacteria · *Nocardia* · Mycobacteria · Resistance

## Contents



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## 1 Introduction

Infectious diseases are among the most frequent complications encountered in cancer management. Optimal patient care necessitates a familiarization with common bacterial pathogens and their treatment. *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and viridans group streptococci are the more common gram-positive bacterial pathogens encountered in patients with cancer. Among the gram-negative bacteria, members of the Enterobacteriaceae family and *Pseudomonas aeruginosa* are the more frequently encountered and virulent pathogens. Many patients with cancer, especially those hospitalized, have prior antimicrobial treatment experience. Antimicrobial resistance is an increasing problem, and understanding the mechanisms of resistance is imperative toward prescribing effective therapy. Drug resistance mechanisms of select gram-positive and gram-negative bacteria as well as treatment options are reviewed.

*Nocardia* and mycobacteria both stain acid-fast and can produce severe progressive disease in patients with cancer. *Nocardia* may produce pulmonary disease resembling that of mycobacteria, or more distinct forms of extrapulmonary disease. Tuberculosis is less common in the United States, but must be considered in any patient with compatible features. Atypical presentations of tuberculosis are more common in cancer patients. Non-tuberculosis mycobacteria (NTM) encompass a very large group of organisms with diverse manifestations of localized or disseminated clinical disease. An overview of bacterial infections in patients with cancer is provided.

## 2 Select Gram-Positive Bacteria

### 2.1 *Staphylococcus* spp.

*S. aureus* is a virulent pathogen causing significant disease in both immunocompetent and immunocompromised patients. Clinical infections in patients with cancer caused by *S. aureus* are quite diverse and include intravascular catheter infections, skin and soft tissue infections, visceral abscesses, endocarditis, bone and joint infections, and bloodstream infections. Bloodstream infections with

*S. aureus* are a medical urgency, requiring prompt intervention. Metastatic foci of *S. aureus* infection can develop, requiring prolonged antimicrobial therapy and possible surgery. Intravascular catheters remain one of the most common causes of *S. aureus* nosocomial- and community-acquired bloodstream infections. In the hospital setting, approximately 20 % of bloodstream infections are caused by *S. aureus* [1]. For methicillin- (or oxacillin-) susceptible *S. aureus*, cefazolin or a penicillinase-resistant penicillin is recommended for more serious infections, including bloodstream infections. Vancomycin can be used for B-lactam allergic patients, but is less active. Oral antimicrobials including first-generation cephalosporins, anti-staphylococcal penicillins, trimethoprim–sulfamethoxazole, minocycline, clindamycin, and the newer fluoroquinolones can be used for mild soft tissue infections.

Most *S. aureus* bacteria are resistant to penicillin through plasmid-encoded penicillinase production. Methicillin-resistant *S. aureus* (MRSA) is defined by a minimum inhibitory concentration (MIC) with oxacillin at $\geq$4 mcg/mL. MRSA is becoming an increasing problem in hospitals around the world. Patients who have been treated with an antibiotic within the preceding 3 months (especially B-lactams and fluoroquinolones) are at increased risk for MRSA [2]. In 2003, up to 64 % of hospital-onset *S. aureus* infections in the intensive care units were MRSA [3]. Of the estimated 94,360 MRSA infections that occurred in the USA during 2005, approximately 75 % were bloodstream infections [4]. A surveillance of nine US hospitals in 2005 found the combination of *S. aureus* virulence and the immunosuppression of patients with cancer enables rapid *S. aureus* infection progression and high rates of disease recurrence if not recognized early or treated aggressively [5].

MRSA carries the *mecA* gene that encodes for penicillin-binding protein 2A (PBP2A). PBP2A has very low binding affinity for B-lactam antimicrobials and confers phenotypic bacterial resistance to all B-lactam antimicrobials, including penicillins, cephalosporins (except ceftaroline), and carbapenems. The *mecA* gene is located in a mobile staphylococcal cassette cartridge (SCC), which aids in chromosomal incorporation. There are currently eight SCC *mec* types (I-VIII), that differ in both *mec* and cassette chromosome recombinase gene complexes, along with a number of additional novel SCC subtypes [6, 194]. MRSA is commonly categorized into either health-care-associated (HA) MRSA or community-associated (CA) MRSA. The nomenclature refers to differences in demographic backgrounds, genetic and clonal features, susceptibility patterns, and clinical characteristics of the MRSA strains. About 85 % of all invasive MRSA infections are associated with some type of exposure to health care settings, and approximately 15 % develop within the community. Characteristics and differences between HA-MRSA and CA-MRSA are listed in Table 1.

CA-MRSA typically is more susceptible to non-B-lactam antimicrobials (including fluoroquinolones, macrolides, gentamicin, and clindamycin) and has exotoxin virulence factors [7]. MRSA strains susceptible in vitro to clindamycin but resistant to erythromycin may harbor erythromycin ribosomal methylase (*erm*) genes, conferring an inducible resistance to clindamycin. Clinical failure with

**Table 1** Characteristics of HA-MRSA and CA-MRSA

| | HA-MRSA | CA-MRSA |
|---|---|---|
| Patient risk factors | Prolonged hospitalization, ICU admission, residents of long-term care facilities; comorbidities including diabetes mellitus and hemodialysis | Children, competitive athletes, prisons, soldiers; select ethnic groups (Native Americans, Alaska Natives, Pacific Islanders), intravenous drug users, men who have sex with men |
| Clinical syndromes | Nosocomial pneumonia, intravenous catheter infections and related bacteremias, urinary catheter-associated urinary tract infections, surgical site infections | Skin and soft tissue infections (furuncles, skin abscesses), necrotizing pneumonia |
| Antimicrobial resistance | B-lactam class resistance, resistance to other drug classes common | B-lactam class resistance, more susceptible to other drug classes |
| Predominant SCC types | Types I, II, III | Type IV, V, VII |
| PVL toxin | Rare | Frequent |

(Based on data from Refs. [6] and [192])

clindamycin has been reported in this setting [8]. Inducible clindamycin resistance can be identified in the laboratory with double-disk diffusion testing (D-testing) on erythromycin-resistant, clindamycin-susceptible MRSA strains. USA 300 and USA 400 are the two most commonly encountered CA-MRSA clones. The most common toxin is the Panton–Valentine leukocidin (PVL), a cytotoxin associated with skin and soft tissue infections and necrotizing pneumonia [9]. PVL is characteristically uncommon in HA-MRSA strains.

Treatment options for MRSA depend upon the infection syndrome as well as in vitro drug susceptibility data. Vancomycin, daptomycin, linezolid, ceftaroline, telavancin, teicoplanin and quinupristin-dapfopristin are typically active drugs. Additional options, depending upon drug susceptibility data, may include trimethoprim–sulfamethoxazole, minocycline, doxycycline, tigecycline, clindamycin, and the newer fluoroquinolones. Confirmed vancomycin-intermediate (VISA) or vancomycin-resistant (VRSA) MRSA is fortunately quite rare; however, even 'susceptible' MRSA may be less responsive to vancomycin. Some reports have shown MRSA bacteremia with a vancomycin MIC of $\leq$0.5 ug/mL to have a higher treatment success rate with vancomycin than MRSA with vancomycin MIC 1–2 ug/ml [10, 11].

Coagulase-negative staphylococci (CoNS) comprise a heterogenous group of bacteria that are part of the natural skin microbial flora. Although less virulent compared to *S. aureus*, many CoNS (including *S. epidermidis* and *S. haemolyticus*) are resistant to multiple antibiotics including methicillin. The mechanisms of resistance are similar to those of *S. aureus* and include B-lactamase production and PBP2A production by the *mecA* gene. Both *S. aureus* and CoNS produce a biofilm, enabling attachment to foreign material. CoNS, including *S. epidermidis*, are the

most common cause of intravascular catheter infections [12, 13]. The high usage of short-term and tunneled central venous catheters in patients with cancer (e.g., for chemotherapy and/or blood product infusions) allows for CoNS to be the most common cause of bloodstream infections in this patient group as well as for hospitalized patients in general [1]. Single positive blood cultures with CoNS need to be interpreted with caution as contamination from the skin is common. CoNS are also a common pathogen with other types of foreign body infections including prosthetic valves and other endovascular devices, cerebrospinal fluid shunts, peritoneal dialysis catheters, ocular implants, and prosthetic joints.

*S. lugdunensis* is a CoNS that deserves special mention. *S. lugdunensis* is more virulent than other CoNS and should never be regarded as a contaminant in blood cultures. Up to 50 % of *S. lugdunensis* community-acquired bloodstream infections in one series were associated with endocarditis, whereas nosocomial *S. lugdunensis* bacteremias were commonly catheter associated [14]. *S. lugdunensis* has also been associated with infections of skin and soft tissues (often with abscess formation), central nervous system (CNS), bone and joint, peritoneum, and oral cavity [15]. Despite its enhanced pathogenicity, *S. lugdunensis* remains susceptible to most B-lactam antimicrobials.

## 2.2 *Enterococcus* spp. and Viridans Group *Streptococcus*

*Enterococcus* spp. are a component of the normal gastrointestinal bacterial flora and occasionally may be found in the vagina and oral cavity [16]. Enterococcal infections may develop secondary to a compromise in bowel wall integrity, fecal contamination, genitourinary complications, animal contact, and through nosocomial acquisition. Before the emergence of vancomycin-resistant enterococci (VRE), 85–90 % of clinical enterococcal isolates were *E. faecalis*, 5–10 % were *E. faecium*, and the remaining 3–4 % were other *Enterococcus* spp. [17]. *Enterococcus* spp. have lower intrinsic virulence compared to *S. aureus* and group *A Streptococcus* as well as no exotoxin production.

Although a wide array of clinical infections have been ascribed to *Enterococcus* spp. (including endocarditis, urinary tract infections, and osteomyelitis), enteric and other-related intraabdominal infections as well as bacteremias are especially common in patients with cancer. Any compromise in bowel wall integrity increases the risk for infection with *Enterococcus* spp. Cancers of the gastrointestinal, genitourinary and biliary tracts, antineoplastic chemotherapy, neutropenic colitis (typhlitis), and enteric graft-versus-host disease all enable enterococci and other enteric flora to translocate beyond the bowel lumen and produce clinical disease. Infection in these settings is often polymicrobial and should generally be managed with broadened antibacterial therapy.

Because of lower affinity for the penicillin-binding proteins, *Enterococcus* spp. are less susceptible to B-lactams compared to other gram-positive bacteria. Rarely, enterococci also produce a B-lactamase. The MICs of active penicillins to

*Enterococcus* spp. are significantly higher compared to most streptococci [16]. Penicillin, ampicillin, amoxicillin, piperacillin, imipenem, meropenem, and doripenem are moderately active against susceptible enterococci, but remain bacteriostatic. The addition of gentamicin or streptomycin may provide additional activity when combined with a B-lactam and is typically recommended in cases of enterococcal endocarditis. The cephalosporins (except ceftaroline against E. faecalis) and clindamycin are not active. Although trimethoprim–sulfamethoxazole (TMP-SMX) may have mild in vitro activity, enterococci can metabolically utilize exogenous folinic acid, dihydrofolate, and tetrahydrofolate to survive, rending this drug clinically ineffective [18]. The fluoroquinolones also have low-level anti-enterococcal activity, but their clinical usefulness is quite limited outside of simple lower urinary tract infections, and rates of quinolone resistance remain high. Enterococci have the ability to exchange genes encoded on plasmids for additional drug resistance. Such acquired drug resistance has rendered most macrolides, tetracyclines, and occasionally vancomycin ineffective.

Peptidoglycan is a crucial component of the bacterial cell wall, and vancomycin exerts it activity through the inhibition of peptidoglycan biosynthesis. Specifically, vancomycin binds to the D-alanyl-D-alanine terminus of the pentapeptide peptidoglycan precursor and inhibits subsequent enzymatic steps in cell wall development [19]. Vancomycin resistance develops through the synthesis of peptidoglycan cell wall precursors that contain an altered terminal dipeptide (e.g., D-alanyl-D-lactate or D-alanyl-D-serine) instead of a D-alanyl-D-alanine terminus. Vancomycin is subsequently not able to bind with the altered enterococcal dipeptide terminus.

VRE were first identified in Europe in 1988 [20, 21] and have subsequently spread worldwide. Vancomycin resistance is much more prevalent in *E. faecium*; however, vancomycin-resistant *E. faecalis* has been isolated, usually as a nosocomial pathogen [22]. The incidence of VRE colonization and infection are increasing. Up to 10 % of hemodialysis patients in one center were reported to be colonized with VRE [23]. Within the USA, a recent multicenter study found 28 % of the enterococci cultured from intensive care unit (ICUs) to be VRE [24]. In a recent national surveillance study of bloodstream infections, 60 % of *E. faecium* and 2 % of *E. faecalis* isolated were VRE [1]. Patients with cancer, especially hematologic malignancies, have a high risk for VRE morbidity and mortality because of extended health care facility and antimicrobial exposures, chemotherapy-associated bowel wall compromise and sustained periods of post-chemotherapy neutropenia [25]. Pretransplant VRE colonization is an independent risk factor for increased mortality in patients receiving allogeneic hematopoietic stem cell transplantations [26]. The increase in mortality in this group correlates with the presence of VRE bacteremia.

There are multiple VRE phenotypes (including A-G and select others) depending upon the altered terminal dipeptide (D-alanyl-D-lactate for VanA, B, and D types; D-alanyl-D-serine for VanC, E, and G types) and elimination of high affinity precursors [27]. VanA is the most common VRE phenotype and demonstrates high-level resistance to both vancomycin and teicoplanin. Transfer of VanA-type resistance via plasmid DNA from enterococci to *S. aureus* has been

identified and poses great concern [28, 29]. VanB is the next most common and exhibits moderate to high resistance to vancomycin but remains susceptible to teicoplanin. The VanC phenotype is characteristic of *E. gallinarum* and *E. casseliflavus/flavescens* and has an intrinsic low-level resistance to vancomycin that is chromosomally encoded [30]. It remains susceptible to teicoplanin. Although *E. gallinarum* and *E. casseliflavus/flavescens* are infrequently encountered, they are more commonly found in patients with immunosuppression, including hematologic malignancies, hematopoietic stem cell, and solid organ transplantation [31]. VanD has been found in *E. faecium* that has moderate levels of resistance to both vancomycin and teicoplanin. VanE and G have been found in *E. faecalis* with a similar terminal D-serine substitution and phenotypic effect as the VanC [30].

Most VRE are resistant to penicillin and ampicillin, but on rare occasions these agents may show in vitro activity. Treatment options for VRE include linezolid, daptomycin, quinupristin/dalfopristin (for *E. faecium* only), and tigecycline. Resistance to each of these agents has been demonstrated. Currently, linezolid is the only oral agent approved by the Food and Drug Administration for the treatment of VRE infection; however, the myelosuppressive effects (including leukopenia and thrombocytopenia) may limit its sustained use in patients with some cancers. Nitrofurantoin may be active for uncomplicated VRE urinary tract [32].

Viridans group streptococci constitute a heterogenous group of bacteria that are found throughout the gastrointestinal and female genital tracts. Contrasting enterococci which predominate more in the lower small bowel and colon, viridans group streptococci are more prevalent in the oral cavity and upper respiratory tract. A breakdown in the mucosal barrier through chemotherapy-associated oral stomatitis and enteritis allows viridans group streptococci to cause infection. *S. mitis* and other viridans group streptococcal infections have been well identified following high-dose cytosine arabinoside therapy for acute leukemia [33]. Other risk factors for the development of viridans group streptococcal infections include profound neutropenia, antimicrobial prophylaxis with TMP-SMX or select fluoroquinolones, and use of stomach acid suppressants [34, 35]. In neutropenic patients, viridans group streptococci can produce a toxic shock-like syndrome, involving multiorgan dysfunction and respiratory failure [35, 36]. Such a syndrome may occur despite early clearance of bacteria from the bloodstream. An unusual outbreak of toxic shock-like syndrome caused by a toxigenic clone of *S. mitis* has also been described in immunocompetent patients [37].

Viridans group streptococci are generally susceptible to most B-lactam antimicrobials. Ceftriaxone is commonly used for its favorable clinical experience and convenient once daily administration. Penicillin historically was the drug of choice, but resistance through altered penicillin-binding proteins is not uncommon and may confer resistance to other beta-lactam antimicrobials. Alternative intravenous agents include vancomycin, daptomycin, quinupristin/dalfopristin, and tigecycline [38, 39], while the newer fluoroquinolones, linezolid, macrolides, and tetracyclines remain oral options. Fluoroquinolone-resistant viridans group streptococci have been increasingly identified in neutropenic patients receiving fluoroquinolone prophylaxis [40, 41].

## 2.3 Other Gram-Positive Bacteria

*Streptococcus bovis* is another constituent of normal gastrointestinal tract flora. Similar to other enteric bacteria, *S. bovis* bacteremia can develop when the there is compromise of the bowel wall secondary to either tumor invasion or antineoplastic chemotherapy. Bloodstream infections with *S. bovis* appear to have a higher association than other bacteria with the presence of bowel wall cancers. Patients with otherwise unexplained *S. bovis* bacteremia should undergo appropriate intestinal cancer screening [42]. Many providers also consider enteric evaluation in patients with otherwise unexplained *Clostridium septicum* bloodstream infection [43, 44].

The nutritionally variant streptococci (NVS), *Abiotrophia defectiva*, and *Granulicatella* spp. are fastidious bacteria that may grow as satellite colonies around *S. aureus* and other select bacteria or on pyridoxal- or L-cysteine-supplemented agar. NVS are part of the normal bacterial flora of the upper respiratory, gastrointestinal, and genitourinary tracts. NVS bacteremia can occur in patients with cancers of the gastrointestinal, genitourinary, or upper respiratory tracts and in those receiving antineoplastic chemotherapy. NVS have also been associated with destructive valvular lesions in patients with endocarditis. NVS are less susceptible to penicillin compared to *Streptococcus* spp., and combination therapy with aminopenicillin and aminoglycoside is commonly used for the treatment of endocarditis and refractory infections. Activity of cephalosporins against NVS is variable, but vancomycin and expanded fluoroquinolones remain active [45, 46].

*Streptococcus pneumoniae* infections are especially problematic in anatomically and functionally asplenic patients. Numerous hematologic indications for splenectomy exist, including hereditary spherocytosis, thalassemia major, myeloproliferative disorders with symptomatic splenomegaly, select cases of non-Hodgkin's disease, and occasionally for immune thrombocytopenia, thrombotic thrombocytopenic purpura, hairy cell leukemia, and as a staging procedure in Hodgkin's disease [47, 48]. *S. pneumoniae* is the most common bacterial infection associated with post-splenectomy severe sepsis. Other pathogens associated with severe disease in asplenic patients include *Neisseria meningitidis*, *Haemophilus influenza* type B, *Capnocytophaga canimorsus*, and *Babesia microti*. Estimates of post-splenectomy infection incidence and mortality vary although two large reviews reported a combined severe infection incidence of 3.2–4.2 % with a mortality of 1.4–2.5 % [49, 50].

*Listeria monocytogenes* is predominantly seen in neonates, the elderly, pregnant women, and in immunosuppressed patients, primarily those with cell-mediated immunity (CMI) dysfunction. Although an infrequently encountered pathogen, this 'diphtheroid-like' appearing gram-positive bacillus can produce bloodstream infections with a particular tropism for the meninges and brainstem (meningoencephalitis and rhombencephalitis) (see Chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients), as well as food-borne illness and disseminated neonatal disease. A recent review of listeriosis

in patients with cancer at the MD Anderson Cancer Center identified 59 % of patients had a hematologic malignancy (60 % lymphoma and 40 % leukemia or myeloma) and the remaining 41 % had solid tumors [51]. Bloodstream infection was the most common presentation, although 21 % had CNS involvement. *Listeria* bloodstream infection has been associated with CMV reactivation in recipients of allogeneic hematopoietic stem cell transplantation [52, 53].

## 3 Select Gram-Negative Bacteria

Although the incidence of gram-negative bacterial bloodstream infections in patients with febrile neutropenia is less than that of gram-positive bacteria [54, 55], the mortality of gram-negative bacteremia remains substantially higher [56]. Members of the Enterobacteriaceae family, primarily *E. coli* and *Klebsiella* spp., and *P. aeruginosa* are most commonly encountered [57]. Gram-negative bacteria isolated from a sterile body site should never be discounted as a contaminant.

### 3.1 The Enterobacteriaceae

The family Enterobacteriaceae contributes to the normal microbial flora of the lower gastrointestinal tract, oropharynx, and vagina and is the most common group of gram-negative bacteria isolated in the laboratory. Enterobacteriaceae produce the vast majority of gram-negative bacterial infections in patients with cancer. They frequently produce bloodstream, urinary tract, peritoneal, hepatobiliary, and nosocomial- and ventilator-associated pulmonary infections. The more commonly encountered members of this family include *E. coli, Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Proteus* spp., *Morganella* spp., *Providencia* spp., *Plesiomonas* sp., *Hafnia* sp., *Yersinia* spp., *Salmonella* spp., and *Shigella* spp. Although some of the Enterobacteriaceae including *Salmonella*, *Shigella*, *Aeromonas*, and *E. coli* 0157:H7 can produce distinct infection syndromes, many other species of this large family share similarities in clinical disease.

Gram-negative bacteremia in a neutropenic patient can rapidly turn fatal if effective antimicrobial therapy is not promptly started. *E. coli* is the most common gram-negative bacteria isolated from blood cultures and is also the most common pathogen in urinary tract infections. *E. coli* O157:H7 comprises most of the enterohemorrhagic *E. coli* and can produce shiga-toxin-mediated hemorrhagic colitis in both immunocompromised and immunocompetent patients. *E. coli* O157:H7 often is acquired through the consumption of contaminated ground beef and is the most common cause of hemolytic uremic syndrome (hemolytic anemia with schistocytes, thrombocytopenia, and renal insufficiency). *Klebsiella* spp. are the more commonly encountered Enterobacteriaceae in respiratory tract infections. Although often associated with ‘currant jelly’ sputum and the ‘bulging fissure

sign' on chest X-ray, these findings are not specific to *Klebsiella* spp. *Proteus mirabilis* causes 90 % of *Proteus* infections and is readily identifiable in culture for its 'swarming' tendency on agar. A variety of extended-spectrum penicillins, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and TMP-SMX are active against the Enterobacteriaceae; however, drug resistance is not uncommon. Select tetracyclines and macrolides may also be active. Knowledge of both the species and antimicrobial susceptibility data are needed for optimal drug therapy (see gram-negative bacterial drug resistance).

## 3.2 *Pseudomonas aeruginosa*

*P. aeruginosa* is one of the most concerning bacteria to produce infection in the immunocompromised patient. Inherent bacterial virulence leading to high mortality and progressive drug resistance through numerous mechanisms have necessitated preemptive treatment in patients suspected of having infection with *P. aeruginosa*. *P. aeruginosa* infections are generally considered to be nosocomially acquired; however, community-acquired primary *Pseudomonas* bloodstream infections occasionally occur [58].

Three sequential studies performed at the University of Texas, MD Anderson Cancer Center, during the 1960s, 1970s, and 1990s on the mortality of *P. aeruginosa* bloodstream infections in patients with underlying malignancies found the overall cure rate of *P. aeruginosa* bacteremia in patients with underlying malignancies to be 21, 62, and 80 %, respectively [59–61]. The favorable trend in outcome may reflect both the additional anti-*Pseudomonas* antimicrobials developed during the past three decades and changes in cancer management, including new chemotherapy regimens and antimicrobial prophylaxis. Despite these medical advances, the morbidity and mortality attributed to *P. aeruginosa* infections remain significant. Compared to immunocompetent patients, both *P. aeruginosa* and Enterobacteriaceae bloodstream infections are more common in patients with neutropenia (absolute neutrophil count $<$500 cells/uL) [62]. *P. aeruginosa* bloodstream infections are also more common in patients with acute leukemia compared to other hematologic or solid organ malignancies [60, 62]. More severe forms of graft-versus-host disease in allogenic hematopoietic stem cell transplantation are another risk factor for *P. aeruginosa* infection [63]. Empiric antibacterial therapy in patients with neutropenia and fever must contain activity against gram-negative bacteria, including *P. aeruginosa*.

*P. aeruginosa* can also cause serious skin and soft tissues infections in patients receiving antineoplastic chemotherapy. Ecthyma gangrenosum can develop in neutropenic patients with bacteremia. Ecthyma gangrenosum appears as erythematous round skin lesions with developing central necrosis and ulceration. Cutaneous *Pseudomonas* infection in the form of folliculitis may develop after exposure to contaminated hot tubs, whirlpools, or swimming pools. Deep tissue wounds with *P. aeruginosa* may follow puncture wounds to the foot (e.g., nail punctures through tennis shoes). Although not common for patients with cancer, *P. aeruginosa* infections can also produce pulmonary disease, especially in

patients with underlying bronchiectasis or cystic fibrosis; bone and joint disease; CNS infections associated with recent neurosurgery; endocarditis from intravenous drug usage; ear and eye infections, as well as nosocomial urinary tract infections.

Effective antimicrobials against *P. aeruginosa* include cefepime, ceftazidime, meropenem, imipenem, doripenem, piperacillin, piperacillin–tazobactam, aztreonam, ciprofloxacin, levofloxacin, gentamicin, tobramycin, amikacin, and colistin. Aminoglycoside or colistin therapy alone is not appropriate for the treatment of *P. aeruginosa* bacteremia [64]. *P. aeruginosa* has significant potential for the development of antimicrobial drug resistance. Risk factors for the development of multidrug-resistant *P. aeruginosa* include the use of carbapenems for one or more weeks, a history of *P. aeruginosa* infection or colonization during the preceding year, and a history of chronic obstructive pulmonary disease (COPD) [65].

## 3.3 Gram-Negative Bacterial Drug Resistance

Antimicrobial drug resistance through B-lactamase production by the Enterobacteriaceae and other gram-negative bacteria pose increasing therapeutic challenges. Over the last two decades, more types of B-lactamase production have been identified, decreasing effective therapeutic drug options. Also concerning is that routine antimicrobial susceptibility testing will not reliably identify some types of B-lactamase production nor predict clinical response to expanded B-lactam therapy. Comparative longitudinal antibiograms show an increasing number of bacterial pathogens with multiple drug resistance mechanisms [66]. Patients with cancer have a high risk for colonization and infection with drug-resistant bacteria. Frequent hospitalizations of this patient group combined with exposures to multiple antibiotics contribute to this risk [67]. Drug-resistant nosocomial infections are most often encountered in the ICU setting, followed by non-ICU hospital wards and outpatient hospital settings [68]. Within the ICU setting, rates of nosocomial drug-resistant bacterial infections are more prevalent in developing countries compared to the United States [69]. Such discrepancies may reflect differences in infection control policies and lack of adequate funding, compliance problems with adequate hand hygiene practices, differences in nurse-to-patient ratios and hospital overcrowding. Efforts to curb the propagation of multidrug-resistant pathogens will require enhanced national and global antimicrobial stewardship as well as appropriate infection control measures.

The first plasmid-mediated B-lactamase identified in gram-negative bacteria was the penicillin hydrolysis enzyme TEM-1 found in *E. coli* during the 1960s. TEM-1 is now the most commonly encountered B-lactamase in gram-negative bacteria, accounting for up to 90 % of the ampicillin resistance in *E. coli* as well as ampicillin and penicillin resistance in strains of *H. influenzae* and *N. gonorrhoeae* [70, 71]. SHV-1 is another common B-lactamase and is found predominantly in *K. pneumoniae* and *E. coli*. The SHV-1 B-lactamase is chromosomally

encoded in the majority of isolates of *K. pneumoniae*, but is usually plasmid mediated in *E. coli* [71].

Continued antimicrobial selective pressure has allowed for the emergence of additional TEM and SHV enzymes that enable select bacteria to hydrolyze an expanded group of B-lactam antimicrobials, including most cephalosporins. Extended-spectrum beta-lactamase (ESBL) enzymes confer resistance to the oxyimino-cephalosporins (cefotaxime, ceftazidime, ceftriaxone, cefuroxime, and cefepime) and monobactams (aztreonam), but not the cephamycins (cefoxitin, cefotetan) or carbapenems (imipenem, meropenem, ertapenem, and doripenem) [72]. Additionally, ESBL-producing bacteria are resistant to penicillins, but can be inhibited by beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam [73]. Genes encoding for ESBL production are transmissible and problematic in hospitals and long-term care facilities with congregate patient populations [74]. Currently over 150 different ESBL enzymes have been identified.

ESBL production is most commonly found in *K. pneumoniae*, *K. oxytoca*, and *E. coli* [71, 75]. Occasionally, ESBL production has also been seen with *Citrobacter* spp., *Enterobacter* spp., *Proteus* spp., *Salmonella* spp., *Serratia* spp., and other enteric bacteria, as well as in isolates of *Acinetobacter baumannii* and *P. aeruginosa* [66]. Prolonged mechanical ventilation is a significant risk factor for acquiring ESBL-producing bacteria [76] as these patients are usually more debilitated with a higher likelihood of receiving excessive antimicrobial therapy. Other risk factors for ESBL-producing bacterial infection include repetitive and prolonged hospitalizations, use of central venous and urinary catheters, administration of total parenteral nutrition, and exposure to third-generation cephalosporins, aminoglycosides, and TMP-SMX [72, 76]. The use of B-lactam/B-lactamase inhibitor combinations, rather than third-generation cephalosporins, in ventilated patients may help protect against development of ESBL-producing bacterial infections [77].

The Clinical and Laboratory Standards Institute (CLSI) testing platform for ESBL-producing gram-negative bacteria applies only to *E. coli*, *Klebsiella* spp., and *P. mirabilis*. Testing methodologies to identify ESBL production in other bacteria have not yet been validated [72]. In vitro susceptibility testing with ESBL-producing bacteria can be misleading as some antimicrobials may appear falsely active in vitro [66]. Unless proven otherwise, CLSI recommends all phenotypically confirmed ESBL-producing bacteria, irrespective of species, be reported as resistant to all penicillins, cephalosporins (except cefoxitin and cefotetan), and aztreonam in order to avoid therapy with potentially ineffective antimicrobials [72].

ESBL-producing bacteria pose significant therapeutic challenges as resistance genes for other antimicrobials including aminoglycosides, tetracyclines, and TMP-SMX are often present on the same plasmid [76]. Carbapenems should be considered first-line treatment for serious infections with ESBL-producing gram-negative bacteria [72]. Treatment with either imipenem or meropenem produces the most effective bacterial clearance and favorable patient outcomes. Ertapenem is effective as well. Combination therapy with a carbapenem is not superior to carbapenem therapy alone. B-lactam/B-lactamase inhibitor combinations, such as

piperacillin–tazobactam, can be active against bacteria possessing a single plasmid-mediated ESBL. Many bacteria, however, can produce multiple ESBL types, significantly reducing piperacillin–tazobactam activity [78, 79]. Cefepime is less effective than the carbapenems, but may provide some activity when used in higher doses (at least 2 g twice daily) against organisms with a cefepime MIC <2 ug/mL [72]. Cefepime MIC values are generally higher in ESBL-producing strains of *E. cloacae* compared to non-ESBL-producing strains [80]. Cefepime and piperacillin–tazobactam therefore should not be used as first-line treatment against ESBL-producing bacteria and only considered when other more effective antimicrobials are not available. The fluoroquinolones may be effective for some mild-to-moderate ESBL-producing bacterial infections; however, fluoroquinolone resistance rates over 55 % have been reported among ESBL-producing Enterobacteriaceae [81].

Resistance to expanded-spectrum cephalosporins and many broad-spectrum penicillins can also develop with the hyperproduction of the Bush group 1, chromosomal-mediated (AmpC) B-lactamase. The AmpC B-lactamase is inducible and has been most commonly found in *E. cloacae*, *E. aerogenes*, *C. freundii*, and *S. marcescens* [75, 82]. In a surveillance study of nosocomial bloodstream infections in US hospitals, 50 % of *E. aerogenes*, 35 % of *E. cloacae*, and 39 % of *C. freundii* isolates produced AmpC B-lactamase and were resistant to ceftazidime, ceftriaxone, piperacillin, and piperacillin–tazobactam [83]. Less common bacteria that have been found to occasionally harbor chromosomal-mediated AmpC B-lactamases include *Acinetobacter* spp., *Aeromonas* spp., *Chromobacterium violaceum*, *C. freundii*, *Enterobacter* spp., *E. coli*, *H. alvei*, *Morganella morganii*, *Ochrobactrum anthropi*, *P. rettgeri*, *P. stuartii*, *P. aeruginosa*, *S. marcescens*, and *Y. enterocolitica* [75]. In addition, plasmid-mediated AmpC B-lactamases have been found in *K. pneumoniae*, *Salmonella* spp., and *P. mirabilis* [84].

Although *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp. may appear susceptible to penicillins and cephalosporins in vitro, select antibiotic pressure (e.g., third-generation cephalosporins) can facilitate production of high levels of AmpC B-lactamase production [85, 86]. Of the third-generation cephalosporins, ceftriaxone appears to be most provocative toward inducing AmpC B-lactamase production in *E. cloacae* [87] and possibly in other bacteria. The higher biliary concentration of ceftriaxone and broad activity against the Enterobacteriaceae may contribute to this effect. Interestingly, the fluoroquinolones may offer a protective effect against AmpC B-lactamase production [87]. In addition to antimicrobial pressure, AmpC B-lactamase production may develop through a spontaneous gene mutation enabling a 'de-repressed' state of B-lactamase hyperproduction [83].

Many AmpC B-lactamase-producing bacteria are resistant to the semisynthetic penicillins (e.g., piperacillin) and combination B-lactam/B-lactamase inhibitors. Antimicrobials that generally remain active include carbapenems, cefepime, aminoglycosides, TMP-SMX, and fluoroquinolones. ESBL- and AmpC-type B-lactamase production can occur together in some *E. cloacae* and *E. aerogenes*. Although cefepime may be clinically useful against AmpC B-lactamase producing gram-negative bacteria, it remains less effective against ESBL-producing bacteria.

Of significant concern has been the propagation of carbapenemase production among select Enterobacteriaceae. Carbapenemase-producing Enterobacteriaceae differ from ESBL- and AmpC B-lactamase-producing bacteria in that no reliably effective antimicrobial treatment options exist. The carbapenemases can hydrolyze all penicillins, cephalosporins, and carbapenems, rendering these drug classes ineffective. Currently, *K. pneumoniae* is the most commonly encountered bacteria with carbapenemase production [88]. Carbapenemase-producing genes have also occasionally been identified in *E. coli* and other genera of the Enterobacteriaceae family, including *Proteus*, *Serratia*, *Salmonella*, and *Citrobacter* [89–92]. Plasmid and chromosomal carbapenemase enzyme production have also been identified in non-Enterobacteriaceae pathogens including *Acinetobacter* sp., *P. aeruginosa*, and *Stenotrophomonas* sp. [74].

Genes encoding seven types of *Klebsiella pneumoniae* carbapenemase (KPC) have been identified on plasmids that can be readily transferred within the same or different species of Enterobacteriaceae [93, 94]. Such drug resistance transmissibility has led to KPC-producing *Enterobacteriaceae* outbreaks in the Northeastern USA and hospitals around the world. From 2000 to 2007, reported cases of carbapenemase-producing *K. pneumoniae* increased from <1 to 8 % of all identified *Klebsiella* spp. [88]. Investigators at Mount Sinai Hospital in New York City found a 26 % prevalence of carbapenemase-producing *K. pneumoniae* among all invasive *K. pneumoniae* isolates identified between 2004 and 2006 [95]. Similarly, one-third of all *K. pneumoniae* isolated in separate surveillance study in New York City were carbapenemase-producing strains [96]. Previously recognized in India and Pakistan, a new carbapenemase called the New Delhi metallo-beta-lactamase (NDM-1), conferring resistance to all beta-lactam agents except aztreonam, was confirmed in *E. coli*, *K. pneumoniae*, and *E. cloacae* within the United States in 2010 [97].

Risk factors for the development of carbapenemase-producing bacteria include solid organ or hematopoietic stem cell transplantation, mechanical ventilation, longer hospital stay, exposure to cephalosporins and carbapenems [95]. Mortality attributed to carbapenemase-producing *Klebsiella* has been estimated at 35–44 % [93]. Currently, there are no CLSI-validated tests for detecting AmpC B-lactamase or carbapenemase production [75]. Treatment options remain quite limited. In addition to broad B-lactam drug resistance, resistance to fluoroquinolones and sulfonamides is common. Aminoglycosides, colistin, tetracycline, and tigecycline have variable activity.

## 4 Other Bacterial Pathogens

*Clostridium difficile* is an anaerobic, spore-forming gram-positive bacillus that is the most common cause of antibiotic-associated pseudomembranous colitis. *C. difficile* infection (CDI) is also the most common nosocomial enteric infection in patients with recent antibiotic use or hospitalization. The spectrum of disease

ranges from an asymptomatic carrier state to fulminant toxic megacolon. Antimicrobials that are active against anaerobic bacteria (especially clindamycin, third-generation cephalosporins, and broad-spectrum penicillins) are more likely to provoke *C. difficile* colitis development. The risk is less with linezolid, aminoglycosides, rifampin, and vancomycin. *C. difficile* toxins can be identified in the stool of 15–25 % of patients with antibiotic-associated diarrhea and in more than 95 % of patients with pseudomembranous colitis [98]. Symptoms of CDI are attributed to two exotoxins (A and B), which produce mucosal damage and inflammation to the colon. The BI/NAP1 strain of *C. difficile* has recently been identified to have a higher toxin production and hypersporulation capacity secondary to deletions in the *tcdC* regulatory gene [99]. Both 18- and 39-base pair deletions have been detected in up to 30 % of patients with CDI in one study but without direct correlation to clinical disease severity. Thus, other genetic and/or patient clinical factors likely contribute toward the severity of CDI [100].

The overall incidence of *C. difficile* colitis in hospitalized patients is 1–2 %; however, in patients with a solid organ or hematopoietic stem cell transplant or receiving myeloablative antineoplastic therapy, the incidence is higher. The increased incidence may reflect a higher usage of antimicrobials, underlying disease, and select chemotherapeutic agents (including adriamycin, cyclophosphamide, methotrexate, 5-fluorouracil, and tacrolimus) [101]. Although the incidence of CDI is variable among different patient groups, it has been reported as high as 15–20 % in hematopoietic stem cell recipients in some centers [102, 103].

Initial steps toward CDI management include cessation of any unnecessary antibiotics. Oral metronidazole or oral vancomycin remains first-line treatment options. For more severe disease, a combination of oral vancomycin and intravenous metronidazole can be used [104]. Intravenous immunoglobulins have been used in select cases but with mixed results. *C. difficile* disease can recur, and the risk of disease relapse progressively increases after each episode of *C. difficile* infection. Options for more refractory or relapsing cases of *C. difficile* include high-dose vancomycin (which may also be given as pulse dosing and tapering regimens), rifaximin, nitazoxanide, fidaxomicin and use of probiotics such as *Saccharomyces boulardii* (see Chapter Enteric Infections). Fecal bacteriotherapy / instillation has been used successfully in more treatment refractory cases but not well studied in patients recently receiving antineoplastic chemotherapy.

Many other anaerobic bacteria can produce significant disease when the integrity of gastrointestinal tract is compromised. Myeloablative chemotherapy, especially idarubicin and cytosine arabinoside, used for the treatment of acute myelogenous leukemia, predispose to mucositis, enteritis, and colitis [105]. *Fusobacterium* spp., *Peptostreptococcus* spp., *and Porphyromonas* spp. are commonly encountered in oral and para-pharyngeal infections, whereas *Bacteroides* spp., *Clostridium* spp., *Prevotella* spp., and *Peptostreptococcus* spp. are frequently identified in intra-abdominal infections. Significant pathogen overlap exists, and anaerobic bacterial infections are typically polymicrobial. Novel bacteria include *Fusobacterium necrophorum*, commonly involved with Lemierre's syndrome, and *C. septicum*, commonly involved in neutropenic colitis.

## 5 Nocardia

The genus *Nocardia* is a ubiquitous group of environmental bacteria containing over 50 species [106]. *Nocardia* is a novel gram-positive branching filamentous aerobic saprophyte, found in soil, decomposing vegetation and other organic matter, and in fresh and salt water. Both *Nocardia* and *Rhodococcus* are members of the family Nocardiaceae, which belongs to a suborder of 'aerobic actinomycetes' that also includes *Mycobacterium*, *Corynebacterium*, *Gordona*, and *Tsukamurella*. *Nocardia* exhibits varying degrees of acid fastness depending upon the mycolic acid composition in the cell wall and type of stain used [106]. The modified Kinyoun acid-fast stain uses a 1 % sulfuric acid as a decolorizer (instead of the more potent hydrochloric acid used in the decoloration step in Ziehl–Neelsen staining procedure), which enhances the ability of *Nocardia* to retain the colored fuchsin [107]. Unlike mycobacteria, *Nocardia* has a 'beaded' acid-fast appearance on microscopy. In contrast to other gram-positive bacteria, *Nocardia* appears as filamentous bacteria with hyphae-like branching. *Nocardia* can resemble *Actinomyces* spp. on gram stain; however, *Actinomyces* spp. are not acid-fast and grow under anaerobic conditions.

The majority of *Nocardia* infections occur in patients with immunosuppressive conditions; however, up to one-third of patients are immunocompetent [108]. Patients with depressed CMI are especially at high risk including those with lymphoma and other hematologic malignancies, patients taking steroids or other CMI-suppressing medications [109]. Patients with allogenic hematopoietic stem cell transplants are at much higher risk for nocardiosis than autologous hematopoietic stem cell transplant recipients [110, 111]. The development of graft-versus-host disease and subsequent additional immunosuppressive treatments may account for much of the increased risk in allogenic hematopoietic stem cell transplant patients. In hematopoietic stem cell transplant patients, nocardiosis can develop at varying time periods, which range from two–three months to one–two years after the transplant [110, 111]. Although the use of cyclosporin has been associated with the development of nocardiosis [112, 113], combination therapy with cyclosporin and prednisone in some patient groups may pose less risk than azathioprine and prednisone or high-dose prednisone alone [114, 115]. Solid tissue cancers with associated chemotherapy represent another novel category for *Nocardia* disease development. Comorbidities including diabetes, chronic lung disease, and alcoholism contribute as well.

Pulmonary nocardiosis is the most common form of *Nocardia* infection. The onset of symptoms may be subacute to more chronic and can include cough which may be productive, shortness of breath, chest pain, hemoptysis, fever, night sweats, weight loss, and progressive fatigue. The chest X-ray may show focal or multifocal disease containing nodular and/or consolidation infiltrate as well as cavitary lesions [116]. Pleural effusions can develop in up to one-third of patients. It can be very difficult clinically and radiographically to differentiate *Nocardia* from filamentous fungal (e.g., aspergillosis, mucormycosis) or mycobacterial

disease. Occasionally, *Nocardia* spp. may be isolated from the respiratory tract in a person without respiratory disease. *Nocardia* found as an 'airway colonizer' is more typical in patients with underlying structural lung disease such as bronchiectasis and cystic fibrosis [106] and should be interpreted cautiously. The isolation of *Nocardia* in an immunocompromised patient should never be ignored, especially if any abnormal clinical or radiologic pulmonary findings are present.

Extrapulmonary nocardiosis is relatively common and can occur through hematogenous dissemination or a contiguous spread of necrotizing pneumonitis into the pleura, pericardium, mediastinum, and vena cava. Abscess formation is characteristic of extrapulmonary nocardiosis and can resemble a pyogenic bacteria process or evolve into a chronic granulomatous or mixed progressive inflammatory mass. The CNS is the most common extrapulmonary location for nocardiosis (up to 44 % in one series) [116] (see Chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients). Patients may have one or more brain abscesses and present with headache, nausea, vomiting, seizures, or alternation in consciousness [106]. Neurologic symptoms typically develop gradually, although an acute presentation with rapid progression may occasionally occur. Cerebral nocardiosis commonly accompanies pulmonary disease, but isolated CNS disease can present. In immunocompetent patients, cerebral nocardiosis is less common and may resemble a brain tumor or vascular infarct [117, 118].

Primary cutaneous and soft tissue nocardiosis can result from traumatic injury to the skin that involves contamination with soil [119]. Unlike other forms of nocardiosis, primary cutaneous disease usually develops in immunocompetent hosts. After skin inoculation, a superficial abscess or localized cellulitis can develop. Cutaneous nocardiosis can resemble soft tissue infections produced by *S. aureus* or streptococci; however, this form of *Nocardia* disease is usually more indolent [116]. The infection can spread to the regional lymph nodes and produce a single or linear chain of nodular lesions. Lymphocutaneous nocardiosis is often called 'sporotrichoid' nocardiosis given the similar presentation of sporotrichosis. In more advanced disease, a mycetoma can develop with sinus tract development. *N. brasiliensis* is the most common *Nocardia* spp. in cutaneous disease (especially progressive and lymphocutaneous disease) although *N. asteroides* and *N. otitidiscaviarum* have also occasionally been isolated [119].

*Nocardia* bacteremia is less frequently encountered. In one review of *Nocardia* bacteremia, 64 % patients had concurrent pulmonary nocardiosis, 28 % had concurrent cutaneous disease, and 19 % had concurrent CNS disease [120]. *Nocardia* bacteremia associated with central venous catheter infections has been reported [121, 122]. Polymicrobial bloodstream infections with *Nocardia* spp. and gram-negative bacilli have also been identified. Hematogenously disseminated nocardiosis has led to infection in the eyes (keratitis), heart valves, liver, spleen, adrenal glands, thyroid gland, and organ tissues.

General treatment recommendations for nocardiosis are hindered by the lack of prospective controlled trials. Optimal antimicrobial treatment regimens have not been firmly established. *Nocardia* spp. display variable in vitro antimicrobial

susceptibility patterns, and the management of nocardia infections must be individualized [123]. CLSI has published recommendations for antimicrobial susceptibility testing for *Nocardia* spp. and other aerobic actinomycetes [124]. *Nocardia* isolated from clinically significant infections should undergo antimicrobial susceptibility testing to assist in treatment decisions. Drug susceptibility patterns to major *Nocardia* spp. are listed in Table 2.

Sulfonamides, including sulfadiazine and sulfisoxazole, have been the antimicrobials of choice to treat nocardiosis for the past 50 years despite bacteriostatic activity [125]. TMP-SMX is the most commonly used sulfonamide preparation in the USA, although the benefit of the trimethoprim component is unclear. Divided doses of 5–10 mg/kg/d of the trimethoprim component or (25–50 mg/kg/d sulfamethoxazole) are recommended to produce sulfonamide serum concentrations between 100 and 150 mcg/mL. Adverse reactions to high-dose TMP-SMX are frequent and include myelosuppression, hepatoxicity, and renal insufficiency. TMP-SMX is active against the vast majority of *Nocardia* spp.; however, *N. otitidiscaviarum* is typically resistant to TMP-SMX, and *N. nova* and *N. farcinica* are occasionally resistant as well [119, 125].

Alternative antimicrobial agents with activity against *Nocardia* spp. include amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin–clavulanic acid. Imipenem is more active than either meropenem or ertapenem against most *Nocardia* spp. [126]. Ertapenem should not be used as a replacement for imipenem or meropenem. Minocycline appears to have the best anti-*Nocardia* activity of the tetracyclines and is an alternative oral agent in patients allergic to sulfonamides. Tigecycline, a glycylcycline, appears to be active in vitro against most *Nocardia* spp. Of the fluoroquinolones, moxifloxacin is fairly active in vitro against *N. asteroides* complex [126, 127]. Linezolid, an oxazolidinone, is quite active against virtually all known pathogenic *Nocardia* spp. and has successfully been used in the treatment of patients with disseminated and CNS nocardiosis [128]. Amoxicillin/clavulanate is moderately active against many strains of *N. asteroides*, *N. farcinica*, and *N. braziliensis*, but inactive against most strains of *N. nova*, *N. otitidiscaviarum*, and *N. transvalensis* [119].

Combination therapy with imipenem–cefotaxime, amikacin–TMP-SMX, imipenem–TMP-SMX, amikacin–cefotaxime, or amikacin–imipenem may provide enhanced activity [129]. In mice models, amikacin and imipenem were more effective in the treatment of cerebral and pulmonary nocardiosis then TMP-SMX alone [130, 131]. For most forms of nocardiosis, initial combination drug therapy is recommended. In patients with CNS disease, therapy should include drugs with favorable CNS penetration (e.g., TMP-SMX plus ceftriaxone). Patients with severe nocardiosis may benefit from the addition of a third agent such as linezolid. Combination therapy should continue until clinical patient improvement, *Nocardia* speciation, and antimicrobial drug susceptibility information can be confirmed. Single drug therapy may suffice thereafter. Duration of treatment is generally prolonged to minimize risk of disease relapse. Immunocompetent patients with pulmonary or multifocal (non-CNS) nocardiosis

**Table 2** Major *Nocardia* pathogens and antimicrobial susceptibility patterns

| Species | Antimicrobial susceptibility patterns | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sulfamethoxazole | Ampicillin | Amoxicillin/ clavulanate | Ceftriaxone | Linezolid | Amikacin | Imipenem | Ciprofloxacin | Clarithromycin | Other |
| *N. abscessus* | + | + | + | + | + | + | − | − | − | |
| *N. brevicatena/ paucivorans* complex | + | + | + | + | + | + | − | + | − | a |
| *N. nova* complex | + | + or − | − | + | + | + | + | | + | b |
| *N. transvalensis* complex | + | | + | + | + | − | + | + | − | b |
| *N. farcinica* | + or − | − | | − | + | + | + | + | − | c |
| *N. asteroides* | + | − | − | + | + | + | + | − | − | d |

(continued)

**Table 2** (continued)

| Species | Antimicrobial susceptibility patterns | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sulfamethoxazole | Ampicillin | Amoxicillin/ clavulanate | Ceftriaxone | Linezolid | Amikacin | Imipenem | Ciprofloxacin | Clarithromycin | Other |
| *N. brasiliensis* | + | − | + | | + | | | − | − | e |
| *N. pseudo–brasiliensis* | + | − | − | | + | | | + | + | |
| *N. otitidiscaviarum* | + or − | − | − | − | + | + | − | + | | |

(+) active
(−) less active/inactive
(+ or −) may be active, but resistance common
(no entry) variable susceptibility results
*a* Usually resistant to gentamicin, kanamycin MICs low (<1 ug/mL)
*b* Usually resistant to all aminoglycosides
*c* Resistant to all aminoglycosides except amikacin
*d N. cyriacigeorgica* is susceptible to ampicillin; otherwise, the same as the other *N. asteroides* complex
*e* Susceptible to minocycline
*Note Nocardia asteroides* complex is a group of bacteria with a heterozygous pattern of antimicrobial drug susceptibilities [193] and responsible for the majority of clinical human *Nocardia* infections. The subsequent taxonomy of *Nocardia asteroides* complex is reorganized into six species based on drug susceptibility patterns: *N. abscessus, N. brevicatena/paucivorans* complex, *N. nova* complex (which includes *N. nova, N. veterana, N. africana, N. keuczakiae*), *N. transvalensis* complex, *N. farcinica*, and *N. asteroides*
(Based on data from Ref. [106])

may be successfully treated with 6–12 months of antimicrobial therapy. Immunosuppressed patients and those with CNS disease should receive at least 12 months antimicrobial therapy with the appropriate clinical monitoring.

TMP-SMX is an effective prophylaxis agent to prevent *Pneumocystis* pneumonia and also can decrease the risk of nocardia infections. Daily TMP-SMX prophylaxis most reliably prevents nocardiosis and may also account for the decreased prevalence of nocardiosis in patients with advanced HIV infection [132]. Intermittent therapy with oral TMP-SMX (two double-strength tablets twice weekly or one single strength tablet thrice weekly) is less protective against nocardiosis [110, 114, 115].

## 6 Mycobacteria

Mycobacteria are aerobic bacilli that contain long-chain mycolic acid glycolipids in their cell wall and belong to the family Mycobacteriaceae, order Actinomycetales. All mycobacteria are acid-fast bacilli. Using either the Ziehl–Neelsen or Kinyoun stain, mycobacteria do not decolorize with acidified alcohol after staining with carbolfuchsin. The fluorescent stain auramine–rhodamine is more sensitive for mycobacteria identification but generally less specific compared to the Ziehl–Neelsen or Kinyoun stains. Gram staining mycobacteria occasionally reveal gram-positive or gram-variable bacilli; however, mycobacteria may also appear as unstained silhouettes against the background [133].

Compared to other pathogens, mycobacteria are less commonly encountered in patients with cancer; however, mycobacterial infections in patients who have received a solid organ transplant, hematopoietic stem cell transplant, or antineoplastic chemotherapy are becoming increasingly recognized. This may reflect increased environmental exposures, chemotherapy-induced immunosuppression, improved laboratory diagnostic techniques, and international travel for medical care. *Mycobacteria tuberculosis* is more commonly isolated in patients from countries where tuberculosis is endemic, whereas NTM infections predominate in countries with a lower incidence of tuberculosis [134].

The treatment of mycobacteria poses numerous challenges. Mycobacteria are resistant to many ‘conventional’ antimicrobials and require combination drug therapy for prolonged durations. Drug interactions between antimycobacterial treatment regimens and select antineoplastic drugs along with difficulties in drug susceptibility data interpretation for many NTM species create additional complexities. A multidisciplinary management approach between the hematologist–oncologist and the infectious diseases specialist is essential for favorable patient outcomes.

### 6.1 *Mycobacteria tuberculosis* Complex

*Mycobacteria tuberculosis* complex in humans and animals includes *M. tuberculosis*, *M. bovis*, and the less commonly encountered *M. africanum, M. microti,*

*M. canettii, M. caprae,* and *M. pinnipedii* is primarily responsible for tuberculosis in humans. *M. bovis* commonly infects animals (bovine tuberculosis) and occasionally produces disease in humans consuming unpasteurized milk products or though bladder instillation therapies containing the Bacillus Calmette-Guerin strain of *M. bovis*. Approximately one-third of the global population, including more than 11 million persons in the United States, has been infected with *M. tuberculosis*. In 2007, a total of 13,299 tuberculosis cases were reported in the United States with approximated incidence of 4.6 cases per 100,000 persons [135]. The incidence of tuberculosis in foreign-born persons in the United States is nearly 10 times greater than that of US-born persons. It is therefore consistent that the incidence of tuberculosis in patients with cancer is highest in foreign-born patients [136]. Among patients with cancer, *M. tuberculosis* is most commonly seen in those with hematologic malignancies including acute leukemia, Hodgkin's and non-Hodgkin's lymphoma, and those who have undergone allogenic hematopoietic stem cell transplantation comprise [136–139]. Among allogenic hematopoietic stem cell recipients, chronic graft-versus-host disease and total body irradiation augment the risks for tuberculosis development [140, 141]. Rates of tuberculosis in patients with hematologic cancers are approximately 40 times higher than the general US population [137]. With the exception of head and neck cancers, solid tissue cancers do not present as high of a risk for tuberculosis development. Interestingly, there may be an association between pulmonary tuberculosis and the subsequent development of pulmonary adenocarcinoma [142].

Pulmonary tuberculosis can be divided into primary pulmonary tuberculosis and reactivation (post-primary) tuberculosis. Primary tuberculosis develops as an uninterrupted proliferation of *M. tuberculosis* after initial infection and without a period of quiescence [143]. Symptomatic primary pulmonary tuberculosis is typically encountered in young infants and in HIV-infected patients. However, patients with other immunosuppressive conditions, including hematologic malignancies and cell-mediated immune defects, also may present with primary disease (see Chapter Respiratory Infections). Hilar and mediastinal adenopathy are common with primary disease along with confluent infiltrates in the mid and lower lung fields. Reactivation tuberculosis is most commonly encountered in immunocompetent adults and often radiographically presents as upper lobar fibronodular infiltrates, often with thick-walled cavitary disease and volume loss of the lung. Lower lung and other atypical lung findings occur in up to 1/3 of patients. Hilar adenopathy is unusual with reactivation tuberculosis. Among immunosuppressed patients, especially those with advanced HIV infection and hematopoietic stem cell transplantation, pulmonary tuberculosis commonly radiologically presents as multilobar airspace consolidation or nodular disease [144].

In the setting of immunosuppression, extrapulmonary presentations of tuberculosis are common [145, 146]. Lymphadenitis is the most common form of extrapulmonary tuberculosis and historically has been called scrofula when referring to lymphadenitis of the head and neck region. The cervical lymph nodes (about 60 %) and supraclavicular lymph chains are most commonly involved in TB lymphadenitis; however, the submandibular and auricular nodes may be

affected. Other less common lymph nodes affected include the axillary, inguinal, mesenteric, mediastinal, and inframammary nodes. The most common presenting symptom is a gradually enlarging neck mass (98 % in one case series) [147]. Infected lymph nodes can become fluctuant, matted, or suppurative with sinus formation and spontaneous drainage. They can coalesce into an enlarging mass that can eventually compress other structures, including the esophagus and blood vessels [148]. Fine-needle aspirate (FNA) generally should be the first diagnostic step (with multiple needle passes). Excisional biopsy should be performed if the results (histology and staining) of FNA are indeterminate.

Mycobacterial infectious of the CNS are almost always caused by *M. tuberculosis* [149]. Isolated CNS tuberculosis can occur, or present as a component of disseminated disease. Tuberculosis meningitis is the most common presentation of CNS disease, although tuberculomas, parenchymal abscesses, and spinal arachnoiditis (typically in the basilar meninges) can occur. Tuberculosis meningitis is more common in children under 5 years of age but can also occur in adults, especially those with immunosuppressive conditions or HIV infection [150, 151]. The spinal fluid typically has a lymphocyte-predominant pleocytosis with elevated protein and low glucose. An early neutrophil predominance in up to 25 % of HIV-negative patients, although an ensuing shift to lymphocytes usually occurs in the subsequent 24–48 h [152]. Untreated, progressive CNS tuberculosis leads to cognitive decline, seizures, coma, and death.

Abdominal tuberculosis can present in many forms, including infection of the gastrointestinal tract and the peritoneum. Any part of the gastrointestinal tract may be involved; however, ileocecal disease is most common [153]. Peritoneal tuberculosis develops from hematogenous and lymphatic seeding or from contiguous microbial spread from adjacent infected organs. Hepatosplenic lesions of tuberculosis may appear soon after resolution of chemotherapy-induced neutropenia and clinically resemble hepatosplenic candidiasis [154, 155]. Elevations in CA-125 in women, commonly seen in ovarian carcinoma, may be present in patients with abdominal tuberculosis [156]. Other forms of extrapulmonary tuberculosis including bone and joint disease, pericardial and renal disease should also be considered in the appropriate setting among patients with cancer [139, 157].

Treatment guidelines for pulmonary and extrapulmonary tuberculosis have been published and recommend combination anti-tuberculosis drug therapy [158]. First-line drugs include isoniazid, rifampin, pyrazinamide, and ethambutol. Combination drug therapy is generally recommended for 6–12 months depending upon the type of infection, antimicrobial susceptibility data, and combination drug regimen used in treatment. Drug toxicities and interactions with chemotherapeutic agents require monitoring. Rifampin induces the hepatic metabolism and lowers the serum concentration of many drugs (Table 3).

*Mycobacteria bovis* is a member of *M. tuberculosis* complex and is a component of intramuscular Bacille Calmette–Guérin (BCG) vaccine given to young children throughout much of the world and intravesicular BCG used in men with bladder cancer. The BCG vaccine is one of the most commonly administered vaccines outside of the United States and administered to prevent or reduce miliary

**Table 3** Drug interactions with rifampin

| Rifampin induces the hepatic cytochrome P450 enzymatic pathway, resulting in increased metabolism and lower serum concentrations of the following drugs[a]: | | |
|---|---|---|
| Anticonvulsants (e.g., phenytoin) | | |
| Antiarrhythmics (e.g., disopyramide, mexiletine, quinidine, tocainide) | | |
| Azole antifungals (e.g., fluconazole, itraconazole, voriconazole) | | |
| Calcium channel blockers (e.g., diltiazem, nifedipine, verapamil) | | |
| Oral and systemic contraceptive agents[b] | | |
| Oral hypoglycemic agents (sulfonylureas) | | |
| Opiate analgesics including methadone | | |
| Protease inhibitors (atazanivir, indinavir, amprenavir, daurunavir, saquinavir) | | |
| Tricyclic antidepressants (e.g., amitriptyline, nortriptyline) | | |
| Select immunosuppressants (corticosteroids, cyclosporine, tacrolimus) | | |
| Select antimicrobials (e.g., macrolides, doxycycline, ciprofloxacin, chloramphenicol) | | |
| Other: | | |
| Benzodiazepines | Beta-blockers | Theophylline |
| Levothyroxine | Coumadin | Quinine |
| Dapsone | Barbiturates | Digoxin |

[a]It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin

[b]Patients using oral or other systemic hormonal contraceptives should be advised to change to non-hormonal form of birth control (e.g., condoms) during rifampin therapy

and meningeal tuberculosis in children. The protective effects of the BCG vaccine against tuberculosis development in adults remain ill defined [159]. Because both the intramuscular and intravesicular vaccines contain live bacteria, progressive *M. bovis* infection can develop in patients with immunosuppressive conditions. Disseminated infection with marrow and visceral organ involvement has been reported in patients with hematologic malignancies and/or receiving alemtuzumab [160]. *M. bovis* infection can also be acquired through consumption of contaminated unpasteurized milk from cattle with bovine tuberculosis. Contrasting to *M. tuberculosis*, *M. bovis* is universally resistant to pyrazinamide. First-line active drugs include isoniazid, rifampin, and ethambutol.

## 6.2 Non-tuberculosis Mycobacteria

NTM are ubiquitous environmental organisms found in water, soil, animals, birds, milk, and other foods [161]. There are over 125 species of NTM [162]; however, a relatively small number of species cause the bulk of human disease. The Runyon classification is an older method using bacterial growth rate, colony morphology, and pigment formation to distinguish common NTM pathogens [133]; however,

current laboratory diagnostics incorporate the use of nucleic acid probes and gene sequencing for speciation.

In contrast to *M. tuberculosis*, NTM are generally less pathogenic, acquired through environment exposure, and not transmitted from person to person. NTM infection may develop from direct skin inoculation or trauma, ingestion, and possibly via inhalation of contaminated aerosols. The precise source of infection, however, usually remains inapparent [163]. Phagocytosis by macrophages and subsequent upregulation of interleukin-12 and interferon-gamma are the primary host defense mechanisms against NTM [164]. Suppression of IL-12 and IFN-$\gamma$ through select cancers, antineoplastic chemotherapy, or genetic deficiency enables progression and dissemination of NTM disease. The incidence of NTM infections ranges from 0.4 to 4.9 % in hematopoietic stem cell transplant patients [134]. Advanced immunosuppression may preclude granuloma formation and lead to mycobacteria-laden histiocytes or macrophages, as seen with Fite or Ziehl–Neelsen stains [133].

Although *Mycobacterium avium* complex (MAC) can be found worldwide, many NTM have a geographic predominance. *M. kansasii* is more commonly isolated from patients living in the central/midwest states and southern/southwestern states as well as in southeast England and Wales [162, 165, 166]. *M. xenopi* is the second most common NTM isolated in Canada and the UK but is rarely encountered in the USA. *M. malmoense* is more commonly seen in Scandinavia. *M. haemophilum* has a wide geographic distribution including Europe, Israel, Australia, Canada, United Kingdom, Africa, Fiji, and the USA. Pulmonary disease with rapidly growing mycobacteria is more prevalent in the warm, humid southern and Gulf coastal regions of the USA [167]. Other forms of rapid growing mycobacterial disease, however, appear to be less geographically restricted.

Pulmonary disease is the most common manifestation of NTM infection, but extrapulmonary and disseminated NTM disease is increasingly common in immunosuppressed patients and those with underlying cancers. MAC is the most common cause of pulmonary NTM disease in the USA [162] and is the most common disseminated opportunistic bacterial infection in patients with advanced HIV infection [168]. Fibronodular MAC pulmonary disease may appear similar to pulmonary tuberculosis with upper lobe predominance, cavitary disease, and a higher organism burden. Nodular bronchiectasis MAC disease tends to present with scattered pulmonary nodular or micro-nodular infiltrates with underlying bronchiectasis. In contrast to immunocompetent patients and those with underlying chronic lung disease, pulmonary MAC disease is less frequently encountered in patients with advanced HIV infection or other forms of significant immunosuppression. *M. kansasii* is the second most common NTM pulmonary pathogen in the USA and a common pathogen encountered in patients with advanced HIV infection and other immunosuppressive conditions [169]. The pulmonary disease produced by *M. kansasii* can resemble tuberculosis with upper lobe disease and cavitary lesions. *M. kansasii* disease often occurs in patients with hematologic and solid organ cancers, occupational lung disease, and COPD [170–172]. Other significant NTM pulmonary pathogens include *M. abscessus*, *M. fortuitum*, and less commonly *M. szulgai*, *M. simiae*, *M. xenopi*, *M. malmoense*, and *M. celatum*. Lung

infections with rapidly growing mycobacteria, including *M. fortuitum* complex and *M. abscessus* complex, are more common with underlying gastrointestinal disorders including GERD and repetitive vomiting.

The isolation of NTM from respiratory specimens without significant clinical or radiologic findings of disease may represent a more indolent infection and not require treatment [164]. The diagnosis NTM pulmonary disease is based on a collective assessment of clinical patient symptoms with radiologic and microbiologic information. Guidelines for the diagnosis of pulmonary NTM disease have been published [162]. Hematologic and solid organ cancers are not common risk factors for the development of NTM pulmonary disease, but the immunomodulatory effects of some cancers and chemotherapy regimens can significantly augment and accelerate disease progression in patients already infected. Multifocal or diffuse pulmonary NTM disease in patients with cancer and immunosuppression may reflect disseminated disease, especially in the presence of unexplained adenopathy, organomegaly, or cytopenias. Hypersensitivity pneumonitis is another form of pulmonary NTM disease that can occur in select patients from exposure to aerosolized droplets of MAC, especially from indoor hot tubs [173, 174]. Cases have also been identified after exposure from swimming pool water and showers.

Disseminated NTM disease is best described in patients with advanced HIV infection, but has also been associated with hematologic malignancies (including acute leukemias, CML, and hairy cell leukemia) and hematopoietic stem cell transplantation [175–177]. Mycobacteria may be identified in blood cultures, bone marrow, lymph nodes, liver, spleen, and other organ tissues. MAC, *M. kansasii*, *M. xenopi*, *M. fortuitum* complex, *M. chelonae*, and *M. abscessus* complex are the most frequent NTM identified in patients with disseminated disease. Disseminated MAC may result from either previous enteric or respiratory tract infection [178]. Hepatosplenomegaly, diffuse adenopathy, chronic diarrhea, anemia, and leukopenia are common with disseminated disease. Specialized mycobacterial blood cultures provide a good diagnostic measure for disseminated MAC and have a sensitivity above 90 % in HIV-infected patients [179].

Central venous catheter-related infections are the most common NTM disease in hematopoietic stem cell transplant recipients [134]. The rapidly growing mycobacteria (*M. fortuitum* complex, *M. abscessus* complex, *M. chelonae*) are more frequently associated with catheter infections, although *M. haemophilum* and *M. mucogenicum* have occasionally been encountered. Infected venous catheters with mycobacteria should be promptly removed [180].

NTM lymphadenitis may indicate disseminated NTM disease when multiple lymph nodes are involved or localized infection when isolated in the head and neck region of immunocompetent individuals. FNA or excision biopsy is typically used to make the diagnosis and to exclude other infectious causes as well as lymphoma and some soft tissue tumors. Localized MAC and *M. scrofulaceum* infection of the preauricular, submandibular, and cervical lymph notes are common in children. MAC represents over 90 % of mycobacteria causes for pediatric cervical lymphadenitis [181, 182]. Cervical and perihilar lymphadenitis from *M. haemophilum* infection can also develop in immunocompetent children.

Skin and soft tissue NTM disease is well reported in patients with hematologic malignancies [183, 184], although less than 20 % of NTM infections identified in hematopoietic stem cell recipients present with cutaneous disease [134]. The rapidly growing mycobacteria, including *M. fortuitum* complex, *M. chelonae*, and *M. abscessus* complex, are especially common in cutaneous and soft tissue infections. Localized infections can develop after surgery or penetrating trauma, whereas multifocal and disseminated lesions are more frequent in immunosuppressed patients. *M. fortuitum* complex tends to be more closely associated with recent penetrating trauma or surgery, whereas *M. chelonae* and *M. abscessus* complex occur more commonly in patients with more immunomodulatory conditions [184]. Cutaneous *M. marinum* infection can develop in both immunocompetent and immunosuppressed patients and may present as skin nodules, commonly in the line of lymphatic drainage. This ascending appearance of infection closely resembles that of sporotrichosis and cutaneous nocardiosis. Single or multiple cutaneous lesions, monoarticular or oligoarticular septic arthritis, and osteomyelitis have been frequently reported with *M. haemophilum* [185, 186].

In vitro drug susceptibility testing for NTM species is problematic. There are little data with NTM correlating in vitro antimicrobial susceptibility results and clinical outcomes. Exceptions that correlate susceptibility data with clinical outcomes include clarithromycin for MAC treatment [187–189] and rifampin for *M. kansasii* treatment. Antimicrobial susceptibility testing for MAC should only routinely be performed for clarithromycin. Amikacin susceptibility testing should also be considered when used in combination therapy [195]. Clarithromycin testing results are predictive of susceptibility to azithromycin, and specific testing for azithromycin activity is more difficult to perform. For *M. kansasii,* susceptibility testing should be performed for rifampin, with additional testing performed for other drugs only if rifampin is resistant in vitro (MIC >1 mcg/mL) [162, 190]. *M. kansasii* may be reported as resistant to isoniazid at MIC 0.2–1.0 mcg/mL but clinically remain susceptible at higher concentrations (e.g., MIC ≤5 mcg/mL) [190]. Despite the lack of clear data, antimicrobial susceptibility testing is still recommended for certain NTM species including the rapidly growing mycobacteria [167]. Ciprofloxacin susceptibility testing correlates with susceptibilities to levofloxacin and ofloxacin, but may not predict nor correlate with susceptibilities to moxifloxacin.

### 6.2.1 Select NTM Species and Treatment Options

MAC is composed of two related species, *M. avium* and *M. intracellulare*. These species generally are considered together as there is no therapeutic or prognostic value in distinguishing between them. The three most common infections caused by MAC include pulmonary disease, lymphadenitis, and disseminated disease. Pulmonary disease is more readily identified in immunocompetent patients, whereas disseminated disease is more commonly seen in advanced HIV infection and other immunosuppressed patients.

The newer macrolides (clarithromycin and azithromycin) remain the cornerstone of MAC treatment. Combination therapy with a newer macrolide is

recommended as monotherapy can lead to the development of drug resistance [189]. Ethambutol is another active drug, and coadministration with clarithromycin has shown to decrease the emergence of macrolide-resistant MAC [191]. Current recommendations for the treatment of pulmonary MAC disease include clarithromycin or azithromycin plus ethambutol and a rifamycin [162]. Daily or intermittent therapy with amikacin or streptomycin can be added for severe disease or in patients with macrolide resistance. Oral fluoroquinolone, especially moxifloxacin, can also be considered for macrolide-resistant MAC.

*M. kansasii* is one of the most virulent NTMs and a common human pathogen. Tap water is a primary reservoir for *M. kansasii*. *M. kansasii* can appear as a long, banded, or beaded bacillus when stained with Ziehl–Neelsen or Kinyoun stains. The isolation of *M. kansasii* from any site should generally not be disregarded as a contaminant or colonizer; *M. kansasii* usually has a pathogenic role when isolated in culture [165]. In addition to pulmonary disease, *M. kansasii* occasionally can cause lymphadenitis, granulomatous skin lesions, and osteomyelitis. Rifampin is the cornerstone of *M. kansasii* treatment and usually given in combination therapy with isoniazid and ethambutol. Other active drugs include clarithromycin, newer fluoroquinolones, amikacin, streptomycin, and sulfamethoxazole.

The rapidly growing mycobacteria are defined by their faster growth in solid media with mature mycobacterial colonies developing on solid agar within 7 days, compared to other mycobacteria. In addition to *M. fortuitum* complex, *M. chelonae*, and *M. abscessus* complex, other occasionally encountered rapidly growing mycobacteria include the *M. smegmatis* group (including *M. smegmatis*, *M. wolinsky*, and *M. goodii*) and *M. immunogenicum*. As with other NTM, the rapidly growing mycobacteria group is ubiquitous in the environment and flourishes in warm humid environments such as hot tubs, spas, and hot water pipes. Although this group typically stains positive with the Ziehl–Neelsen stain or Kinyoun method, these organisms can be weakly acid-fast or even occasionally appear negative on acid-fast staining. Clinical disease with rapidly growing mycobacteria usually is more pronounced in patients with immunosuppressive conditions; however, these organisms produce significant disease in immunocompetent patients as well. Infections more commonly seen with rapidly growing mycobacteria include skin and soft tissue infections, intravenous catheter, and other foreign-body-associated infections, laser in site keratomileusis (LASIK) surgery, and pulmonary disease [167].

The treatment of rapidly growing mycobacteria depends upon the species of bacteria. *M. fortuitum* complex is typically susceptible to more antibiotics than other rapid growers and may include the tetracyclines and sulfamethoxazole. *M. chelonae* is resistant to cefoxitin and usually susceptible to tobramycin. The newer macrolides, moxifloxacin, linezolid, imipenem, and tigecycline often remain active. *M. abscessus sensu stricto* is commonly multidrug resistant (including relative resistance to tobramycin) although may be susceptible to cefoxitin and amikacin. Although the newer macrolides are often active against the rapid growing mycobacteria, *M. fortuitum* complex and *M. abscessus sensu stricto* both contain an erythromycin methylase gene (*erm*), which can produce inducible

resistance to the macrolides (including clarithromycin and azithromycin). Thus, macrolide monotherapy is not recommended.

*M. marinum* is closely associated with exposures to fish tanks, swimming pools, and other water reservoirs. It typically causes a granulomatous cutaneous disease and tenosynovitis. Infection is acquired through skin inoculation or exposure with preferential growth in the cooler areas of the body (commonly the extremities). Antimicrobials that are usually active against *M. marinum* include clarithromycin (or azithromycin), TMP-SMX, minocycline, doxycycline, moxifloxacin, rifampin, and ethambutol. For most cases of cutaneous disease, combination therapy with two active drugs can be used. Clarithromycin and ethambutol have been commonly used with the addition of rifampin in cases of more severe disease [162]. Tenosynovitis and joint disease may require surgical debridement. Transplant recipients and other immunosuppressed patients should wear gloves to clean fish tanks [134].

*M. haemophilum* infections occur in two general groups: the severely immunocompromised patients (e.g., lymphoma, solid organ and hematopoietic stem cell transplant recipients, and HIV/AIDS patients) and immunocompetent children [185]. *M. haemophilum* infection is more severe in immunosuppressed patients and includes cutaneous lesions, lymphadenitis, septic arthritis, osteomyelitis, and disseminated disease [185, 186]. Disseminated disease in the lung, blood, and lymph nodes may occur. *M. haemophilum* requires hemin- or iron-supplemented culture media and low temperatures for growth. Amikacin, clarithromycin, the fluoroquinolones, and the rifamycins may be active, but treatment should be guided by antimicrobial susceptible data.

## References


1. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 39(3):309–317
2. Lyes RD, Weinstein RA, Hota B (2008) Predictors of methicillin resistance in patients with serious *Staphylococcus aureus* infections. In: ICAAC/IDSA Washington, D.C
3. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R (2006) Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. Clin Infect Dis 42(3):389–391
4. Klevens RM, Morrison MA, Nadle J et al (2007) Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA 298(15):1763–1771
5. Kaye KS, Anderson DJ, Choi Y, Link K, Thacker P, Sexton DJ (2008) The deadly toll of invasive methicillin-resistant *Staphylococcus aureus* infection in community hospitals. Clin Infect Dis 46(10):1568–1577
6. Deurenberg RH, Stobberingh EE (2008) The evolution of *Staphylococcus aureus*. Infect Genet Evol 8(6):747–763
7. Naimi TS, LeDell KH, Como-Sabetti K et al (2003) Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 290(22):2976–2984
8. Siberry GK, Tekle T, Carroll K, Dick J (2003) Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. Clin Infect Dis 37(9):1257–1260

9. Gillet Y, Issartel B, Vanhems P et al (2002) Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359(9308):753–759
10. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM (2004) Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 42(6):2398–2402
11. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A (2006) High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 166(19):2138–2144
12. Mermel LA, Farr BM, Sherertz RJ et al (2001) Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 32(9):1249–1272
13. Winston DJ, Dudnick DV, Chapin M, Ho WG, Gale RP, Martin WJ (1983) Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 143(1):32–36
14. Zinkernagel AS, Zinkernagel MS, Elzi MV et al (2008) Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. Infection 36(4):314–321
15. Frank KL, Del Pozo JL, Patel R (2008) From clinical microbiology to infection pathogenesis: how daring to be different works for *Staphylococcus lugdunensis*. Clin Microbiol Rev 21(1):111–133
16. Murray BE (1990) The life and times of the *Enterococcus*. Clin Microbiol Rev 3(1):46–65
17. Ruoff KL, de la Maza L, Murtagh MJ, Spargo JD, Ferraro MJ (1990) Species identities of enterococci isolated from clinical specimens. J Clin Microbiol 28(3):435–437
18. Hamilton-Miller JM (1988) Reversal of activity of trimethoprim against gram-positive cocci by thymidine, thymine and 'folates'. J Antimicrob Chemother 22(1):35–39
19. Courvalin P (2006) Vancomycin resistance in gram-positive cocci. Clin Infect Dis 42(Suppl 1):S25–S34
20. Leclercq R, Derlot E, Duval J, Courvalin P (1988) Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. New England J Med 319(3):157–161
21. Uttley AH, Collins CH, Naidoo J, George RC (1988) Vancomycin-resistant enterococci. Lancet 1(8575–6):57–58
22. Oprea SF, Zaidi N, Donabedian SM, Balasubramaniam M, Hershberger E, Zervos MJ (2004) Molecular and clinical epidemiology of vancomycin-resistant *Enterococcus faecalis*. J Antimicrob Chemother 53(4):626–630
23. Burrell LJ, Grabsch EA, Padiglione AA, Grayson ML (2005) Prevalence of colonisation with vancomycin-resistant enterococci (VRE) among haemodialysis outpatients in Victoria: implications for screening. The Medical journal of Australia 182(9):492
24. Streit JM, Jones RN, Sader HS, Fritsche TR (2004) Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents 24(2):111–118
25. DiazGranados CA, Jernigan JA (2005) Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis 191(4):588–595
26. Zirakzadeh A, Gastineau DA, Mandrekar JN, Burke JP, Johnston PB, Patel R (2008) Vancomycin-resistant enterococcal colonization appears associated with increased mortality among allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant 41(4):385–392
27. Courvalin P (2005) Genetics of glycopeptide resistance in gram-positive pathogens. Int J Med Microbiol 294(8):479–486
28. Miller D, Urdaneta V, Weltman A (2002) Vancomycin-resistant *Staphylococcus aureus*–Pennsylvania. Mmwr 51(40):902

29. Sievert DM, Boulton ML, Stoltman G, Johnson D, Stobierski MG et al (2002) *Staphylococcus aureus* resistant to vancomycin–United States. Mmwr 51(26):565–567
30. Reynolds PE, Courvalin P (2005) Vancomycin resistance in enterococci due to synthesis of precursors terminating in D-alanyl-D-serine. Antimicrob Agents Chemother 49(1):21–25
31. Reid KC, Cockerill IF, Patel R (2001) Clinical and epidemiological features of *Enterococcus casseliflavus/flavescens* and *Enterococcus gallinarum* bacteremia: a report of 20 cases. Clin Infect Dis 32(11):1540–1546
32. Zhanel GG, Hoban DJ, Karlowsky JA (2001) Nitrofurantoin is active against vancomycin-resistant enterococci. Antimicrob Agents Chemother 45(1):324–326
33. Engelhard D, Elishoov H, Or R et al (1995) Cytosine arabinoside as a major risk factor for *Streptococcus viridans* septicemia following bone marrow transplantation: a 5-year prospective study. Bone Marrow Transplant 16(4):565–570
34. Tunkel AR, Sepkowitz KA (2002) Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis 34(11):1524–1529
35. Elting LS, Bodey GP, Keefe BH (1992) Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis 14(6):1201–1207
36. Shenep JL (2000) Viridans-group streptococcal infections in immunocompromised hosts. Int J Antimicrob Agents 14(2):129–135
37. Lu HZ, Weng XH, Zhu B et al (2003) Major outbreak of toxic shock-like syndrome caused by *Streptococcus mitis*. J Clin Microbiol 41(7):3051–3055
38. Kennedy HF, Gemmell CG, Bagg J, Gibson BE, Michie JR (2001) Antimicrobial susceptibility of blood culture isolates of viridans streptococci: relationship to a change in empirical antibiotic therapy in febrile neutropenia. J Antimicrob Chemother 47(5):693–696
39. Moet GJ, Dowzicky MJ, Jones RN (2007) Tigecycline (GAR-936) activity against *Streptococcus gallolyticus* (bovis) and viridans group streptococci. Diagn Microbiol Infect Dis 57(3):333–336
40. Prabhu RM, Piper KE, Litzow MR, Steckelberg JM, Patel R (2005) Emergence of quinolone resistance among viridans group streptococci isolated from the oropharynx of neutropenic peripheral blood stem cell transplant patients receiving quinolone antimicrobial prophylaxis. Eur J Clin Microbiol Infect Dis 24(12):832–838
41. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R (2002) Bacteremia due to viridans group Streptococci with diminished susceptibility to Levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. Clin Infect Dis 34(11):1469–1474
42. Leport C, Bure A, Leport J, Vilde JL (1987) Incidence of colonic lesions in *Streptococcus bovis* and enterococcal endocarditis. Lancet 1(8535):748
43. Bodey GP, Rodriguez S, Fainstein V, Elting LS (1991) Clostridial bacteremia in cancer patients. A 12-year experience. Cancer 67(7):1928–1942
44. Mirza NN, McCloud JM, Cheetham MJ (2009) *Clostridium septicum* sepsis and colorectal cancer—a reminder. World J Surg Oncol 7:73
45. Senn L, Entenza JM, Greub G et al (2006) Bloodstream and endovascular infections due to *Abiotrophia defectiva* and *Granulicatella* species. BMC Infect Dis 6:9
46. Liao CH, Teng LJ, Hsueh PR et al (2004) Nutritionally variant streptococcal infections at a University Hospital in Taiwan: disease emergence and high prevalence of beta-lactam and macrolide resistance. Clin Infect Dis 38(3):452–455
47. Katz SC, Pachter HL (2006) Indications for splenectomy. American Surg 72(7):565–580
48. Russell SJ, Richards JD (1989) Medical indications for splenectomy. Br J Hosp Med 42(2):120–123, 5–6, 7
49. Bisharat N, Omari H, Lavi I, Raz R (2001) Risk of infection and death among post-splenectomy patients. J Infect 43(3):182–186
50. Singer DB (1973) Postsplenectomy sepsis. Perspect Pediatr Pathol 1:285–311
51. Rivero GA, Torres HA, Rolston KV, Kontoyiannis DP (2003) Listeria monocytogenes infection in patients with cancer. Diagn Microbiol Infect Dis 47(2):393–398

52. Safdar A, Papadopoulous EB, Armstrong D (2002) Listeriosis in recipients of allogeneic blood and marrow transplantation: thirteen year review of disease characteristics, treatment outcomes and a new association with human cytomegalovirus infection. Bone Marrow Transplant 29(11):913–916
53. Girmenia C, Iori AP, Bernasconi S et al (2000) Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. Eur J Clin Microbiol Infect Dis 19(9):711–714
54. Klastersky J (1998) Science and pragmatism in the treatment and prevention of neutropenic infection. J Antimicrob Chemother 41 Suppl D:13–24
55. Ramphal R (2004) Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis 39(Suppl 1):S25–S31
56. Klastersky J, Ameye L, Maertens J et al (2007) Bacteraemia in febrile neutropenic cancer patients. Int J Antimicrob Agents 30(Suppl 1):S51–S59
57. Feld R (2008) Bloodstream infections in cancer patients with febrile neutropenia. Int J Antimicrob Agents 32(Suppl 1):S30–S33
58. Cheong HS, Kang CI, Wi YM et al (2008) Clinical significance and predictors of community-onset *Pseudomonas aeruginosa* bacteremia. Am J Med 121(8):709–714
59. Whitecar JP Jr, Luna M, Bodey GP (1970) *Pseudomonas* bacteremia in patients with malignant diseases. Am J Med Sci 60(4):216–223
60. Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G (2000) Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: retrospective analysis of 245 episodes. Arch Intern Med 160(4):501–509
61. Bodey GP, Jadeja L, Elting L (1985) *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. Arch Intern Med 145(9):1621–1629
62. Escande MC, Herbrecht R (1998) Prospective study of bacteraemia in cancer patients. Results of a French multicentre study. Support Care Cancer 6(3):273–280
63. Hakki M, Limaye AP, Kim HW, Kirby KA, Corey L, Boeckh M (2007) Invasive *Pseudomonas aeruginosa* infections: high rate of recurrence and mortality after hematopoietic cell transplantation. Bone Marrow Transplant 39(11):687–693
64. Bodey GP (2001) *Pseudomonas aeruginosa* infections in cancer patients: have they gone away? Curr Opin Infect Dis 14(4):403–407
65. Ohmagari N, Hanna H, Graviss L et al (2005) Risk factors for infections with multidrug-resistant *Pseudomonas aeruginosa* in patients with cancer. Cancer 104(1):205–212
66. Thomson KS, Smith Moland E (2000) Version 2000: the new beta-lactamases of Gram-negative bacteria at the dawn of the new millennium. Microbes Infect/Institut Pasteur 2(10):1225–1235
67. Nseir S, Di Pompeo C, Cavestri B et al (2006) Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: prevalence, risk factors, and outcome. Crit Care Med 34(12):2959–2966
68. Cardo D, Horan T, Andrus M, Dembinski M, Edwards J, Peavy G et al (2004) National nosocomial infections surveillance (NNIS) system report data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 32(8):470–485
69. Rosenthal VD, Maki DG, Mehta A et al (2008) International nosocomial infection control consortium report, data summary for 2002–2007, issued January 2008. Am J Infect Control 36(9):627–637
70. Livermore DM (1995) beta-Lactamases in laboratory and clinical resistance. Clin Microbiol Rev 8(4):557–584
71. Bradford PA (2001) Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 14(4):933-951, table of contents
72. Paterson DL, Bonomo RA (2005) Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 18(4):657–686

73. Pitout JD (2010) Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs 70(3):313–333
74. Thomson KS (2010) Extended-spectrum-beta-lactamase, AmpC, and Carbapenemase issues. J Clin Microbiol 48(4):1019–1025
75. Jacoby GA, Munoz-Price LS (2005) The new beta-lactamases. N Engl J Med 352(4):380–391
76. Graffunder EM, Preston KE, Evans AM, Venezia RA (2005) Risk factors associated with extended-spectrum beta-lactamase-producing organisms at a tertiary care hospital. J Antimicrob Chemother 56(1):139–145
77. Piroth L, Aube H, Doise JM, Vincent-Martin M (1998) Spread of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*: are beta-lactamase inhibitors of therapeutic value? Clin Infect Dis 27(1):76–80
78. Rice LB, Carias LL, Bonomo RA, Shlaes DM (1996) Molecular genetics of resistance to both ceftazidime and beta-lactam-beta-lactamase inhibitor combinations in *Klebsiella pneumoniae* and in vivo response to beta-lactam therapy. J Infect Dis 173(1):151–158
79. Rice L (2001) Evolution and clinical importance of extended-spectrum beta-lactamases. Chest 119(2 Suppl):391S–396S
80. Gottlieb T, Wolfson C (2000) Comparison of the MICs of cefepime for extended-spectrum beta-lactamase-producing and non-extended-spectrum beta-lactamase-producing strains of *Enterobacter cloacae*. J Antimicrob Chemother 46(2):330–331
81. Pitout JD (2008) Multiresistant Enterobacteriaceae: new threat of an old problem. Expert Rev Anti-infect Ther 6(5):657–669
82. Talon D, Bailly P, Bertrand X, Thouverez M, Mulin B (2000) Clinical and molecular epidemiology of chromosome-mediated resistance to third-generation cephalosporins in *Enterobacter* isolates in eastern France. Clin Microbiol Infect 6(7):376–384
83. Pfaller MA, Jones RN, Marshall SA et al (1997) Inducible amp C beta-lactamase producing gram-negative bacilli from blood stream infections: frequency, antimicrobial susceptibility, and molecular epidemiology in a national surveillance program (SCOPE). Diagn Microbiol Infect Dis 28(4):211–219
84. Philippon A, Arlet G, Jacoby GA (2002) Plasmid-determined AmpC-type beta-lactamases. Antimicrob Agents Chemother 46(1):1–11
85. Kaye KS, Cosgrove S, Harris A, Eliopoulos GM, Carmeli Y (2001) Risk factors for emergence of resistance to broad-spectrum cephalosporins among *Enterobacter* spp. Antimicrob Agents Chemother 45(9):2628–2630
86. Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y (2002) Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. Arch Intern Med 162(2):185–190
87. Muller A, Lopez-Lozano JM, Bertrand X, Talon D (2004) Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of *Enterobacter cloacae*. J Antimicrob Chemother 54(1):173–177
88. Lledo W, Hernandez M, Lopez E, Molinari OL, Soto RQ, Hernandez E et al (2009) Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. Mmwr 58(10):256–260
89. Tibbetts R, Frye JG, Marschall J, Warren D, Dunne W (2008) Detection of KPC-2 in a clinical isolate of *Proteus mirabilis* and first reported description of carbapenemase resistance caused by a KPC beta-lactamase in *P. mirabilis*. J Clin Microbiol 46(9):3080–3083
90. Zhang R, Zhou HW, Cai JC, Chen GX (2007) Plasmid-mediated carbapenem-hydrolysing beta-lactamase KPC-2 in carbapenem-resistant *Serratia marcescens* isolates from Hangzhou, China. J Antimicrob Chemother 59(3):574–576

91. Miriagou V, Tzouvelekis LS, Rossiter S, Tzelepi E, Angulo FJ, Whichard JM (2003) Imipenem resistance in a *Salmonella* clinical strain due to plasmid-mediated class A carbapenemase KPC-2. Antimicrob Agents Chemother 47(4):1297–1300
92. Rasheed JK, Biddle JW, Anderson KF et al (2008) Detection of the *Klebsiella pneumoniae* carbapenemase type 2 Carbapenem-hydrolyzing enzyme in clinical isolates of *Citrobacter freundii* and *K. oxytoca* carrying a common plasmid. J Clin Microbiol 46(6):2066–2069
93. Schwaber MJ, Carmeli Y (2008) Carbapenem-resistant Enterobacteriaceae: a potential threat. JAMA 300(24):2911–2913
94. Nordmann P, Cuzon G, Naas T (2009) The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis 9(4):228–236
95. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP (2008) Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol 29(12):1099–1106
96. Bratu S, Mooty M, Nichani S et al (2005) Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection. Antimicrob Agents Chemother 49(7):3018–3020
97. (2010) Detection of Enterobacteriaceae isolates carrying metallo-beta-lactamase—United States. Mmwr 59(24):750
98. Bartlett JG (1994) *Clostridium difficile*: history of its role as an enteric pathogen and the current state of knowledge about the organism. Clin Infect Dis 18(Suppl 4):S265–S272
99. Dupuy B, Govind R, Antunes A, Matamouros S (2008) *Clostridium difficile* toxin synthesis is negatively regulated by TcdC. J Med Microbiol 57(Pt 6):685–689
100. Verdoorn BP, Orenstein R, Rosenblatt JE et al (2010) High prevalence of tcdC deletion-carrying *Clostridium difficile* and lack of association with disease severity. Diagn Microbiol Infect Dis 66(1):24–8
101. Schaier M, Wendt C, Zeier M, Ritz E (2004) *Clostridium difficile* diarrhoea in the immunosuppressed patient–update on prevention and management. Nephrol Dial Transplant 19(10):2432–2436
102. Chakrabarti S, Lees A, Jones SG, Milligan DW (2000) *Clostridium difficile* infection in allogeneic stem cell transplant recipients is associated with severe graft-versus-host disease and non-relapse mortality. Bone Marrow Transplant 26(8):871–876
103. Arango JI, Restrepo A, Schneider DL et al (2006) Incidence of *Clostridium difficile*-associated diarrhea before and after autologous peripheral blood stem cell transplantation for lymphoma and multiple myeloma. Bone Marrow Transplant 37(5):517–521
104. Gerding DN, Muto CA, Owens RC Jr (2008) Treatment of *Clostridium difficile* infection. Clin Infect Dis 46(Suppl 1):S32–S42
105. Hogan WJ, Letendre L, Litzow MR et al (2002) Neutropenic colitis after treatment of acute myelogenous leukemia with idarubicin and cytosine arabinoside. Mayo Clin Proc 77(8):760–762
106. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr (2006) Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev 19(2):259–282
107. McNeil MM, Brown JM (1994) The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev 7(3):357–417
108. Beaman BL, Burnside J, Edwards B, Causey W (1976) Nocardial infections in the United States, 1972–1974. J Infect Dis 134(3):286–289
109. Rubin R, Young LS (2002) A clinical approach to infection in the compromised host, chapter 7, *Mycobacteria* and nocardial disease in the compromised host, pages 257–61, 4th edn. Kluwer Academic, New York
110. Choucino C, Goodman SA, Greer JP, Stein RS, Wolff SN, Dummer JS (1996) Nocardial infections in bone marrow transplant recipients. Clin Infect Dis 23(5):1012–1019
111. van Burik JA, Hackman RC, Nadeem SQ et al (1997) Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis 24(6):1154–1160

112. Stack WA, Richardson PD, Logan RP, Mahida YR, Hawkey CJ (2001) *Nocardia asteroides* lung abscess in acute ulcerative colitis treated with cyclosporine. Am J Gastroenterol 96(7):2255–2256
113. Tada Y, Fukuoka M, Mitamura M et al (2008) Nocardiosis in adult-onset Still's disease and vasculitis syndrome. Am J Med Sci 336(1):77–80
114. Arduino RC, Johnson PC, Miranda AG (1993) Nocardiosis in renal transplant recipients undergoing immunosuppression with cyclosporine. Clin Infect Dis 16(4):505–512
115. Roberts SA, Franklin JC, Mijch A, Spelman D (2000) *Nocardia* infection in heart-lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989–1998. Clin Infect Dis 31(4):968–972
116. Beaman BL, Beaman L (1994) Nocardia species: host-parasite relationships. Clin Microbiol Rev 7(2):213–264
117. Borm W, Gleixner M (2003) *Nocardia* brain abscess misinterpreted as cerebral infarction. J Clin Neurosci 10(1):130–132
118. Menku A, Kurtsoy A, Tucer B, Yildiz O, Akdemir H (2004) *Nocardia* brain abscess mimicking brain tumour in immunocompetent patients: report of two cases and review of the literature. Acta Neurochirurgica 146(4):411–414, discussion 4
119. Lerner PI (1996) Nocardiosis. Clin Infect Dis 22(6):891–903, quiz 4–5
120. Kontoyiannis DP, Ruoff K, Hooper DC (1998) *Nocardia* bacteremia. Report of 4 cases and review of the literature. Medicine 77(4):255–67
121. Kontoyiannis DP, Jacobson KL, Whimbey EE, Rolston KV, Raad II (2000) Central venous catheter-associated *Nocardia* bacteremia: an unusual manifestation of nocardiosis. Clin Infect Dis 31(2):617–618
122. Lai CH, Chi CY, Chen HP, Lai CJ, Fung CP, Liu CY (2004) Port-A catheter-associated *Nocardia* bacteremia detected by gallium inflammation scan: a case report and literature review. Scand J Infect Dis 36(10):775–777
123. Munoz J, Mirelis B, Aragon LM et al (2007) Clinical and microbiological features of nocardiosis 1997–2003. J Med Microbiol 56(Pt 4):545–550
124. Woods GL, Brown-Elliott BA, Desmond EP, Hall GS, Heifets L, Pfyffer GE et al (2003) Susceptibility testing of mycobacteria, *Nocardiae*, and other aerobic actinomycetes; approved standard. NCCLS document M24-A, vol 23. Clinical and Laboratory Standards Institute (formerly NCCLS), Wayne
125. McNeil MM, Brown JM, Hutwagner LC, Schiff TA (1995) Evaluation of therapy for *Nocardia asteroides* complex infection. CDN/NCID report. Infect Dis Clin Pract 4(4):287–292
126. Cercenado E, Marin M, Sanchez-Martinez M, Cuevas O, Martinez-Alarcon J, Bouza E (2007) In vitro activities of tigecycline and eight other antimicrobials against different *Nocardia* species identified by molecular methods. Antimicrob Agents Chemother 51(3):1102–1104
127. Hoogkamp-Korstanje JA, Roelofs-Willemse J (2000) Comparative in vitro activity of moxifloxacin against Gram-positive clinical isolates. J Antimicrob Chemother 45(1):31–39
128. Moylett EH, Pacheco SE, Brown-Elliott BA et al (2003) Clinical experience with linezolid for the treatment of nocardia infection. Clin Infect Dis 36(3):313–318
129. Gombert ME, Aulicino TM (1983) Synergism of imipenem and amikacin in combination with other antibiotics against *Nocardia asteroides*. Antimicrob Agents Chemother 24(5):810–811
130. Gombert ME, Aulicino TM, duBouchet L, Silverman GE, Sheinbaum WM (1986) Therapy of experimental cerebral nocardiosis with imipenem, amikacin, trimethoprim-sulfamethoxazole, and minocycline. Antimicrob Agents Chemother 30(2):270–273
131. Gombert ME, Berkowitz LB, Aulicino TM, duBouchet L (1990) Therapy of pulmonary nocardiosis in immunocompromised mice. Antimicrob Agents Chemother 34(9):1766–1768
132. Peterson PK, Ferguson R, Fryd DS, Balfour HH Jr, Rynasiewicz J, Simmons RL (1982) Infectious diseases in hospitalized renal transplant recipients: a prospective study of a complex and evolving problem. Medicine 61(6):360–372

133. Jarzembowski JA, Young MB (2008) Nontuberculous mycobacterial infections. Arch Pathol Lab Med 132(8):1333–1341
134. Doucette K, Fishman JA (2004) Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis 38(10):1428–1439
135. Pratt R, Robison V, Navin T, Menzies H (2008) Trends in tuberculosis–United States, 2007. Mmwr 57(11):281–285
136. Libshitz HI, Pannu HK, Elting LS, Cooksley CD (1997) Tuberculosis in cancer patients: an update. J Thorac Imaging 12(1):41–46
137. Kamboj M, Sepkowitz KA (2006) The risk of tuberculosis in patients with cancer. Clin Infect Dis 42(11):1592–1595
138. Silva FA, Matos JO, de QMFC, Nucci M (2005) Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignances. Haematologica 90(8):1110–1115
139. De La Rosa GR, Jacobson KL, Rolston KV, Raad II, Kontoyiannis DP, Safdar A (2004) *Mycobacterium tuberculosis* at a comprehensive cancer centre: active disease in patients with underlying malignancy during 1990-2000. Clin Microbiol Infect 10(8):749–752
140. Ip MS, Yuen KY, Woo PC et al (1998) Risk factors for pulmonary tuberculosis in bone marrow transplant recipients. Am J Respir Crit Care Med 158(4):1173–1177
141. Lee J, Lee MH, Kim WS et al (2004) Tuberculosis in hematopoietic stem cell transplant recipients in Korea. Int J Hematol 79(2):185–188
142. Liang HY, Li XL, Yu XS et al (2009) Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. Int J Cancer 125(12):2936–2944
143. Iseman M (2000) A clinician's guide to tuberculosis, chapter 6- pulmonary tuberculosis in adults, page 129. Lippincott Williams & Wilkins
144. Jung JI, Lee DG, Kim YJ, Yoon HK, Kim CC, Park SH (2009) Pulmonary tuberculosis after hematopoietic stem cell transplantation: radiologic findings. J Thorac Imaging 24(1):10–16
145. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF (1993) Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 148(5):1292–1297
146. Khan B, Ahmed P, Ullah K, Hussain CA, Hussain I, Raza S (2005) Frequency of tuberculosis in haematological malignancies and stem cell transplant recipients. J Coll Physicians Surg Pak 15(1):30–33
147. Polesky A, Grove W, Bhatia G (2005) Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. Medicine 84(6):350–362
148. Lazarus AA, Thilagar B (2007) Tuberculous lymphadenitis. Dis Mon 53(1):10–15
149. Garcia-Monco JC (1999) Central nervous system tuberculosis. Neurol Clin 17(4):737–759
150. Yaramis A, Gurkan F, Elevli M et al (1998) Central nervous system tuberculosis in children: a review of 214 cases. Pediatrics 102(5):E49
151. Lesprit P, Zagdanski AM, de La Blanchardiere A et al (1997) Cerebral tuberculosis in patients with the acquired immunodeficiency syndrome (AIDS). Report of 6 cases and review. Medicine 76(6):423–431
152. Verdon R, Chevret S, Laissy JP, Wolff M (1996) Tuberculous meningitis in adults: review of 48 cases. Clin Infect Dis 22(6):982–988
153. Sharma MP, Bhatia V (2004) Abdominal tuberculosis. Indian J Med Res 120(4):305–315
154. Chakrabarti S, Varma S, Kochhar R, Gupta S, Gupta SK, Rajwanshi A (1998) Hepatosplenic tuberculosis: a cause of persistent fever during recovery from prolonged neutropenia. Int J Tuberc Lung Dis 2(7):575–579
155. Lee DG, Choi JH, Kim YJ et al (2001) Hepatosplenic tuberculosis mimicking disseminated candidiasis in patients with acute leukemia. Int J Hematol 73(1):119–121
156. Uzunkoy A, Harma M, Harma M (2004) Diagnosis of abdominal tuberculosis: experience from 11 cases and review of the literature. World J Gastroenterol 10(24):3647–3649
157. Aisenberg GM, Jacobson K, Chemaly RF, Rolston KV, Raad II, Safdar A (2005) Extrapulmonary tuberculosis active infection misdiagnosed as cancer: *Mycobacterium*

*tuberculosis* disease in patients at a Comprehensive Cancer Center (2001–2005). Cancer 104(12):2882–2887
158. Blumberg HM, Burman WJ, Chaisson RE et al (2003) American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 167(4):603–662
159. Colditz GA, Brewer TF, Berkey CS et al (1994) Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. Jama 271(9):698–702
160. Abad S, Gyan E, Moachon L et al (2003) Tuberculosis due to *Mycobacterium bovis* after alemtuzumab administration. Clin Infect Dis 37(2):e27–e28
161. Wolinsky E (1979) Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 119(1):107–159
162. Griffith DE, Aksamit T, Brown-Elliott BA et al (2007) An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175(4):367–416
163. von Reyn CF, Arbeit RD, Horsburgh CR et al (2002) Sources of disseminated *Mycobacterium avium* infection in AIDS. J Infect 44(3):166–170
164. Johnson MM, Waller EA, Leventhal JP (2008) Nontuberculous mycobacterial pulmonary disease. Curr Opin Pulm Med 14(3):203–210
165. Marras TK, Daley CL (2002) Epidemiology of human pulmonary infection with nontuberculous mycobacteria. Clin Chest Med 23(3):553–567
166. Griffith DE (2002) Management of disease due to *Mycobacterium kansasii*. Clin Chest Med 23(3):613–621, 6
167. De Groote MA, Huitt G (2006) Infections due to rapidly growing mycobacteria. Clin Infect Dis 42(12):1756–1763
168. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA (1992) Incidence of Mycobacterium avium-intracellulare complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 165(6):1082–1085
169. Marras TK, Daley CL (2004) A systematic review of the clinical significance of pulmonary *Mycobacterium kansasii* isolates in HIV infection. J Acquir Immune Defic Syndr (1999) 36(4):883–889
170. Jacobson KL, Teira R, Libshitz HI et al (2000) *Mycobacterium kansasii* infections in patients with cancer. Clin Infect Dis 30(6):965–969
171. Bloch KC, Zwerling L, Pletcher MJ et al (1998) Incidence and clinical implications of isolation of *Mycobacterium kansasii*: results of a 5-year, population-based study. Ann Intern Med 129(9):698–704
172. Corbett EL, Churchyard GJ, Hay M et al (1999) The impact of HIV infection on *Mycobacterium kansasii* disease in South African gold miners. Am J Respir Crit Care Med 160(1):10–14
173. Kahana LM, Kay JM, Yakrus MA, Waserman S (1997) *Mycobacterium avium* complex infection in an immunocompetent young adult related to hot tub exposure. Chest 111(1):242–245
174. Embil J, Warren P, Yakrus M et al (1997) Pulmonary illness associated with exposure to Mycobacterium-avium complex in hot tub water. Hypersensitivity pneumonitis or infection? Chest 111(3):813–816
175. Akiyama H, Maruyama T, Uetake T, Kawaguchi K, Sakamaki H, Onozawa Y (1991) Systemic infection due to atypical mycobacteria in patients with chronic myelogenous leukemia. Rev Infect Dis 13(5):815–818
176. Levendoglu-Tugal O, Munoz J, Brudnicki A, Fevzi Ozkaynak M, Sandoval C, Jayabose S (1998) Infections due to nontuberculous mycobacteria in children with leukemia. Clin Infect Dis 27(5):1227–1230
177. Horwitz ME, Uzel G, Linton GF et al (2003) Persistent *Mycobacterium avium* infection following nonmyeloablative allogeneic peripheral blood stem cell transplantation for interferon-gamma receptor-1 deficiency. Blood 102(7):2692–2694

178. Chin DP, Hopewell PC, Yajko DM et al (1994) *Mycobacterium avium* complex in the respiratory or gastrointestinal tract and the risk of *M. avium* complex bacteremia in patients with human immunodeficiency virus infection. J Infect Dis 169(2):289–295
179. Yagupsky P, Menegus MA (1990) Cumulative positivity rates of multiple blood cultures for *Mycobacterium avium*-intracellulare and *Cryptococcus neoformans* in patients with the acquired immunodeficiency syndrome. Arch Pathol Lab Med 114(9):923–925
180. Mermel LA, Allon M, Bouza E et al (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 49(1):1–45
181. Maltezou HC, Spyridis P, Kafetzis DA (1999) Nontuberculous mycobacterial lymphadenitis in children. Pediatr Infect Dis J 18(11):968–970
182. Wolinsky E (1995) Mycobacterial lymphadenitis in children: a prospective study of 105 nontuberculous cases with long-term follow-up. Clin Infect Dis 20(4):954–963
183. Ingram CW, Tanner DC, Durack DT, Kernodle GW Jr, Corey GR (1993) Disseminated infection with rapidly growing mycobacteria. Clin Infect Dis 16(4):463–471
184. Uslan DZ, Kowalski TJ, Wengenack NL, Virk A, Wilson JW (2006) Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment, and susceptibility. Arch Dermatol 142(10):1287–1292
185. Straus WL, Ostroff SM, Jernigan DB et al (1994) Clinical and epidemiologic characteristics of *Mycobacterium haemophilum*, an emerging pathogen in immunocompromised patients. Ann Intern Med 120(2):118–125
186. Dobos KM, Quinn FD, Ashford DA, Horsburgh CR, King CH (1999) Emergence of a unique group of necrotizing mycobacterial diseases. Emerg Infect Dis 5(3):367–378
187. Dautzenberg B, Piperno D, Diot P, Truffot-Pernot C, Chauvin JP (1995) Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. Clarithromycin Study Group of France. Chest 107(4):1035–1040
188. Kobashi Y, Yoshida K, Miyashita N, Niki Y, Oka M (2006) Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of *Mycobacterium avium* complex isolates. J Infect Chemother 12(4):195–202
189. Chaisson RE, Benson CA, Dube MP et al (1994) Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. Ann Intern Med 121(12):905–911
190. Woods GL (2000) Susceptibility testing for mycobacteria. Clin Infect Dis 31(5):1209–1215
191. Bermudez LE, Nash KA, Petrofsky M, Young LS, Inderlied CB (1996) Effect of ethambutol on emergence of clarithromycin-resistant *Mycobacterium avium* complex in the beige mouse model. J Infect Dis 174(6):1218–1222
192. Kowalski TJ, Berbari EF, Osmon DR (2005) Epidemiology, treatment, and prevention of community-acquired methicillin-resistant *Staphylococcus aureus* infections. Mayo Clinic Proc 80(9):1201–1207, quiz 8
193. Wallace RJ Jr, Steele LC, Sumter G, Smith JM (1988) Antimicrobial susceptibility patterns of *Nocardia asteroides*. Antimicrob Agents Chemother 32(12):1776–1779
194. Deurenberg RH, Stobberingh EE (2009) International working group on the classification of staphylococcal cassette chromosome elements. Antimicrob Agents Chemother 53:4961–4967
195. Brown-Elliott, B et al (2013) *In Vitro* activity of amikacin against isolates of *Mycobacterium avium* complex with proposed MIC breakpoints and finding of a 16S rRNA gene mutation in treated isolates. J Clin Microbiol 51(10):3389–3394

# Fungal Infections in Cancer Patients

Michael Angarone

**Abstract**

Invasive fungal infections (IFI) have become a leading cause of morbidity and mortality in cancer patients. Infections with these organisms are often difficult to diagnose and treat. Appropriate and timely diagnosis requires a high index of suspicion and invasive procedures, including biopsy, to confirm the diagnosis. Treatment may be difficult, secondary to variable susceptibility and difficulty with exact and specific characterization of the fungal pathogen. The pathogens that are seen range from yeasts to invasive molds. Fortunately newer, noninvasive diagnostic techniques are available to aid in the diagnosis and treatments have become better tolerated and more efficacious.

**Keywords**

Malignancy · *Candida* species · Aspergillosis · Mucormycosis

## Contents



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Invasive fungal infections (IFI) are recognized as a leading cause of morbidity and mortality in cancer patients. The highest risk has been seen in those individuals undergoing hematopoietic stem cell transplantation (HSCT); however, these infections are now recognized as significant sequelae in patients with cancer receiving chemotherapy alone. Infections with these organisms are often difficult to diagnose and require a high index of suspicion and invasive procedures with tissue biopsy are often needed to confirm the diagnosis. Treatment of these infections continues to be a challenge as many of these organisms have variable susceptibility to the available antifungal agents, and treatment is often empiric as the causative agent is being identified. This empiric treatment often requires multiple agents or agents with a higher side effect profile, placing the patient at risk for drug-induced complications. In response to these limitations, newer diagnostic protocols, noninvasive testing, and broader spectrum antifungals have been developed to aid in the diagnosis and management of these infections [1].

Three major classes of fungi cause infection: yeasts, molds, and dimorphic fungi. The yeasts, which include *Candida* spp., *Cryptococcus* spp., and *Trichosporon* spp., lack true hyphae, and infection is related to invasion through compromised host defenses. The molds, which include *Aspergillus* spp., *Fusarium* spp., and the agents of mucormycosis, are transmitted via inhalation of conidial (spore) forms, and these organisms have true hyphae. The dimorphic fungi, *Blastomycosis*, *Histoplasma*, and *Coccidioides*, have both yeast and hyphal forms and are generally restricted to specific geographic areas. The majority of fungal infections in cancer patients are caused by *Candida* and *Aspergillus*. Over the past two to three decades, there has been an increasing trend and recognition of non-candidal infections, especially those caused by non-*Aspergillus* molds. See Table 1 for a brief description of the various fungal pathogens, typical diseases they cause, and treatments of choice.

This chapter will focus on a general overview of fungal infections. It will offer a review of the epidemiology and risk factors for fungal infections as well as a description of the commonly encountered fungal pathogens and the infections that they cause. A review of the available antifungal agents will also be described.

**Table 1** Typical fungal pathogens, type of infection, and treatment of choice

| Pathogen | Type of infection | Treatment of choice |
|---|---|---|
| ***Candida* spp.** | | |
| • *C. albicans*<br>• *C. krusei*<br>• *C. tropicalis*<br>• *C. glabrata*<br>• *C. parapsilosis*<br>• *C. lusitaniae* | Mucocutaneous<br>Blood infections<br>Endocarditis<br>Disseminated (Hepatosplenic)<br>Ocular | **Azoles**<br>• *C. krusei* and *C. glabrata* azole resistant<br>**Echinocandins**<br>• *C. parapsilosis* resistant to echinocandins<br>**Polyenes**<br>• *C. lusitaniae* resistant to polyenes |
| ***Tricosporon* spp.** | | |
| • *T. asahii*<br>• *T. asteroides*<br>• *T. cutaneum*<br>• *T. inkin*<br>• *T. mucoides*<br>• *T. ovoides*<br>• *Geotrichum capitatum* | Cutaneous<br>Pneumonia | Fluconazole |
| ***Pneumocystis jirovecii*** | | |
| | Pneumonia | TMP–SMX<br>Pentamidine<br>Primaquine + clindamycin<br>Atovaquone |
| ***Cryptococcus* spp.** | | |
| • *C. neoformans*<br>• *C. gattii* | Pneumonia<br>Cutaneous<br>CNS (meningoencephalitis) | AMB-D/L-AMB + 5-FC<br>*Disseminated and CNS disease<br>Fluconazole |
| ***Aspergillus* spp.** | | |
| • *A. fumigatus*<br>• *A. terreus*<br>• *A. flavus*<br>• *A. niger* | Pneumonia<br>Sinusitis<br>Cerebral | Voriconazole<br>Polyenes |
| **Mucormycosis** | | |
| • *Mucor* spp.<br>• *Rhizopus* spp.<br>• *Rhizomucor* spp.<br>• *Cunninghamella* spp.<br>• *Absidia* spp.<br>• *Basidiobolus* spp.<br>• *Conidiobolus* spp. | Sino-orbital<br>Rhinocerebral<br>Pneumonia | L-AMB<br>AMB-D<br>Posaconazole |

(continued)

**Table 1** (continued)

| Pathogen | Type of infection | Treatment of choice |
|---|---|---|
| ***Fusarium* spp.** | | |
| • *F. solami*<br>• *F. oxysporum* | Sino-pulmonary<br>Skin and soft tissue<br>Fungemia | Voriconazole<br>Posaconazole |
| ***Scedosporium* spp.** | | |
| • *S. apiospermum* (*Pseudallescheria boydii* asexual state)<br>• *S. prolificans* | Mycetoma<br>Fungemia<br>Disseminated infection (brain abscess, muscle) | Voriconazole<br>***Optimal therapy unknown**<br>***Typically resistant to most antifungal agents** |
| ***Paecilomyces* spp.** | | |
| • ***P. variotti***<br>• ***P. lilacinus*** | Pneumonia<br>Cutaneous | Voriconazole<br>Posaconazole |
| **Phaeohyphomycoses (dematiaceous/black molds)** | | |
| • *Cladophialophora* spp.<br>• *Wangiella* spp.<br>• *Ramichloridium* spp.<br>• *Chaetomium* spp.<br>• *Alternaria* spp.<br>• *Curvularia* spp. | Sinusitis<br>CNS infection (brain abscess) | Voriconazole<br>Surgical debridement<br>***Optimal therapy unknown** |
| ***Histoplasma capsulatum*** | | |
| | Pneumonia<br>Lymphadenitis<br>Disseminated (CNS, bone marrow, skin) | AMB-D, L-AMB<br>Itraconazole |
| ***Blastomyces dermatitidis*** | | |
| | Pneumonia<br>Cutaneous<br>Bone and joint | AMB-D, L-AMB<br>Itraconazole |
| ***Coccidioides immitis*** | | |
| | Pneumonia<br>Pleuritis<br>Cutaneous<br>Meningitis<br>Brain abscess | AMB-D, L-AMB<br>Fluconazole |

*AMB-D* amphotericin B deoxycholate; *5-FC* 5-flucytosine; *L-AMB* lipid amphotericin B; *TMP–SMX* trimethoprim–sulfamethoxazole

## 1 Epidemiology

The epidemiology of IFI in cancer patients is continually changing. In the 1980s, *Candida* species played a significant role in infection in cancer patients, and candidiasis was more prevalent than infections caused by molds. With the introduction of azole antifungals, a shift in fungal pathogens was seen. The azoles offered increased tolerability, compared with polyene antifungals, and their widespread use as prophylaxis led to a decrease in the incidence of candidal infections [2]. Along with this decrease, there has been an increase in infections caused non-*Candida albicans* yeast, *Aspergillus,* and other molds over the last two decades.

A major consequence of azole use has been a shift in the *Candida* species causing infection, with a shift to azole-resistant species such as *Candida krusei* and *C. glabrata*. These azole-resistant species now account for more than half of candidal isolates identified [3–5]. Newer antifungal agents, such as the echinocandins, have a broader spectrum of activity and are useful in treating azole-resistant candidal isolates. As the use of these agents has increased, there has also been a rise in the incidence of echinocandin-resistant organisms such as *C. parapsilosis* [6]. It remains unclear if this shift is secondary to the pressures of the antifungal agents or other host and treatment factors.

The true incidence of IFIs is difficult to assess as much of the data have come from single centers or regional retrospective studies, with most studies having an incidence ranging from 5 to 30 % in patients with cancer. Over the past two decades, there has been a shift in the causative agents of IFI, with an increase in infections by molds such as *Aspergillus* spp., *Fusarium* spp., and the agents of mucormycosis [7–9]. Autopsy studies from the MD Anderson Cancer Center have evaluated the prevalence of IFI from 1989 to 2003. Over the study period, the overall rate of IFI remained stable at approximately 30 %. The major finding was a rise in the prevalence of invasive mold infections, from 60 to 76 %, and a corresponding decrease in candidal infections, from 40 to 26 %. Major increases were seen in infections caused by *Aspergillus* spp. and endemic fungi and in mucormycosis [8, 10].

Retrospective case series have identified similar trends in the epidemiology of IFI in cancer patients. Auberger et al. reviewed the incidence and outcomes of IFI in a single Austrian center between 1995 and 2004. During the study period, IFIs occurred in 167 of 1,095 (15 %) patients. A significant increase in the incidence of IFI was seen over time, 12.7 % (1995–2000) to 18.1 % (2001–2004). The vast majority of cases were attributed to invasive mold infections (87 %), with *Aspergillus* spp. predominating. Overall mortality from IFI was 35 %, with a significant reduction in mortality between the periods studied, 44 % (1995–2000) versus 28 % (2001–2004) [11]. Similar results have been reported by Hahn-Ast et al. who compared the incidence of IFI from 1995 to 2006 in a German cancer center. In this series, the incidence of IFI was 8.8 %, with an increase in the incidence over time, 7.1 % (1995–2001) to 10.9 % (2001–2006). Most of IFIs

(approximately 63 %) occurred in individuals with acute mylogenous leukemia (AML). The overall mortality from these infections was 41 %; however, there was a decrease in the mortality seen over the two time periods, 56.9 versus 28.6 %. Better survival was observed in those with controlled cancer, age <60 years, infection during 2002–2006 and the use of novel antifungal agents (echinocandin and/or voriconazole) [12]. In an Italian multicenter review, Pagano et al. found that a majority of IFIs were secondary to molds, especially *Aspergillus* spp., and the incidence was greatest in individuals with AML. Mortality from these infections was high, especially for mucormycosis (mortality rate of ~64 %) [13].

There are limited data available on the epidemiology of IFI in pediatric cancer patients. Children with acute leukemia are at the highest risk of IFI, with incidence rates varying between 4.9 and 29 % [14–18]. Neutropenia, diagnosis of acute leukemia, corticosteroid use, and antifungal prophylaxis are associated with the development of IFI in pediatric cancer patients [16–18]. As seen in the adult population, there is a declining incidence of candidal infections with an increase in aspergillosis [14, 16, 17]. Other studies in the pediatric population have confirmed similar rates of fungal infections in children, with a majority of cases occurring in the setting of acute leukemia and with *Candida* spp. and *Aspergillus* spp. the leading causative organisms [14, 16].

## 2 Risk Factors

Fungal organisms are ubiquitous in the environment, and humans are constantly exposed to fungal spores via the respiratory tract and on skin and mucosal surfaces. Anatomic barriers and an intact immune system are highly efficient at containing these fungal elements in the immune competent host. Systemic fungal infections occur as a result of breaks in the normal host defenses such as those seen in patients with cancer. The first line of defense against these organisms is the anatomic barrier provided by structures such as skin and mucous membranes. These surfaces prevent the entry of microorganisms from entering the body and produce enzymes and other antimicrobial secretions that lead to the removal of fungal organisms. These barriers are compromised in cancer patients through invasive procedures such as indwelling central venous catheters and mucosal damage, resulting from chemotherapy. Compromise of these structures allows for the penetration of fungal organisms into the tissues and accesses the bloodstream [19]. The next line of defense against fungal infection is an intact immune system. The complement cascade, phagocytosis, and cell-mediated immunity all play a critical role in controlling and protecting against IFI. Many of the components of the immune system become compromised in patients with cancer secondary to the malignancy itself, chemotherapy, radiation therapy, and the use of immunosuppressive agents [20, 21]. This breakdown of immune defenses increases the susceptibility of cancer patients to fungal infections.

The major risk factors for IFI in cancer patients are the underlying malignancy, neutropenia, older age, and degree of immunosuppression. Other factors that contribute to the development of IFI are the state of the underlying malignancy, indwelling venous catheters, broad spectrum anti-bacterial therapy, renal insufficiency, intensive care unit admission, total parenteral nutrition, prior IFI, mucosal colonization with *Candida* spp., and innate immune defects [20]. To assess the risk of IFI, Prentice et al. developed a risk stratification that categorizes patients into low-, intermediate-, and high-risk groups. Those individuals at the highest risk of infection have prolonged and severe neutropenia, use of high doses of corticosteroids, treatment with high-dose cytarabine, AML, and colonization with *Candida* spp. [22]. This stratification tool has been validated and may help to provide more effective antifungal prophylaxis and early detection and treatment of IFI in cancer patients [23].

The two most significant risk factors for IFI are the underlying malignancy diagnosis and neutropenia. The risk of IFI is greater for individuals with hematologic malignancy, compared with those of solid tumors, and is greatest among those with acute leukemia (AML and acute lymphocytic leukemia, ALL) [20, 24]. Patients with acute leukemia are also at risk of developing these infections early, even before chemotherapy or during induction chemotherapy. A review of invasive filamentous fungal infections in cancer patients found that 7 % of infections occurred prior to initiation of chemotherapy, mostly in patients with acute leukemia and myelodysplastic syndrome [24]. The study also found that nearly half of the infections occurred during the first-induction chemotherapy [24]. The reason for the high rate of early infection is unclear, but it has been suggested that the bone marrow aplasia as a result of the leukemia may play a role [18].

Neutropenia is the most important risk factor for the development of IFI. Almost all patients undergoing chemotherapy will develop neutropenia during the course of therapy; however, the degree and duration of neutropenia varies. Individuals with solid tumors typically have short-lived neutropenia (usually less than 7 days), and IFI is an infrequent complication [19]. The degree of neutropenia is an important risk factor, and those with an absolute neutrophil count of $<0.1 \times 10^9$ cells/μL have the highest risk of infection [22]. Prolonged neutropenia greater than 10 days confers a much higher risk of IFI than shorter durations of neutropenia [24–26]. It is estimated that there is a 1 % risk of developing an IFI for each day a patient is neutropenic. This risk increases to >4 % per day if the patient remains neutropenic for more than 24 days [25]. Furthermore, short intervals between neutropenic episodes (<14 days) increase the risk of IFI [26].

Many of the chemotherapies used to treat malignancy have also been associated with increased risk of IFI. Studies have demonstrated an increased risk of IFI with the use of high doses of corticosteroids and fludarabine-based regimens [20, 27–29]. Use of monoclonal antibodies has also demonstrated an increase risk of infection, especially with fungi. Alemtuzumab, a humanized anti-CD52 antibody, leads to the depletion of CD4 and CD8 T-cells. This depletion increases the risk of severe infection, especially with *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii* [30, 31].

Genetic immune defects in host recognition and response to fungal organisms may also play a role in the risk of infection. The mannose-binding lectin (MBL) and toll-like receptors (TLR) play a critical role in immune recognition of fungal organisms, and defects in these proteins have been linked to increased risk of fungal infection [32]. MBL is a secreted pattern-recognition receptor of the innate immune system. These proteins bind to conserved carbohydrates found on many microorganisms and promote the initiation of the compliment cascade and phagocytosis [32]. Mutations in the *mbl2* gene led to a non-functional protein that has been linked to an increased risk of fever and serious infection, including fungal infections [33–36]. MBL binds to the mannan-rich outer wall of *Aspergillus* leading to the clearance of the organisms, and MBL-deficient mice are much more susceptible to infection with *Aspergillus* [36]. In immunocompromised humans, MBL deficiency has been significantly linked to the development of invasive *Aspergillus* infection [32]. The TLR is a transmembrane protein that detects specific "microbe-associated molecular patterns," and binding of these receptors leads to cytokine release and immune activation [37]. TLR2 and TLR4 are major components of the initial immune response to fungal pathogens, and defects in these receptors lead to decreased neutrophil recruitment and reduced cytokine production [37, 38]. In humans, genetic polymorphisms within the TLR4 gene have been associated with an increased risk of cavitary aspergillosis [39]. Defects in dectin-1, tumor necrosis factor (TNF), and interleukin-10 (IL10) have also been linked with increased risk of fungal infections [40–44].

The environment, geographic location, and hospital exposure can all play a role in acquisition of fungal pathogens. Fungal spores are ubiquitous in the environment, and humans are constantly exposed to these organisms. Climate can have a profound impact on the burden of fungal spores in the environment, with higher rates of infection seen in warm, dry climates compared with more temperate climates [45, 46]. For example, *Aspergillus* spore counts have been shown to increase during warm and dry months in Seattle, Washington; *Coccidioides* proliferate during periods of high precipitation, and spread of infection has been linked to the warm and dry months in Arizona [46–48]. Nosocomial spread of infection has been linked with fireproofing material, carpets, hospital water supply (especially showers), and food products such as tea, pepper, fruit, and freeze-dried soups [49–56]. Hospital air has also been found to contain fungal spores, especially during building construction, and the use of HEPA filtration in hospital can dramatically reduce the spore load of air [50, 56].

## 3 Diagnosis of IFI

The diagnosis of fungal infections remains a challenge. Infections with these organisms can present in a myriad of ways, including persistent fever, sepsis, fungemia, and organ invasive disease. Isolation and identification of the causative fungus often require invasive procedures, and many of the molds are difficult to

cultivate in the laboratory. The primary step in identification of an IFI is having a high index of suspicion based on the clinical signs of illness. An aggressive search should be made to identify a causative fungus. This may require cultures performed on tissue specimens, histopathology of these specimens, the use of fungal antigen assays, and molecular tests to identify fungal specific DNA.

The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) have developed definitions to classify IFI and aid in the diagnosis of IFI [1]. This classification system assigns levels of probability to the diagnosis of an IFI in individuals with cancer or recipients of an HSCT. The classification system is divided into "proven," "probable," or "possible" IFI based on the patients' underlying condition and clinical factors combined with histopathologic, microbiologic, and radiographic data. "Proven" infection is based on the identification of fungal elements with tissue destruction on biopsy specimens and microbiologic identification of a fungus from a normally sterile site, such as blood, cerebrospinal fluid (CSF), or biopsy specimen. "Probable" infection requires the presence of a host factor (e.g., neutropenia and prolonged use of corticosteroids), a clinical criterion (e.g., symptoms of sinus infection and radiographic findings concerning for a nodular pneumonia), and a mycological criterion (e.g., growth of a mold on culture, positive antigen-detection assay). "Possible" infection is defined as the presence of host and clinical factors in the absence of mycological data. The primary use of this system has been in the development of clinical trials for the treatment of fungal infection and validation of diagnostic assays; however, their implementation into clinical practice has not identified a difference in clinical outcomes between the categories [20]. Given the difficulty in making a "proven" diagnosis, individuals with a "probable/possible" diagnosis should be treated as aggressive as those with "proven" infection while continuing to confirm the diagnosis.

The gold standard for the diagnosis of fungal infection is the histopathologic identification of fungal elements on biopsy specimens and the growth of fungal organisms in culture from blood or other clinical specimens; however, there are limitations to obtaining these specimens. Often patients are not suitable to undergo invasive procedures due to their illness or high risk of complication. Also the sensitivity of fungal culture is limited and may be as low as 35 %, especially for *Aspergillus* spp. and other molds [57]. Currently, there are multiple non-culture-based assays available that can help to aid in the diagnosis of fungal infections and can be performed on serum or urine specimens. These assays include serologic assays and fungal antigen-detection assays. Serology can be helpful in the diagnosis of infections with coccidioidomycosis and paracoccidioidomycosis [1, 58]. Antigen detection has also been useful in the diagnosis of infections caused by cryptococcosis, histoplasmosis, and blastomycosis [59, 60].

Two antigen assays are currently available for the diagnosis of candidiasis and aspergillosis, the (1→3)-B-D-glucan and the galactomannan assays. The (1→3)-B-D-glucan is a cell wall component present in many fungi, limiting the specificity of the assay. The assay identifies (1→3)-B-D-glucan in serum, and the presence of

the antigen can aid in early treatment for fungal infection. The sensitivity to the (1→3)-B-D-glucan is variable, with a range of 61–88 % sensitivity for the diagnosis of aspergillosis [61–63] and 71–97 % for candidiasis [61, 64–67]. Another major issue with the (1→3)-B-D-glucan is the lack of specificity among fungal organisms and the high rate of false positive results in patients on hemodialysis and those with bacteremia [60]. The galactomannan assay offers increased specificity for the diagnosis of aspergillosis. This assay detects specific components of the *Aspergillus* cell wall and for some patients, detection of galactomannan in the serum may precede clinical signs and symptoms of infection [60, 68]. The sensitivity of the galactomannan assay on serum specimens is variable, between 49 and 89 %, with a lower sensitivity seen in those individuals receiving mold active agents as either prophylaxis or treatment [61, 69]. The assay has also been tested on respiratory specimens to increase the sensitivity and diagnostic yield of the assay. Performance of the assay on bronchoalveolar lavage (BAL) specimens has demonstrated an increased sensitivity when compared with serum galactomannan results. Maertens et al. evaluated the performance of BAL galactomannan compared with culture and microscopy of BAL fluid. A greater sensitivity was found on the BAL galactomannan (91 %) compared with that of culture and microscopy (50 and 53 %, respectively) [70]. The galactomannan assay can also be followed serially, usually twice per week, to help provide early diagnosis of IFI [71]. These assays may allow for earlier diagnosis and earlier treatment for individuals suspected of having a fungal infection, especially *Aspergillus* infection.

Polymerase chain reaction (PCR) is a diagnostic technique with the potential to offer an accurate and definitive diagnosis via noninvasive testing. PCR assays demonstrate high specificity, ranging from 92 to 100 % depending on the gene that is amplified [63, 72–74]. White et al. evaluated the utility of monitoring twice weekly the blood PCR assay specific to *Aspergillus*. The negative predictive value for this approach was >99 %, and serial positive results were predictive of proven or probable infection [74]. It has been suggested to combine PCR testing with galactomannan testing; however, the accuracy and practicality of this approach have not been evaluated. The major drawback to PCR assays for the diagnosis of aspergillosis is that they lack standardization, are prone to contamination, and have not been shown to be superior to the galactomannan assay [60]. At this time, PCR assays remain experimental; perhaps with the development of a commercial or standardized assay, this testing method may develop more widespread use and acceptance.

## 4 Selected Fungal Organisms

### 4.1 Candidal Infections

Candidal species are part of the normal microbiota of the skin, airways, genitourinary tract, and the gastrointestinal tract. Individuals with malignancies are predisposed to invasion with these organisms secondary to neutropenia, mucositis,

broad spectrum antibacterial therapy, total parenteral nutrition, and invasive central venous catheters [75]. Prior to the use of anti-fungal prophylaxis *Candida* spp. represented 20 % of all blood stream isolates and were the fourth leading cause of death from nosocomial sepsis [76, 77]. Incidence rates for candidal infections have remained stable in recent years despite increased use of antifungal prophylaxis [6]. *Candida albicans* is the most frequently isolated species; however, there has been a shift to azole-resistant non-*C. albicans* yeast, especially *C. krusei* and *C. glabrata* [4, 78]. A recent single center review identified a greater than 50 % reduction in the number of infections caused by *C. albicans* and a 2–3 fold increase in infections caused by *C. krusei* and *C. glabrata*. In patients with hematologic malignancies, 86 % of candidal isolates were non-*C. albicans* species, and the major risk factor for infection with these organisms was the use of fluconazole prophylaxis and neutropenia [79].

Candidal infections range from mucosal infection, such as thrush and esophagitis, to bloodstream and multi-organ-disseminated infection. Breakdown of skin and mucosal barriers allows for the invasion into the blood stream and eventual dissemination of the organisms. The most common source for invasion is the gastrointestinal and genitourinary tracts; however, isolation of *C. parapsilosis* usually indicates contamination of a central venous device. Candidemia is associated with significant morbidity and mortality, with mortality rates ranging from 30 to 75 % [6, 79, 80]. The major factors associated with mortality are hematologic malignancy, neutropenia, and infection with *C. glabrata* [6, 79–81]. Disseminated (hepatosplenic) candidiasis typically arises as a complication of candidemia and is the result of seeding of candidal organisms in various organs, especially the liver and spleen. Often, the only symptom present is persistent fevers. As neutropenia resolves, lesions within the affected organ(s) may become apparent on imaging and with the development of organ dysfunction. Disseminated candidiasis has been reported in about 6 % of individuals with acute leukemia, and remission of the leukemia is associated with recovery from the candidal infection [82].

Mucocutaneous candidiasis can be treated with topical agents, such as nystatin for thrush or clotrimazole for vulvovaginal infection, or with systemic triazoles such as fluconazole for esophagitis [83]. All patients with suspected or documented candidemia require systemic antifungal therapy. The current recommendation for treatment of neutropenic patients with candidemia is to initiate an echinocandin and tailor therapy once the organism has been identified. Typically, *C. albicans* and *C. tropicalis* are susceptible to the triazoles, such as fluconazole and voriconazole. *C. glabrata* and *C. krusei* tend to be resistant to the triazoles; therefore, it is recommended that an echinocandin can be used for treatment. *C. parapsilosis* has in vitro resistance to the echinocandins, and treatment with an azole or polyene (amphotericin B product) is recommended [83]. In addition to antifungal therapy, indwelling catheters should be removed. In non-neutropenic individuals, catheter removal has been associated with earlier sterilization of the blood, which may decrease the likelihood of dissemination. In neutropenic individuals, catheter removal may be problematic since removal of the central line

may lead to access problems. Additionally, there is a lack of association between early catheter removal and improved survival [84, 85]. However, catheter removal should be undertaken in all patients with persistent candidemia or with worsening infection while on appropriate antifungal therapy, and in all other individuals with candidemia, central venous catheter removal is strongly recommended [83].

## 4.2 Trichosporonosis

Trichosporonosis is an uncommon infection usually seen in immunocompromised hosts, especially those with hematologic malignancies. The major causes of trichosporonosis are the *Trichosporon* spp. (*T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, *T. ovoides*) and *Geothrichum capitatum* [86]. These yeasts are part of the normal skin, gastrointestinal, and pulmonary microbiota and have also been identified in multiple environmental sources [86, 87]. Portal of entry for these organisms is via breaks in mechanical barriers such as skin or mucosa. Fungemia and pneumonia are the primary infections seen with these yeasts. A large Italian review identified 52 cases of trichosporonosis over a 20-year period, with 33 % secondary to *Trichosporon* spp. and 67 % secondary to *G. capitatum*. Fungemia was the most frequent manifestation of infection, and mortality was high (57 % for *G. capitatum*, 65 % *Trichosporon* spp.) [87]. Pulmonary infection resembles classic mycetoma with round lung lesions and a halo sign on imaging [88]. Respiratory tract infection with these fungi is difficult to diagnose since these organisms may colonize the airways.

The azoles, such as fluconazole, are the treatment of choice for these infections based on in vitro susceptibility testing. Despite in vitro susceptibility data, recurrent or breakthrough infections are common [86, 89, 90]. Mortality rates are high, ranging between 55 and 65 % [86, 87]. Factors associated with favorable outcomes are neutrophil recovery, lack of hyperglycemia, and azole therapy [86].

## 4.3 *Pneumocystis jiroveci* Infection

*Pneumocystis jiroveci* was initially classified as a protozoan; however, it is now considered a fungus based on gene sequencing and analysis of cell wall constituents. There are multiple species of *Pneumocystis*, each with its own genetic distinctiveness and host specificities. Based on this species uniqueness, the human pathogen has been renamed *P. jiroveci*, formerly known as *P. carinii*. Infection with *Pneumocystis* relies on defective T-cell immunity. This T-cell defect is most commonly seen in individuals with T-cell depletion such as those with acquired immunodeficiency syndrome (AIDS) and is less common in patients with malignancy. The highest risk appears to be individuals with lymphoproliferative conditions [91, 92]. In a series of 55 cases of *P. jiroveci* pneumonia (PJP) over a 10-year period, patients with non-Hodgkin's lymphoma and lymphoid leukemia

had the highest risk of infection [93]. Infection is also seen in patients with solid tumors, especially those treated with long-term steroids [91, 94]. A more recent risk factor for the development of PJP is the use of lymphocyte-depleting antibodies, such as rituximab [95, 96]. It is estimated that 11–14 % of individuals treated with rituximab develop PJP [95, 96]. *P. jiroveci* has a unique tropism for the lung where it resides as an alveolar pathogen, rarely causing disseminated disease. Infection typically presents with the slow onset of dyspnea, cough, and fevers. Examination may reveal tachycardia, crackles, and hypoxia.

Unlike other fungal infections, antifungal agents have little to no effect in the treatment of PJP. The treatment of choice is trimethoprim–sulfamethoxazole (TMP/SMX). Acute therapeutic alternatives are intravenous pentamidine, primaquine combined with clindamycin, or atovaquone. Given the high risk of infection with *P. jiroveci* in patients treated with steroids or rituximab, primary prophylaxis should be considered. As with treatment, TMP/SMX is the preferred agent for prophylaxis and is administered daily or thrice per week. Alternatives are monthly inhaled pentamidine, daily oral atovaquone, or dapsone.

## 4.4 Cryptococcosis

Infection with *Cryptococcus* results in a wide spectrum of illness, ranging from asymptomatic disease to life-threatening meningoencephalitis [97]. *Cryptococcus* is ubiquitous environmental yeast, with the *C. neoformans* species complex causing most human infection. Cryptococcosis is an infrequent complication in patients with malignancy, and underlying hematologic malignancy accounts for the majority of cases [98]. The major risk factors for cryptococcosis are steroid use, chemotherapy with fludarabine, and lymphopenia [98]. Pulmonary infection occurs in >60 % of cases with patients presenting with nonspecific symptoms, such as fever (37 %), dyspnea (37 %), cough (37 %), chest pain (16 %), and ARDS (11 %). Asymptomatic disease is seen in more than 30 % of cases pulmonary cryptococcosis [98]. Only 10 % of cryptococcal infections involve the central nervous system (CNS) in patients with malignancy, much less frequent when compared with other patient populations. The signs and symptoms of CNS infection are similar to other patient populations and include altered mental status, headaches, and fevers [98] (see Chapter Central Nervous System Infectionsin Cancer Patients and Hematopoietic Stem Cell Transplant Recipients).

## 4.5 Aspergillosis

Infection with *Aspergillus* is the most common invasive mold infection encountered in individuals with malignancy. There are more than 200 species of *Aspergillus*, but only a few cause disease in humans, namely *Aspergillus fumigatus*, *A. terreus*, *A. flavus,* and *A. niger* [8].

Infection may occur in the lung, sinuses, skin, mucosal surfaces, eye, and CNS. The most common sites of acquisition are the lungs and sinuses. Clinical manifestations of invasive pulmonary aspergillosis (IPA) may be varied and range from cough and fever to hemoptysis and respiratory failure. The most frequent manifestations of disease in neutropenic individuals are fever, cough, and dyspnea [99]. The earliest indications of IPA are radiographic findings, especially with computerized tomography (CT) scanning of the lung. CT scan of the lung may identify micronodules, macronodules, diffuse interstitial infiltrates, the "halo sign" or the "air-crescent sign" [100, 101]. These findings can allow for early recognition of IPA, and appropriate testing can be obtained to make an early diagnosis.

Cerebral aspergillosis is a rare condition with an incidence of approximately 7 % but a mortality rate greater than 90 % [13, 102]. The clinical presentation is nonspecific with fevers, altered mental status, focal neurologic deficits, and seizures [103, 104]. These nonspecific findings can be found in other infectious and non-infectious conditions of the CNS. Diagnosis of CNS aspergillosis relies on neuroimaging. The typical findings associated with aspergillosis on CT or magnetic resonance (MR) imaging are multiple, complex ring-enhancing lesions within the brain parenchyma [105, 106]. Those with sinus disease may have dural enhancement adjacent to the involved sinuses [105, 106]. Evaluation of the cerebral spinal fluid (CSF) is of limited use, and culture positivity is rare. However, in a small series of patients, levels of galactomannan in CSF were significantly higher in patients with CNS aspergillosis versus controls [107]. This assay may provide a means to establish an early diagnosis and allow for early directed therapy against CNS aspergillosis.

Sinus infection with *Aspergillus* is most often symptomatic with facial swelling, periorbital swelling, and sinus drainage that is bloody or black [108]. It is often difficult to distinguish sinus infection with *Aspergillus* from other causes, including bacteria and other molds. Diagnosis is most often made by sinus endoscopy. Endoscopic findings include crusting of the nasal mucosa, nasal ulceration, and necrotic, or dusky nasal mucosa [109]. Therapy involves a combination of surgical debridement and anti-fungal medications (either voriconazole of amphotericin B-based therapy) [108].

Evaluation of biopsy specimens reveals tissue invasion of the fungus, with invasion into blood vessels. The fungus appears as 45° angle branching, septated hyphae; this is not a unique feature of *Aspergillus* and may be seen with other invasive molds such as *Fusarium* and the agents of mucormycosis. Given the similarity of the various molds on pathologic specimens, culture is required to make a definitive diagnosis. *Aspergillus* can be grown easily on routine fungal culture media, and large white or black colonies are seen on the media plates [110]. Microscopically, the mold consists of hyphal stalks and a conidial head. Newer PCR techniques can be performed directly on tissue specimens, but identification may only be to the genus level and susceptibility information cannot be obtained.

## 4.6 Mucormycosis

Over the last few decades, there has been a steady increase in cases of mucormycosis with a stable mortality rate between 40 and 50 % [111]. The increase in these infections may be related to newer chemotherapies, increased longevity of individuals with malignancy, and increased awareness of this infection in this population [111]. Infections with the Zygomycetes class of fungi belong to two orders, Mucorales and Entomophthorales. Multiple genera within these two orders can lead to infection, but the most frequently encountered genera are *Rhizopus*, *Mucor,* and *Rhizomucor* [111]. These molds are ubiquitous in the soil and decaying organic material. Infection occurs through inhalation of fungal spores in a susceptible host; however, infection can also occur via direct cutaneous inoculation or ingestion of contaminated foods [112]. Infection in patients with malignancy is uncommon, and the vast majority of infections occur in individuals with hematologic malignancies, especially those with acute leukemias [13]. The major sites of infection are the lung and sinuses, with infection of the skin, throat, and gastrointestinal tract seen less frequently. The major findings with respiratory tract infection are fever, cough, thoracic pain, and dyspnea. Patients with sinus infection may develop orbital cellulitis, paresis of the extraocular muscles, or proptosis. These molds can result in vascular invasion and destruction of bone that may lead to direct invasion of the brain in sinus infections [13, 111].

Diagnosis is often based on the combination of clinical signs and symptoms along with radiographic imaging. Infection results in vascular invasion with resultant vascular occlusion and infarction and necrosis of infected tissue. Radiographic imaging may identify hemorrhage, abscess or consolidation of inflammation within the lungs [113]. Rhinocerebral or sino-orbital infection may demonstrate inflammation of the sinuses with destruction of boney structures and direct invasion into the orbit or brain [113]. Biopsy specimens will identify the characteristic right angle branching, pseudoseptate, and ribbon-like hyphae [114]. Fungal cultures can help to identify the genera and species of the mold; however, they are positive in less than 50 % of cases [111].

Treatment of mucormycosis involves surgical debridement, reduction or correction of immunosuppression, and antifungal medications. Surgical resection of necrotic, infected tissue can help to enhance antifungal activity and decrease the fungal burden [112]. Antifungal therapy is limited to the polyenes and posaconazole. The polyenes remain the initial treatment of choice (amphotericin B deoxycholate, liposomal amphotericin B, and lipid complex amphotericin B). The lipid formulations of amphotericin (AmB-L) offer the advantage of higher doses of amphotericin and a decrease in nephrotoxicty [111, 115]. Retrospective data demonstrate response rates of 52–69 % and improved survival with AmB-L compared with amphotericin B deoxycholate [115]. A newer extended spectrum azole, posaconazole, has in vitro and in vivo activity against Mucorales. Posaconazole has been evaluated as salvage therapy for treatment of mucormycosis [116, 117]. In 91 patients treated with posaconazole as salvage therapy for mucormycosis, successful treatment was seen in

60 % of patients at 12 weeks, complete response was seen in 14 %, and partial or clinical response was seen in 46 % of patients [117]. The major disadvantage to posaconazole is that it is only available as an oral formulation and requires a high fat meal to enhance absorption, making it difficult to administer to all patients. Other therapies have been investigated for the treatment of mucormycosis such as colony stimulating factor, interferon therapy, iron chelation, and combination antifungal therapy, all with varying results, and are not recommended for use at this time [118]. Currently, it is recommended that therapy begin with a polyene and any surgical debridement, if possible, followed by a change to posaconazole once a response to therapy has been identified [118].

## 4.7 Other Mold Infections (Fusarium, Alternaria, Phaeohyphomycosis, Endemic Fungi)

Over the past few decades, there has been an increase in infections with exotic, environmental molds. The genera most commonly identified are *Fusarium* spp., *Scedosporium* spp., and the dematiaceous molds. These molds are ubiquitous in the environment and have been identified in water, soil, and on vegetation worldwide, and it is believed that acquisition of these infections primarily occurs outside the hospital [112, 119]. A variety of infections, from cutaneous infection to disseminated disease with fungemia, may be caused by these molds. *Fusarium* spp. is a common mold of plants and decaying matter. A majority of reported infections with these molds have occurred in patients with hematologic malignancy and neutropenia [120]. The major syndrome related to *Fusarium* is disseminated disease with fungemia and multiple organ involvement; however, this mold may also cause skin, sinus, and pulmonary infection [120–122]. Most patients are treated with a combination of antifungals, and, despite therapy, mortality rates are >50 %, especially for patients with fungemia and disseminated disease [120]. The two major *Scedosporium* spp., *Scedosporium apiospermum* and *S. prolificans*, are found worldwide and are the major causative agents of mycetoma (*S. apiospermum*) and localized bone infection (*S. prolificans*) [123]. Infection typically involves the lungs with dissemination of the mold to secondary sites of infection including muscle, brain, and fungemia [124–126]. Resistance to the polyenes and echinocandins occurs in both species of *Scedosporium,* and the most active agent in vitro is voriconazole; however, mortality rates remain very high for this infection [126, 127]. Phaeohypohomycosis results from infection with the pigmented molds. These infections remain extremely rare in patients with malignancy, but can lead to brain abscess, pneumonia, and fungemia [128].

*Histoplasma*, *Blastomyces,* and *Coccidioides* all can cause endemic mycoses. These fungi are dimorphic and have a yeast phase seen at human body temperatures and a mold phase seen on culture or in the environment. These infections are rare in patients with malignancy and are often restricted to the geographic location of the fungus. Disease results from newly acquired infection related to

environmental exposure or reactivation of latent infection. Most individuals will develop pneumonia from these molds, but cutaneous, CNS, and disseminated disease can occur [129–131]. The key to diagnosis is early recognition of a potential endemic mycoses and identification of the yeast forms on histopathologic specimens and early institution of therapy [131].

## 5 Antifungal Therapy

Multiple antifungal agents are currently available with diverse mechanisms of action, spectrum of activity, and tolerability. The major classes of antifungals are the polyenes, echinocandins, and the azoles. Table 2 lists the common antifungal agents, their route of administration, spectrum of activity, and common adverse effects. Specific treatment varies based on the fungal pathogen, the site of infection, drug tolerability, and toxicity profile of the chosen agent.

### 5.1 Polyenes

The polyenes, amphotericin B deoxycholate, and the lipid-associated amphotericin preparations bind to ergosterol in the fungal cell membrane. This binding leads to the formation of ion channels in the cell membrane and the physical disruption of the membrane. The polyenes have a broad spectrum of activity and are reactive against most fungi. The greatest limitation to the use of amphotericin B deoxycholate is nephrotoxicity, which can lead to renal failure and the need for dialysis [132, 133]. The lipid formulations of amphotericin B have the advantage of less nephrotoxicity and allow for infusion of higher doses of amphotericin.

### 5.2 Echinocandins

The echinocandins (caspofungin, micafungin, anidulafungin) are lipopeptides that inhibit the synthesis of 1,3-$\beta$-glucan, a polysaccharide involved in strengthening the cell wall. The inhibition results in changes in the osmotic integrity of the fungal cell leading to cell destruction. Activity of these agents is restricted to those fungi that possess the 1,3-$\beta$-glucan in their cell membrane; in particular *Candida* spp. and *Aspergillus* spp. The utility of the echinocandins has been demonstrated in the treatment of candidal infections, refractory invasive aspergillosis, and as empiric therapy for neutropenic fever [134–137]. These agents have also demonstrated efficacy in the treatment of refractory aspergillosis when combined with voriconazole [138, 139]. Major adverse effects of the echinocandins include elevations in liver aminotransferases (especially caspofungin), gastrointestinal upset, and headaches. Serum levels of the echinocandins may be increased by cyclosporine, and conversely they may increase the serum levels of tacrolimus [140].

**Table 2** Antifungal agents

| Antifungal agent | Route | Dose | Toxicity | Spectrum of activity |
|---|---|---|---|---|
| ***Polyenes*** | | | | |
| Amphotericin B | IV | 0.5–1.0 mg/kg | Nephrotoxicity<br>Hypokalemia<br>Hemolysis<br>Infusion related | Broad spectrum of activity:<br>*Candida*<br>*Aspergillus*<br>Mucormycosis<br>*Blastomyces*<br>*Coccidioides*<br>*Histoplasma*<br>*Cryptococcus* |
| ABCD | IV | 2.5–5 mg/kg | As above,<br>Less nephrotoxicity | |
| ABLC | IV | 2.5–7.5 mg/kg | | |
| L-AMB | IV | 2.5–10 mg/kg | | |
| ***Echinocandins*** | | | | |
| Caspofungin | IV | 70 mg load then, 50 mg | Hepatic | *Candida* spp.<br>*Aspergillus* spp. |
| Micafungin | IV | 50–100 mg | Hepatic<br>GI upset<br>Phlebitis<br>Headache | |
| Anidulafungin | IV | 100 mg load then, 50 mg | GI upset<br>Hepatic | |
| ***Azoles*** | | | | |
| Fluconazole | PO/IV | 200–1,200 mg | Hepatic | *Candida*<br>*Coccidioides*<br>*Cryptococcus* |
| Itraconazole | PO/IV | 100–400 mg | Hepatic<br>Hypokalemia<br>Edema<br>Cardiac<br>Poor absorption | *Candida*<br>*Aspergillus*<br>*Blastomyces*<br>*Histoplasma* |
| Voriconazole | PO/IV | 6 mg/kg load then 4 mg/kg BID | Hepatic<br>Neurologic<br>Vision changes | *Candida*<br>*Aspergillus*<br>*Fusarium*<br>*Scedosporium* |
| Posaconazole | PO | 200–300 mg TID<br>100–200 mg BID | Hepatic<br>Poor absorption | *Candida*<br>*Aspergillus*<br>*Coccidioides*<br>Mucormycosis<br>*Fusarium*<br>*Scedosporium*<br>*Cryptococcus* |

*ABCD* amphotericin B colloidal complex; *ABLC* amphotericin B lipid complex; BID twice daily; IV, intravenous; *L-AMB* liposomal amphotericin B; *PO* per mouth; *TID* thrice a day

### 5.3 Azoles

The azoles constitute a group of antifungals with a similar mechanism of action, but varying spectrum of activity. The azoles inhibit the production of ergosterol biosynthesis by inhibiting lanosterol 14-α demethylase, which results in an altered fungal cell membrane. Currently, there are four widely used azole antifungal compounds used in patients with malignancy, fluconazole, itraconazole, voriconazole, and posaconazole. Fluconazole is a narrow spectrum azole that is primarily used to treat candidal infections. This agent has good tolerability and is available in an oral and intravenous formulation. Itraconazole is a broader spectrum azole with activity against *Candida* spp., *Aspergillus* spp., and the endemic fungi. There are both oral and intravenous formulations; however, the capsular formulation of this agent has erratic GI absorption and may lead to GI upset.

Newer azoles such as voriconazole and posaconazole offer broader spectrum of activity and better tolerability. Voriconazole is structurally similar to fluconazole; but has a spectrum of activity that includes *Aspergillus*. Based on available data, voriconazole is considered the drug of choice for the treatment of proven or suspected invasive aspergillosis [141, 142]. Individual variability of voriconazole metabolism may lead to altered serum drug concentrations. This variability may lead to sub-therapeutic levels or toxic levels of the agent that can lead to decreased efficacy or increased toxicity [143]. The major toxicities of voriconazole are visual disturbances, hepatotoxicity, and renal toxicity (intravenous formulation only). The newest azole available in the United States, posaconazole, has been shown to have enhanced activity against a wide variety of fungi, including the Mucorales [144–146]. Clinical data have demonstrated the efficacy of posaconazole as salvage therapy for aspergillosis, mucormycosis, fusariosis, and coccidioidomycosis [116, 117, 147–150].

## 6 Discussion

IFI are a growing cause of morbidity and mortality in cancer patients. Studies from single, large cancer centers have identified the growing burden of these infections. Strategies to enhance the diagnosis along with the growing armamentarium to treat these infections offer promise at improved survival from these infections. With the use of these newer, broad spectrum agents, the emergence of rare and more resistant fungal pathogens cannot be overlooked.

## References


1. De Pauw B, Walsh TJ, Donnelly JP et al (2008) Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. Clin Infect Dis 46:1813–1821
2. Marr KA (2010) Fungal infections in oncology patients: update on epidemiology, prevention, and treatment. Curr Opin Oncol 22:138–142
3. Horn DL, Neofytos D, Anaissie EJ et al (2009) Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 48:1695–1703
4. Pagano L, Antinori A, Ammassari A et al (1999) Retrospective study of candidemia in patients with hematological malignancies. Clinical features, risk factors and outcome of 76 episodes. Eur J Haematol 63:77–85
5. Pfaller MA, Castanheira M, Messer SA, Moet GJ, Jones RN (2010) Variation in Candida spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: report from the SENTRY antimicrobial surveillance program (2008–2009). Diagn Microbiol Infect Dis 68:278–283
6. Sipsas NV, Lewis RE, Tarrand J et al (2009) Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001–2007): stable incidence but changing epidemiology of a still frequently lethal infection. Cancer 115:4745–4752
7. Husain S, Alexander BD, Munoz P et al (2003) Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-Aspergillus mycelial fungi. Clin Infect Dis 37:221–229
8. Leventakos K, Lewis RE, Kontoyiannis DP (2010) Fungal infections in leukemia patients: how do we prevent and treat them? Clin Infect Dis 50:405–415
9. Marr KA, Carter RA, Crippa F, Wald A, Corey L (2002) Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 34:909–917
10. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP (2005) Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41:60–66
11. Auberger J, Lass-Florl C, Ulmer H et al (2008) Significant alterations in the epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. Int J Hematol 88:508–515
12. Hahn-Ast C, Glasmacher A, Muckter S et al (2010) Overall survival and fungal infection-related mortality in patients with invasive fungal infection and neutropenia after myelosuppressive chemotherapy in a tertiary care centre from 1995 to 2006. J Antimicrob Chemother 65:761–768
13. Pagano L, Caira M, Candoni A et al (2006) The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 91:1068–1075
14. Athanassiadou F, Tragiannidis A, Kourti M, Papageorgiou T, Velegraki A, Drevelengas A (2006) Invasive fungal infections in children with hematological malignancies: a 5-year study. Pediatr Hematol Oncol 23:163–166
15. Gozdasoglu S, Ertem M, Buyukkececi Z et al (1999) Fungal colonization and infection in children with acute leukemia and lymphoma during induction therapy. Med Pediatr Oncol 32:344–348
16. Kaya Z, Gursel T, Kocak U, Aral YZ, Kalkanci A, Albayrak M (2009) Invasive fungal infections in pediatric leukemia patients receiving fluconazole prophylaxis. Pediatr Blood Cancer 52:470–475

17. Rosen GP, Nielsen K, Glenn S, Abelson J, Deville J, Moore TB (2005) Invasive fungal infections in pediatric oncology patients: 11-year experience at a single institution. J Pediatr Hematol Oncol 27:135–140
18. Wiley JM, Smith N, Leventhal BG et al (1990) Invasive fungal disease in pediatric acute leukemia patients with fever and neutropenia during induction chemotherapy: a multivariate analysis of risk factors. J Clin Oncol 8:280–286
19. Maertens J, Vrebos M, Boogaerts M (2001) Assessing risk factors for systemic fungal infections. Eur J Cancer Care (Engl) 10:56–62
20. Bow EJ (2008) Considerations in the approach to invasive fungal infection in patients with haematological malignancies. Br J Haematol 140:133–152
21. Guiot HF, Fibbe WE, van't Wout JW (1994) Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. Clin Infect Dis 18:525–532
22. Prentice HG, Kibbler CC, Prentice AG (2000) Towards a targeted, risk-based, antifungal strategy in neutropenic patients. Br J Haematol 110:273–284
23. McLintock LA, Jordanides NE, Allan EK et al (2004) The use of a risk group stratification in the management of invasive fungal infection: a prospective validation. Br J Haematol 124:403–404
24. Pagano L, Girmenia C, Mele L et al (2001) Infections caused by filamentous fungi in patients with hematologic malignancies. A report of 391 cases by GIMEMA infection program. Haematologica 86:862–870
25. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA (1984) Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 100:345–351
26. Muhlemann K, Wenger C, Zenhausern R, Tauber MG (2005) Risk factors for invasive aspergillosis in neutropenic patients with hematologic malignancies. Leukemia 19:545–550
27. Baddley JW, Stroud TP, Salzman D, Pappas PG (2001) Invasive mold infections in allogeneic bone marrow transplant recipients. Clin Infect Dis 32:1319–1324
28. Fukuda T, Boeckh M, Carter RA et al (2003) Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 102:827–833
29. Malagola M, Peli A, Damiani D et al (2008) Incidence of bacterial and fungal infections in newly diagnosed acute myeloid leukaemia patients younger than 65 yr treated with induction regimens including fludarabine: retrospective analysis of 224 cases. Eur J Haematol 81:354–363
30. Klastersky J (2006) Adverse effects of the humanized antibodies used as cancer therapeutics. Curr Opin Oncol 18:316–320
31. Martin SI, Marty FM, Fiumara K, Treon SP, Gribben JG, Baden LR (2006) Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. Clin Infect Dis 43:16–24
32. Lambourne J, Agranoff D, Herbrecht R et al (2009) Association of mannose-binding lectin deficiency with acute invasive aspergillosis in immunocompromised patients. Clin Infect Dis 49:1486–1491
33. Schlapbach LJ, Aebi C, Otth M et al (2007) Serum levels of mannose-binding lectin and the risk of fever in neutropenia pediatric cancer patients. Pediatr Blood Cancer 49:11–16
34. Schlapbach LJ, Aebi C, Otth M, Leibundgut K, Hirt A, Ammann RA (2007) Deficiency of mannose-binding lectin-associated serine protease-2 associated with increased risk of fever and neutropenia in pediatric cancer patients. Pediatr Infect Dis J 26:989–994
35. Peterslund NA, Koch C, Jensenius JC, Thiel S (2001) Association between deficiency of mannose-binding lectin and severe infections after chemotherapy. Lancet 358:637–638
36. Neth O, Hann I, Turner MW, Klein NJ (2001) Deficiency of mannose-binding lectin and burden of infection in children with malignancy: a prospective study. Lancet 358:614–618
37. Romani L (2004) Immunity to fungal infections. Nat Rev Immunol 4:1–23

38. Meier A, Kirschning CJ, Nikolaus T, Wagner H, Heesemann J, Ebel F (2003) Toll-like receptor (TLR) 2 and TLR4 are essential for Aspergillus-induced activation of murine macrophages. Cell Microbiol 5:561–570
39. Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F (2008) Polymorphisms in toll-like receptor genes and susceptibility to pulmonary aspergillosis. J Infect Dis 197:618–621
40. Bochud PY, Chien JW, Marr KA et al (2008) Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med 359:1766–1777
41. Ferwerda B, Ferwerda G, Plantinga TS et al (2009) Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 361:1760–1767
42. Plantinga TS, van der Velden WJ, Ferwerda B et al (2009) Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clin Infect Dis 49:724–732
43. Sainz J, Hassan L, Perez E et al (2007) Interleukin-10 promoter polymorphism as risk factor to develop invasive pulmonary aspergillosis. Immunol Lett 109:76–82
44. Sainz J, Perez E, Hassan L et al (2007) Variable number of tandem repeats of TNF receptor type 2 promoter as genetic biomarker of susceptibility to develop invasive pulmonary aspergillosis. Hum Immunol 68:41–50
45. Maschmeyer G, Haas A, Cornely OA (2007) Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 67:1567–1601
46. Panackal AA, Li H, Kontoyiannis DP et al (2010) Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. Clin Infect Dis 50:1588–1597
47. Comrie AC (2005) Climate factors influencing coccidioidomycosis seasonality and outbreaks. Environ Health Perspect 113:688–692
48. Park BJ, Sigel K, Vaz V et al (2005) An epidemic of coccidioidomycosis in Arizona associated with climatic changes, 1998–2001. J Infect Dis 191:1981–1987
49. Aisner J, Schimpff SC, Bennett JE, Young VM, Wiernik PH (1976) Aspergillus infections in cancer patients. Association with fireproofing materials in a new hospital. JAMA 235:411–412
50. Alberti C, Bouakline A, Ribaud P et al (2001) Relationship between environmental fungal contamination and the incidence of invasive aspergillosis in haematology patients. J Hosp Infect 48:198–206
51. Anaissie EJ, Stratton SL, Dignani MC et al (2002) Cleaning patient shower facilities: a novel approach to reducing patient exposure to aerosolized Aspergillus species and other opportunistic molds. Clin Infect Dis 35:E86–E88
52. Anaissie EJ, Stratton SL, Dignani MC et al (2002) Pathogenic Aspergillus species recovered from a hospital water system: a 3-year prospective study. Clin Infect Dis 34:780–789
53. Bouakline A, Lacroix C, Roux N, Gangneux JP, Derouin F (2000) Fungal contamination of food in hematology units. J Clin Microbiol 38:4272–4273
54. Hansen D, Blahout B, Benner D, Popp W (2008) Environmental sampling of particulate matter and fungal spores during demolition of a building on a hospital area. J Hosp Infect 70:259–264
55. Oren I, Haddad N, Finkelstein R, Rowe JM (2001) Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemoprophylaxis and institution of HEPA filters. Am J Hematol 66:257–262
56. Walsh TJ, Hiemenz J, Pizzo PA (1994) Evolving risk factors for invasive fungal infections–all neutropenic patients are not the same. Clin Infect Dis 18:793–798
57. Levine SJ (1992) An approach to the diagnosis of pulmonary infections in immunosuppressed patients. Semin Respir Infect 7:81–95
58. Pappagianis D (2001) Serologic studies in coccidioidomycosis. Semin Respir Infect 16:242–250
59. Goodman JS, Kaufman L, Koenig MG (1971) Diagnosis of cryptococcal meningitis. Value of immunologic detection of cryptococcal antigen. N Engl J Med 285:434–436

60. Wheat LJ (2006) Antigen detection, serology, and molecular diagnosis of invasive mycoses in the immunocompromised host. Transpl Infect Dis 8:128–139
61. Hachem RY, Kontoyiannis DP, Chemaly RF, Jiang Y, Reitzel R, Raad I (2009) Utility of galactomannan enzyme immunoassay and (1,3) beta-D-glucan in diagnosis of invasive fungal infections: low sensitivity for Aspergillus fumigatus infection in hematologic malignancy patients. J Clin Microbiol 47:129–133
62. Horiguchi Y (2004) The performance of (1, 3)-beta-D-glucan and Aspergillus galactomannan measurement for early diagnosis of invasive aspergillosis in patients with hematological diseases. Kansenshogaku Zasshi 78:566–573
63. Kawazu M, Kanda Y, Nannya Y et al (2004) Prospective comparison of the diagnostic potential of real-time PCR, double-sandwich enzyme-linked immunosorbent assay for galactomannan, and a (1→3)-beta-D-glucan test in weekly screening for invasive aspergillosis in patients with hematological disorders. J Clin Microbiol 42:2733–2741
64. Digby J, Kalbfleisch J, Glenn A, Larsen A, Browder W, Williams D (2003) Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. Clin Diagn Lab Immunol 10:882–885
65. Odabasi Z, Mattiuzzi G, Estey E et al (2004) Beta-D-glucan as a diagnostic adjunct for invasive fungal infections: validation, cutoff development, and performance in patients with acute myelogenous leukemia and myelodysplastic syndrome. Clin Infect Dis 39:199–205
66. Ostrosky-Zeichner L, Alexander BD, Kett DH et al (2005) Multicenter clinical evaluation of the (1→3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis 41:654–659
67. Pickering JW, Sant HW, Bowles CA, Roberts WL, Woods GL (2005) Evaluation of a (1→3)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol 43:5957–5962
68. Swanink CM, Meis JF, Rijs AJ, Donnelly JP, Verweij PE (1997) Specificity of a sandwich enzyme-linked immunosorbent assay for detecting Aspergillus galactomannan. J Clin Microbiol 35:257–260
69. Marr KA, Laverdiere M, Gugel A, Leisenring W (2005) Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis 40:1762–1769
70. Maertens J, Maertens V, Theunissen K et al (2009) Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis 49:1688–1693
71. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M (2001) Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood 97:1604–1610
72. Loeffler J, Hebart H, Brauchle U, Schumacher U, Einsele H (2000) Comparison between plasma and whole blood specimens for detection of Aspergillus DNA by PCR. J Clin Microbiol 38:3830–3833
73. Pham AS, Tarrand JJ, May GS, Lee MS, Kontoyiannis DP, Han XY (2003) Diagnosis of invasive mold infection by real-time quantitative PCR. Am J Clin Pathol 119:38–44
74. White PL, Linton CJ, Perry MD, Johnson EM, Barnes RA (2006) The evolution and evaluation of a whole blood polymerase chain reaction assay for the detection of invasive aspergillosis in hematology patients in a routine clinical setting. Clin Infect Dis 42:479–486
75. Eggimann P, Garbino J, Pittet D (2003) Epidemiology of Candida species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 3:685–702
76. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP (1999) Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 29:239–244
77. Jarvis WR (1995) Epidemiology of nosocomial fungal infections, with emphasis on Candida species. Clin Infect Dis 20:1526–1530

78. Nguyen MH, Peacock JE Jr, Morris AJ et al (1996) The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. Am J Med 100:617–623
79. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I (2008) The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. Cancer 112:2493–2499
80. Viscoli C, Girmenia C, Marinus A et al (1999) Candidemia in cancer patients: a prospective, multicenter surveillance study by the invasive fungal infection group (IFIG) of the European organization for research and treatment of cancer (EORTC). Clin Infect Dis 28:1071–1079
81. Anaissie EJ, Kontoyiannis DP, O'Brien S et al (1998) Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 129:559–566
82. Anttila VJ, Elonen E, Nordling S, Sivonen A, Ruutu T, Ruutu P (1997) Hepatosplenic candidiasis in patients with acute leukemia: incidence and prognostic implications. Clin Infect Dis 24:375–380
83. Pappas PG, Kauffman CA, Andes D et al (2009) Clinical practice guidelines for the management of candidiasis: 2009 update by the infectious diseases society of America. Clin Infect Dis 48:503–535
84. Cole GT, Halawa AA, Anaissie EJ (1996) The role of the gastrointestinal tract in hematogenous candidiasis: from the laboratory to the bedside. Clin Infect Dis 22(Suppl 2):S73–S88
85. Nucci M, Anaissie E, Betts RF et al (2010) Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 51:295–303
86. Suzuki K, Nakase K, Kyo T et al (2010) Fatal Trichosporon fungemia in patients with hematologic malignancies. Eur J Haematol 84:441–447
87. Girmenia C, Pagano L, Martino B et al (2005) Invasive infections caused by Trichosporon species and Geotrichum capitatum in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature. J Clin Microbiol 43:1818–1828
88. Martino P, Girmenia C, Venditti M et al (1990) Spontaneous pneumothorax complicating pulmonary mycetoma in patients with acute leukemia. Rev Infect Dis 12:611–617
89. Pagano L, Caira M, Fianchi L (2005) Pulmonary fungal infection with yeasts and pneumocystis in patients with hematological malignancy. Ann Med 37:259–269
90. Matsue K, Uryu H, Koseki M, Asada N, Takeuchi M (2006) Breakthrough trichosporonosis in patients with hematologic malignancies receiving micafungin. Clin Infect Dis 42:753–757
91. Bollee G, Sarfati C, Thiery G et al (2007) Clinical picture of Pneumocystis jiroveci pneumonia in cancer patients. Chest 132:1305–1310
92. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D (1992) Pneumocystis carinii pneumonia among patients without AIDS at a cancer hospital. JAMA 267:832–837
93. Pagano L, Fianchi L, Mele L et al (2002) Pneumocystis carinii pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. Br J Haematol 117:379–386
94. Roblot F, Godet C, Le Moal G et al (2002) Analysis of underlying diseases and prognosis factors associated with Pneumocystis carinii pneumonia in immunocompromised HIV-negative patients. Eur J Clin Microbiol Infect Dis 21:523–531
95. Ennishi D, Terui Y, Yokoyama M et al (2008) Increased incidence of interstitial pneumonia by CHOP combined with rituximab. Int J Hematol 87:393–397
96. Kamel S, O'Connor S, Lee N, Filshie R, Nandurkar H, Tam CS (2010) High incidence of Pneumocystis jirovecii pneumonia in patients receiving biweekly rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone. Leuk Lymphoma 51:797–801
97. Mitchell TG, Perfect JR (1995) Cryptococcosis in the era of AIDS–100 years after the discovery of Cryptococcus neoformans. Clin Microbiol Rev 8:515–548

98. Kontoyiannis DP, Peitsch WK, Reddy BT et al (2001) Cryptococcosis in patients with cancer. Clin Infect Dis 32:E145–E150
99. Park SY, Kim SH, Choi SH et al (2010) Clinical and radiological features of invasive pulmonary aspergillosis in transplant recipients and neutropenic patients. Transpl Infect Dis 12:309–315
100. Caillot D, Casasnovas O, Bernard A et al (1997) Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol 15:139–147
101. Caillot D, Couaillier JF, Bernard A et al (2001) Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. J Clin Oncol 19:253–259
102. Patterson TF, Kirkpatrick WR, White M et al (2000) Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus study group. Medicine (Baltimore) 79:250–260
103. Boes B, Bashir R, Boes C, Hahn F, McConnell JR, McComb R (1994) Central nervous system aspergillosis. Analysis of 26 patients. J Neuroimaging 4:123–129
104. Walsh TJ, Hier DB, Caplan LR (1985) Aspergillosis of the central nervous system: clinicopathological analysis of 17 patients. Ann Neurol 18:574–582
105. Ashdown BC, Tien RD, Felsberg GJ (1994) Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: CT and MR imaging findings. AJR Am J Roentgenol 162:155–159
106. Yamada K, Shrier DA, Rubio A et al (2002) Imaging findings in intracranial aspergillosis. Acad Radiol 9:163–171
107. Viscoli C, Machetti M, Gazzola P et al (2002) Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 40:1496–1499
108. Segal BH, Bow EJ, Menichetti F (2002) Fungal infections in nontransplant patients with hematologic malignancies. Infect Dis Clin North Am 16(4):935–964
109. Talbot GH, Huang A, Provencher M (1991) Invasive aspergillus rhinosinusitis in patients with acute leukemia. Rev Infect Dis 13:219–232
110. Wiederhold NP, Lewis RE, Kontoyiannis DP (2003) Invasive aspergillosis in patients with hematologic malignancies. Pharmacotherapy 23:1592–1610
111. Roden MM, Zaoutis TE, Buchanan WL et al (2005) Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 41:634–653
112. Malani AN, Kauffman CA (2007) Changing epidemiology of rare mould infections: implications for therapy. Drugs 67:1803–1812
113. Horger M, Hebart H, Schimmel H et al (2006) Disseminated mucormycosis in haematological patients: CT and MRI findings with pathological correlation. Br J Radiol 79:e88–e95
114. Kara IO, Tasova Y, Uguz A, Sahin B (2009) Mucormycosis-associated fungal infections in patients with haematologic malignancies. Int J Clin Pract 63:134–139
115. Perfect JR (2005) Treatment of non-Aspergillus moulds in immunocompromised patients, with amphotericin B lipid complex. Clin Infect Dis 40(Suppl 6):S401–S408
116. Greenberg RN, Mullane K, van Burik JA et al (2006) Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 50:126–133
117. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP (2006) Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis 42:e61–e65
118. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS (2009) Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis 48:1743–1751
119. Raad I, Tarrand J, Hanna H et al (2002) Epidemiology, molecular mycology, and environmental sources of Fusarium infection in patients with cancer. Infect Control Hosp Epidemiol 23:532–537

120. Campo M, Lewis RE, Kontoyiannis DP (2010) Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998–2009. J Infect 60:331–337
121. Bodey GP, Boktour M, Mays S et al (2002) Skin lesions associated with Fusarium infection. J Am Acad Dermatol 47:659–666
122. Jossi M, Ambrosioni J, Macedo-Vinas M, Garbino J (2010) Invasive fusariosis with prolonged fungemia in a patient with acute lymphoblastic leukemia: case report and review of the literature. Int J Infect Dis 14:e354–e356
123. Guarro J, Kantarcioglu AS, Horre R et al (2006) Scedosporium apiospermum: changing clinical spectrum of a therapy-refractory opportunist. Med Mycol 44:295–327
124. Ochiai N, Shimazaki C, Uchida R et al (2003) Disseminated infection due to Scedosporium apiospermum in a patient with acute myelogenous leukemia. Leuk Lymphoma 44:369–372
125. Simarro E, Marin F, Morales A, Sanz E, Perez J, Ruiz J (2001) Fungemia due to Scedosporium prolificans: a description of two cases with fatal outcome. Clin Microbiol Infect 7:645–647
126. Tintelnot K, Just-Nubling G, Horre R et al (2009) A review of German Scedosporium prolificans cases from 1993 to 2007. Med Mycol 47:351–358
127. Gilgado F, Serena C, Cano J, Gene J, Guarro J (2006) Antifungal susceptibilities of the species of the Pseudallescheria boydii complex. Antimicrob Agents Chemother 50:4211–4213
128. Ben-Ami R, Lasala PR, Lewis RE, Kontoyiannis DP (2010) Lack of galactomannan reactivity in dematiaceous molds recovered from cancer patients with phaeohyphomycosis. Diagn Microbiol Infect Dis 66:200–203
129. Adderson EE (2004) Histoplasmosis in a pediatric oncology center. J Pediatr 144:100–106
130. Ashbee HR, Evans EG, Viviani MA et al (2008) Histoplasmosis in Europe: report on an epidemiological survey from the European confederation of medical mycology working group. Med Mycol 46:57–65
131. Kauffman CA (2002) Endemic mycoses in patients with hematologic malignancies. Semin Respir Infect 17:106–112
132. Bates DW, Su L, Yu DT et al (2001) Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis 32:686–693
133. Wingard JR, Kubilis P, Lee L et al (1999) Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. Clin Infect Dis 29:1402–1407
134. Arathoon EG, Gotuzzo E, Noriega LM, Berman RS, DiNubile MJ, Sable CA (2002) Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiases. Antimicrob Agents Chemother 46:451–457
135. Kuse ER, Chetchotisakd P, da Cunha CA et al (2007) Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 369:1519–1527
136. Reboli AC, Rotstein C, Pappas PG et al (2007) Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 356:2472–2482
137. Walsh TJ, Teppler H, Donowitz GR et al (2004) Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 351:1391–1402
138. Marr KA, Boeckh M, Carter RA, Kim HW, Corey L (2004) Combination antifungal therapy for invasive aspergillosis. Clin Infect Dis 39:797–802
139. Singh N, Limaye AP, Forrest G et al (2006) Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation 81:320–326
140. Walsh TJ, Anaissie EJ, Denning DW et al (2008) Treatment of aspergillosis: clinical practice guidelines of the infectious diseases society of America. Clin Infect Dis 46:327–360

141. Herbrecht R, Denning DW, Patterson TF et al (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415
142. Walsh TJ, Pappas P, Winston DJ et al (2002) Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 346:225–234
143. Trifilio S, Pennick G, Pi J et al (2007) Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. Cancer 109:1532–1535
144. Almyroudis NG, Sutton DA, Fothergill AW, Rinaldi MG, Kusne S (2007) In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antimicrob Agents Chemother 51:2587–2590
145. Lass-Florl C, Mayr A, Perkhofer S et al (2008) Activities of antifungal agents against yeasts and filamentous fungi: assessment according to the methodology of the European committee on antimicrobial susceptibility testing. Antimicrob Agents Chemother 52:3637–3641
146. Pfaller MA, Messer SA, Hollis RJ, Jones RN (2002) Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY antimicrobial surveillance program, 2000. Antimicrob Agents Chemother 46:1032–1037
147. Anstead GM, Corcoran G, Lewis J, Berg D, Graybill JR (2005) Refractory coccidioidomycosis treated with posaconazole. Clin Infect Dis 40:1770–1776
148. Catanzaro A, Cloud GA, Stevens DA et al (2007) Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. Clin Infect Dis 45:562–568
149. Raad II, Hachem RY, Herbrecht R et al (2006) Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. Clin Infect Dis 42:1398–1403
150. Walsh TJ, Raad I, Patterson TF et al (2007) Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 44:2–12

# Advances in the Management of Viral Infections

Jack W. Hsu and John R. Wingard

**Abstract**

Viral infections are common in cancer patients. The risk and severity of infection are influenced by patient, disease, treatment, and viral factors. Severe viral infections are more likely to occur in treatment regimens that are more immunosuppressive. Historically, the most frequent severe infections have been due to herpesviruses, but more recently, other pathogens, especially community respiratory and hepatitis viruses, have received increasing attention as major viral pathogens in cancer patients. Because of the new diagnostic assays and the introduction of better therapeutic options, knowledge of viral infections is important in optimizing antineoplastic therapies.

**Keywords**

Herpesviruses · Viral pathogens · Cytoreductive regimens · Hematopoietic cell transplantation · Neoplastic diseases · Antineoplastic diseases · Purine analogs · Monoclonal antibodies

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## Contents



## 1 Introduction

The immunocompromised cancer patient is vulnerable to a wide spectrum of viral pathogens (Table 1). There has been an increasing recognition for viruses as clinically important pathogens in cancer patients during the past two decades. In part, this is attributable to improved diagnostic techniques to better recognize viral pathogens as causes for illness. In part, this is also due to the increasing dose intensity of cytoreductive regimens used to control cancer, the increasing use of hematopoietic cell (also known as bone marrow) transplantation (HCT) in the treatment for neoplastic diseases, improvements in supportive care that permit patients to survive bacterial and fungal infections that in the past might have led to death before viral illness became manifest, and the introduction of antineoplastic agents (including purine analogs and monoclonal antibodies) that have potent immunosuppressive properties. Thus, there are greater numbers of highly immunosuppressed patients with severe compromise in cell-mediated immunity, the major host defense against most viral pathogens.

Not only are viral infections increasingly recognized today, but a wider array of pathogens have been noted to cause complications of cancer therapy that in the past have been attributable to toxicities. Pneumonitis, cystitis, myelosuppression, mucositis, enteritis, and hepatitis are examples of syndromes that in the past have been attributable to toxicities from cytoreductive regimens, or in the case of HCT patients, graft-versus-host disease (GVHD) (Table 2); in a number of instances, however, it is clear that viral pathogens are either sole causes for the syndrome, or there is an interplay between viral pathogenesis, tissue damage, and disordered immune responses to the virus in the development, severity, and type of manifestations of the syndrome.

**Table 1** Viral pathogens in immunocompromised cancer patients

| |
|---|
| *Herpesviruses* |
| Herpes simplex type 1 |
| Herpes simplex type 2 |
| Cytomegalovirus |
| Varicella zoster virus |
| Epstein–Barr virus |
| Human herpesvirus 6 |
| Human herpesvirus 8 |
| *Hepatitis viruses* |
| Hepatitis A |
| Hepatitis B |
| Hepatitis C |
| Non-A, non-B, non-C hepatitis |
| *Adenoviruses* |
| *Intestinal viruses* |
| Rotavirus |
| Norwalk virus |
| Adenoviruses |
| Astroviruses |
| Coxsackieviruses |
| Caliciviruses |
| *Respiratory viruses* |
| Respiratory syncytial virus |
| Influenza |
| Parainfluenza |
| Metapneumovirus |
| *Papovaviruses* |
| JC |
| BK |
| Human papillomavirus |
| *Retroviruses* |
| HTLV1 |
| HIV |

**Table 2** Syndromes due to viral pathogens often attributed to treatment toxicity

| Syndrome | Patient population | Viral pathogen |
|---|---|---|
| Oral mucositis | Lymphoma, leukemia, HCT | HSV |
| Esophagitis | Lymphoma, leukemia, HCT | HSV, CMV |
| Hepatopathy | HCT | Hepatitis viruses, adenovirus, CMV, VZV |
| Myelosuppression | HCT | CMV, HHV-6 |
| Interstitial pneumonia | HCT | CMV, HHV-6, adenovirus. RSV, influenza, parainfluenza, metapneumovirus |
| Hemorrhagic cystitis | HCT | BK virus, adenovirus, CMV |
| Diarrhea | Leukemia, HCT | CMV, adenovirus, rotavirus, coxsackie |
| Fever of unknown etiology | HCT | CMV, EBV, HHV-6 |
| Treatment-related lymphoma | HCT | EBV |

*HCT* hematopoietic cell transplantation, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus *HHV-6* human herpesvirus-6, *HSV* herpes simplex virus, *RSV* respiratory syncytial virus

The increased recognition for viral pathogenicity has fortunately been accompanied by the introduction of new diagnostics and therapeutics. Several nucleoside analogs, biologic agents, and new vaccines all offer the clinician tools to prevent or reduce the morbidity associated with these organisms. Thus, prompt diagnosis of these potentially treatable syndromes and an understanding of how to use these new therapeutic modalities are important for optimal management of the cancer patient.

## 2 Herpesviruses

The most frequently recognized viral pathogens in cancer patients are members of the herpesvirus family. These have long been recognized to be potential causes of serious and life-threatening illness. Patients receiving therapy for lymphoma, leukemia, and those undergoing bone marrow transplantation are especially susceptible. The human herpesviruses that cause clinically recognizable infection are herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpes virus type 6 (HHV-6). These DNA viruses are prevalent in the normal population. Initial infection often occurs early in life, is mild, is self-limited, and generally requires no therapy. After resolution of the primary infection, the virus typically establishes a latent infection that can be life long. HSV and VZV reside latently in sensory nerve ganglia; leukocytes harbor CMV, EBV, and

HHV-6. With compromises in cell-mediated immunity, reactivation can occur and lead to subsequent morbidity. In the nonimmunocompromised patient, reactivation can also occur but is generally associated with milder symptomatology than with the primary infection. In contrast, in immunocompromised patients, reactivation is both more likely to occur and more apt to lead to serious morbidity. The severity of manifestations tends to correlate with the degree of compromised immunity [1].

## 2.1 Herpes Simplex Virus

The lesions from HSV-1 infection are typically orofacial. Although labial vesicular lesions are common manifestations of active infection in nonimmunocompromised patients, they may be absent in compromised cancer patients after chemotherapy. Intraoral mucosal ulcerations may be the sole manifestation [2]. These lesions can be indistinguishable from the tissue damage that results from chemotherapy or radiotherapy. Thus, a pathogenic role for HSV in stomatitis has been often missed in the past; indeed, the reactivation of HSV and the occurrence of tissue damage from cytoreductive treatment often occur concomitantly, and these can result in severe oral mucositis. Most infections are due to reactivation in HSV seropositive patients. The likelihood of reactivation is a reflection of the intensity of the treatment: 70–80 % after HCT, 60–70 % after induction therapy for acute myelogenous leukemia, 40–50 % during treatment for lymphoma, and 10–25 % for patients undergoing various treatment regimens for solid tumors [3].

HSV-2 infection in cancer patients is less problematic because the virus is less common in the general population. However, reactivation can occur at high rates in patients who harbor latent HSV-2, and severe manifestations can result, especially, in patients with hematologic malignancies and HCT recipients. Genital lesions (especially ulcerations) are frequent manifestations, but extragenital vesicles, in the gluteal and anal regions, can also occur.

Although oral and genital mucosas are the major sites of HSV lesions, extension to the esophagus, urethra, bladder, and tracheal mucosa may also occur. Endoscopic biopsy may be necessary to distinguish a viral etiology from fungal or other possible causes. In profoundly immunocompromised patients, dissemination and involvement of visceral tissues can occasionally occur [4].

Culture of material from an infected lesion can confirm the diagnosis. Rapid detection methods using antigen detection or polymerase chain reaction (PCR) procedures offer quicker and easier alternatives [5–7]. Cytologic examination of cells removed from infected lesions using the Tzanck procedure can demonstrate multinucleated cells but do not permit distinction between HSV and VZV [8]. Serologic tests can be helpful in identifying patients harboring latent virus (and thus, susceptible to reactivation) but are of no value in documenting acute infection.

Acyclovir, a purine analog, is very active against HSV-1 and HSV-2 and has been shown in numerous clinical trials to be an effective treatment for HSV infection [9–13]. Several oral and intravenous regimens have been evaluated and

found to be effective and suitable for different clinical situations. Shortening of the time of viral shedding, time to cessation of pain, and time to healing of lesions have been demonstrated in various studies. Valacyclovir is the L-valyl ester of acyclovir and has excellent bioavailability, providing high blood concentrations of acyclovir, and approximating the levels achieved with intravenous acyclovir [14–16].

Acyclovir has also been shown to be effective as prophylaxis [17–21]. For patients at high risk of HSV reactivation and who are susceptible to serious morbidity, prophylaxis may be preferable to treatment [22–25]. In adult patients undergoing intensive induction therapy for acute leukemia and in patients undergoing HCT who are HSV seropositive, the high reactivation rate (60–70 %) and potentially severe manifestations provide justification for prophylaxis. Indeed, the emergence of drug resistance appears to be less common where acyclovir is used prophylactically than when used as treatment for established infections where repetitive courses of acyclovir may be necessary and the frequency of drug resistance increases with each subsequent treatment episode [24–26].

The emergence of acyclovir resistance has been noted in some patients with uncontrolled HIV infection. Resistance is less frequent in patients receiving cancer therapy but appears most frequent in HCT recipients who have received repetitive courses of acyclovir for repeated infection episodes. Acyclovir resistance usually is conferred by mutations in the genes encoding for the viral-specified thymidine kinase (TK) [27, 28]. This viral-encoded TK is necessary for acyclovir phosphorylation, and without it, little drug is converted to its active form. Thus, acyclovir and other nucleoside analogs that similarly rely on TK-mediated phosphorylation for their activity are inactive against acyclovir-resistant mutants.

Foscarnet is a pyrophosphate analog that directly inhibits viral DNA polymerase and does not require thymidine kinase for its activity. For patients with acyclovir-resistant HSV, Foscarnet is an alternative [29, 30].

## 2.2 Cytomegalovirus

CMV, another member of the herpesvirus family, infects a substantial proportion of the general population. Infection is generally asymptomatic in the nonimmunocompromised host, and although reactivation is frequent in immunocompromised patients, it rarely causes serious manifestations, except in highly immunocompromised patients such as HCT recipients, solid organ transplant recipients, and patients with the acquired immunodeficiency syndrome. Leukocytes are a reservoir of latent virus; thus, blood component transfusions as well as organ (including marrow and peripheral blood progenitor cells) grafts can be sources of viral transmission. CMV can cause fever, hepatitis, pneumonitis, leukopenia, thrombocytopenia, esophagitis, enterocolitis, retinitis, a mononucleosis-like syndrome, and occasionally central nervous system manifestations. In HCT patients, the most common and severe manifestation is interstitial pneumonitis, which if untreated results in death in 80–90 % of cases. Enterocolitis is less common but can represent a cause of severe diarrhea in the transplant recipient and

appears to be increasing in frequency. Chorioretinitis, a common clinical manifestation of CMV infection in HIV-infected patients, is uncommon in HCT recipients. Myelosuppression, a frequent accompaniment of cancer therapies, can have a variety of etiologies but CMV is one treatable cause [31–33].

Viremia can be diagnosed by culture [34, 35], but rapid diagnostic assays using detection of the pp65 antigen or CMV DNA or less commonly pp67 mRNA by quantitative PCR have largely replaced cultural assays [36–44], and such assays are capable of detecting virus 1–2 weeks earlier than culture. In tissue or cytologic specimens, the virus can be suspected by intracellular inclusions and confirmed by immunofluorescent assays or PCR.

Ganciclovir, a nucleoside analog structurally similar to acyclovir, is very active against CMV. It is effective in the treatment and in the prevention of CMV infection in transplant recipients. Ganciclovir exerts a potent antiviral effect in HCT patients with CMV pneumonitis, with a marked reduction in viral titers in infected tissue. However, when ganciclovir was used alone, there was no corresponding clinical benefit and most patients succumbed to relentless ventilatory failure [45]. Several studies have shown that when ganciclovir is used in combination with immunoglobulin both antiviral and clinical benefits ensue [46–48]. Thus, the mortality rate of 80–90 % from CMV pneumonitis has been reduced to approximately 50 %. For gastrointestinal CMV infection, ganciclovir alone and the combination of ganciclovir plus immunoglobulin have not been shown to be conclusively effective [49, 50], but ganciclovir alone is generally used. Foscarnet and cidofovir are alternative therapies to ganciclovir.

Ganciclovir has also been evaluated as prophylaxis in allogeneic HCT patients who are seropositive and thus at high risk of CMV disease [51, 52]. This approach has been found to be highly effective in reducing the risk of serious morbidity from CMV. Unfortunately, ganciclovir's side effects, especially myelosuppression, have led to episodes of neutropenia and bacteremia; thus, survival has not been appreciably improved. An alternative strategy, frequently referred to as early "preemptive therapy," has also been explored [53, 54]. In this approach, patients undergo surveillance screening for viral reactivation. Those patients found to have active infection are then treated with ganciclovir to prevent the subsequent development of clinical manifestations, which generally do not occur for several days to weeks after reactivation. Screening is generally done weekly on specimens of blood. Oral ganciclovir, found to be potentially useful as maintenance therapy in HIV-infected patients [55, 56], is not useful because of poor bioavailability, low serum levels, and the risk of emergence of resistance. Valganciclovir, an oral prodrug of ganciclovir, achieves high blood concentrations of ganciclovir and has also been shown to be effective in preemptive therapy [57–61]. Foscarnet can be used alternatively [62].

Several reviews have discussed the advantages and disadvantages of prophylaxis versus preemptive therapy [63–66]. In general, ganciclovir prophylaxis is more effective in preventing CMV disease, with fewer breakthrough episodes of CMV disease, while early preemptive ganciclovir is associated with fewer episodes of neutropenia and spares a sizable proportion of patients (in which

reactivation does not occur) from the cost and toxicity of ganciclovir. With the introduction into clinical use of PCR and antigen detection assays, it can be expected that there will be fewer failures associated with the preemptive therapy approach. Although initially preemptive therapy was continued to the end of the risk period (typically 100–120 days), today, shorter courses have been shown to be effective. Many centers administer therapy for a minimum of 2 weeks and discontinue once the viremia has resolved. Foscarnet and, to a lesser extent, cidofovir have also been used as preemptive therapy for CMV; however, issues with renal toxicity have limited cidofovir's usefulness in the transplant population [67]. Following discontinuation of preemptive therapy, surveillance should continue since viremia recurs in many patients. If viremia recurs, reinstitution of preemptive therapy should be done.

Resistance to ganciclovir has occasionally been encountered in HIV-infected patients on chronic maintenance dose schedules [68] but is rare in cancer patients. Resistance occurs most commonly by mutations in the UL97 gene region [69], but mutations in DNA polymerase, the U54 gene, can also occur. Foscarnet can be used for most ganciclovir-resistant viral mutants [70].

Acyclovir has not been clinically useful in the treatment for CMV disease. However, several studies in both HCT and solid organ transplant recipients have indicated that prophylaxis acyclovir (or valacyclovir) is effective in reducing the risk of developing CMV disease [71–73]. The explanation for this is not clear, but it would appear that a low level of acyclovir phosphorylation occurs despite the fact that CMV does not encode for a viral-specific TK, the enzyme that most avidly phosphorylates acyclovir to its active metabolites. Thus, low levels of phosphorylated acyclovir may be effective when the viral burden is low, although not efficacious in instances in which the viral burden would be high (the treatment scenario).

For patients who are CMV seronegative, infection can occur through acquisition of virus from blood transfusion or organ donation because leukocytes are a reservoir of latent virus. Accordingly, use of only CMV-seronegative blood products is an effective strategy in preventing CMV infection and disease [74–77]. Unfortunately, a substantial proportion of healthy blood donors are CMV-seropositive and harbor potentially transmissible virus. Accordingly, significant costs are incurred in the provision of CMV-negative blood products by blood banks. An alternative approach is the use of leukocyte filters, which are capable of eliminating most leukocytes that are present in erythrocyte and platelet products [78, 79]. A controlled trial demonstrated that this approach is almost as effective as CMV screening [79] and this is an option if suitable CMV-negative products are not available. This may also have the added advantage of reducing the risk of alloimmunization, another concern for patients who receive multiple blood products.

CMV hyperimmunoglobulin and plasma have also been shown to reduce the risk of CMV disease in the HCT recipient [80–85]. Because the antiviral potency of CMV immunoglobulin appears modest in studies in which it was used for treatment for CMV disease, speculation has been raised as to the mechanism of its

action; it has been suggested that it may be acting more as an immunomodulatory agent affecting antigen presentation or immune responses to CMV antigens rather than as an antiviral agent. Indeed, conventional lots of immunoglobulin not specifically chosen for high antiviral titers against CMV seem to be comparable with high-titer lots of immunoglobulin in preventing CMV disease. It should be noted that most studies have been conducted in CMV-seronegative patients. Only one study conducted in seropositive patients has shown a benefit, and the benefit was modest [85]. It is generally not used today because of its high cost and the advent of antiviral drug alternatives for prevention. An inactivated CMV vaccine is under study in HCT patients.

## 2.3 Varicella Zoster Virus

VZV infection is highly prevalent in the general population. Cancer treatment regimens are associated with a risk of reactivation that is, compared with the nonimmunocompromised host, slightly greater in solid tumor patients, substantially greater in patients treated with hematologic malignancies, and greatest in patients undergoing HCT. The most common manifestation is a dermatomal vesicular eruption, which may be preceded by a prodrome of localized pain and pruritus. Postherpetic neuralgia can persist for many months, especially in older individuals. Dissemination only occasionally occurs, but with highly immunocompromised patients such as allogeneic HCT recipients, dissemination can occur in up to 30–40 % of individuals [86, 87]. Cutaneous dissemination, the most common form of spread, can be complicated by bacterial superinfection. Visceral dissemination can be life threatening, and VZV pneumonia is the most common lethal manifestation. Fulminant hepatitis and pancreatitis are rare manifestations that can occur even in the absence of or before onset of cutaneous lesions [88]. It can be life threatening if not recognized and if treatment is not initiated promptly.

Acyclovir is very active against VZV and has become the treatment for choice [89–93]. Higher concentrations of acyclovir are required to control VZV than HSV. Because of acyclovir's poor bioavailability, intravenous administration is the preferred method of treatment in immunocompromised patients, or alternatively valacyclovir. Although high-dose oral acyclovir, valacyclovir, and famciclovir have shown efficacy in nonimmunocompromised hosts, they have not been well studied in the immunocompromised host. Acyclovir-resistant VZV has only been rarely encountered to date [94]. Foscarnet can be used for resistant pathogens [95]. Immunoglobulin can be given to susceptible immunocompromised patients if exposure is recognized within 3–4 days [96]. An attenuated vaccine has been found to be safe and protective for susceptible children with acute lymphoblastic leukemia [97–100]. Safety has not been evaluated in the early convalescent HCT period [101, 102]. An inactivated VZV vaccine is under study in HCT patients.

## 2.4 Epstein–Barr Virus

EBV, the cause of infectious mononucleosis in the nonimmunocompromised host, only occasionally causes morbidity in the immunocompromised host despite high rates of reactivation. However, in transplant recipients, severe morbidity can result from a mononucleosis-like syndrome or a variety of lymphoproliferative disorders. These can range from polyclonal lymphadenopathy to rapidly progressive monoclonal malignancy. Although these lymphoproliferative diseases are clearly EBV associated, molecular techniques have demonstrated mutations of oncogenes such as C-*myc* and tumor-suppressor genes, which occur in the transition from benign to malignant disease [103, 104]. The risk of EBV-associated lymphoproliferative diseases correlates with the degree of immunodeficiency. The use of multiple immunosuppressive agents, especially anti-thymocyte globulin, the use of T-cell-depletion techniques, the use of mismatched donors in the HCT setting, and the occurrence of multiple rejection episodes in the solid organ transplant setting [105], or severe graft-versus-host disease in the HCT setting [106] all contribute to the risk of these disorders [107, 108]. Although antiviral agents such as acyclovir and ganciclovir are active in vitro against EBV, their effectiveness in treating EBV-associated lymphoproliferative diseases has been disappointing in most cases. Once mutations in oncogenes and tumor-suppressor genes occur, most treatment approaches have been largely ineffectual. The treatment approach that has been most fruitful is reduction in immunosuppressive therapy, which can effect a remission in the benign lymphoproliferative disorders. Rituximab or anti-B cell lymphoma chemotherapy regimens are also usually administered. Serial monitoring for EBV viremia in high-risk patients has been advocated by some. In high-risk patients, weekly monitoring of EBV viremia with preemptive use of rituximab in patients with high levels of circulating viral DNA may be effective in preventing the subsequent development of EBV-associated lymphoma [109].

## 2.5 Human Herpesvirus Types 6 and 8

HHV-6 rarely causes clinical illness in the normal population despite being very prevalent. A self-limited eruption, exanthem subitum, has been noted in children. HHV-6 has been implicated as a potential pathogen causing some cases of interstitial pneumonitis, several CNS syndromes, rash, and sometimes HHV-6 appears to be a cause of myelosuppression (especially thrombocytopenia) in HCT recipients [110–114]. Ganciclovir, cidofovir, Foscarnet, and several other nucleoside analogs are active against HHV-6 in vitro, but to date, there are no clinical trials to establish clinical efficacy [115, 116] (see chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients).

HHV-8 is the causative agent of Kaposi's sarcoma. HHV-8 disease is infrequent in cancer and HCT patients. Treatment and prevention strategies have not been adequately evaluated for HHV-8 disease.

## 3 Immune Responses to the Herpesvirus Family

Both humoral and cellular immune responses occur in response to infection by all of the herpesviruses. The immune responses, felt to be most important in the control of active infection, are the cytotoxic response mediated by T lymphocytes or natural killer (NK) cells. This has been most convincingly demonstrated in CMV infection [117–119]. In the HCT recipient, resolution of active infection occurs only with the development of cytotoxic T cell or NK responses. In the absence of the development of these responses, most patients succumb from infection. In HCT recipients with GVHD, the orderly development of cytotoxic responses may be severely impaired and patients are at much greater risk of more frequent and more severe CMV infection and illness. Similarly, patients who are the recipients of T-lymphocyte-depleted bone marrow grafts are unable to mount robust T-cell responses and are similarly more susceptible to more frequent and severe CMV infection and disease. These observations have led to consideration of cloning cytotoxic T cells (CTL) with anti-CMV activity and expanding them ex vivo for use as lymphocyte transfusions to bolster host immunity in an attempt to prevent severe CMV disease [120–123]. Clinical trials are currently under way.

EBV-specific cytotoxic T-cell precursors are more frequent in the circulation than CMV-specific CTL precursors. Buffy-coat transfusions have been successfully used in the treatment for EBV-associated lymphoproliferative disorders in transplant recipients without the need for ex vivo clonal expansion [124]. These approaches to adoptive transfer of cellular immunity appear quite promising for preemptive therapy as well [125–127].

Bolstering the host immunity through the use of viral vaccines has been hampered by the lack of safe and highly immunogenic vaccines. A live-attenuated varicella vaccine is useful in children with acute leukemia (as noted earlier); however, it have been felt to be too risky for use in the HCT setting, except in patients two or more years after transplant without active GVHD. Attenuated CMV vaccines have been tested in clinical trials in solid organ transplants, but have been similarly felt to be too risky in the HCT setting. Inactivated CMV and VZV vaccines are being evaluated in HCT patients.

## 4 Hepatitis Viruses

The hepatitis viruses are a heterogeneous group of RNA (hepatitis A and C) and DNA (hepatitis B) pathogens. The portal of entry for hepatitis A is generally the enteric route, with transmission by fecal–oral contact, while for hepatitis B and C, sexual and blood transmission are the primary routes of acquisition. Recognition for the potential of transmission through blood products and the development of screening tests have led to a marked reduction in transmission of hepatitis B and C.

For cancer patients who are seropositive for hepatitis B and C prior to treatment, the likelihood of reactivation and disease progression is related to viral and patient treatment factors. Patients with evidence of a high viral load (DNA/RNA in blood) and those receiving more immunosuppressive therapies (e.g., lymphoma and HCT patients) are at greater risk. Accordingly, patients should be screened for prior hepatitis prior to antineoplastic chemotherapy or HCT.

Inactivated hepatitis A and hepatitis B vaccines have been found to be safe and highly immunogenic. Hepatitis B immunization is recommended for seronegative patients. Immunoglobulin can be protective for those who must come in close contact with infected individuals to reduce the risk of infection. After exposure, immunoglobulin can also be efficacious against hepatitis A and B.

For patients with prior infection with hepatitis B, reactivation is likely with immunosuppressive chemotherapy regimens and the risk is greater after more highly immunosuppressive therapies and in patients with higher viral loads before therapy. Mild elevations of transaminases are most common, but severe, even fatal hepatitis can occur in 5–10 % of cases [128]. Lamivudine given prophylactically is highly effective in preventing reactivation, flares of hepatitis, and fewer antineoplastic treatment delays due to liver complications and should be given to patients with circulating HBV DNA [129]. For patients without circulating HBV DNA but with serologic evidence of prior infection (e.g., presence of hepatitis B core antibody), either close monitoring for reactivation in less intensively treated patients or lamivudine prophylaxis in more intensively treated patients should be considered. The optimal duration of lamivudine is not known. Since hepatic injury often occurs (or peaks) with HBV infection at the time of immune reconstitution due to the pathologic effects of the immune response, lamivudine should be continued until immune reconstitution has occurred. Experts recommend its continuation for a minimum of six months after completion of chemotherapy or immunosuppressive therapy [130, 131]. Resistance to lamivudine can occur, especially in patients with actively replicating virus receiving long-term therapy [132]. Other antivirals such as adefovir or entecavir are acceptable alternatives, but there is to date only limited experience with these.

For patients with prior hepatitis C, chronic infection is typical and elevated transaminases may wax and wane during chemotherapy or after HCT. After HCT, HCV infection increases the risk of hepatic veno-occlusive disease; alternatively, hepatic abnormalities may be most prominent several months after immunosuppression is stopped. The risk of late cirrhosis years later is also increased. The combination of pegylated interferon plus ribavirin is the most effective therapy for HCV infection. Genotype 1 virus responds less well to therapy compared with genotypes 2 and 3. Because of myelosuppression and the concern for provoking or worsening GVHD after HCT, treatment is generally delayed if possible until after immunosuppressive therapy is completed. The magnitude and durability of clinical benefit have been debated. Generally, early treatment after transplant is not necessary or advisable due to the toxicities of the treatment. Much later, after the patient has completed immunosuppressive therapy, the presence of chronic active hepatitis may alter the risk benefit balance [133].

A hematopoietic graft from a seropositive individual has the potential for transmitting hepatitis B or C to the recipient. Different reports have suggested different rates of transmission and different degrees of severity of illness in the recipient of such transmission [134]. Donors who have circulating viral RNA/DNA are at higher risk of transmitting virus than those who are seropositive but not viremic. Donors who are hepatitis seropositive should be excluded if possible. If they must be used, they should be treated with antiviral therapy if time permits to reduce the risk of transmission. Donors who are HBV DNA positive should be treated with lamivudine [131] to reduce the likelihood of transmission. Adoptive transfer of immunity to hepatitis B in the HCT setting from an immune donor may be a possible option for some patients [135]. Consideration can be given for treatment for hepatitis C donors with pegylated interferon and ribavirin.

## 5 Adenovirus

Adenovirus is a viral pathogen capable of causing respiratory illness, conjunctivitis, gastroenteritis, interstitial pneumonitis, and hepatitis. Type 11 has been associated with hemorrhagic cystitis. Adenovirus isolation is noted in 5 % of all allogeneic HCT recipients. Illness ensues in approximately 20 % of infected individuals. Types 1, 5, and 7 appear to be the most common types causing invasive disease, which can be fatal in approximately half of cases. HCT patients who are the recipients of unrelated donor grafts, mismatched grafts, cord blood, or grafts in which T-cell depletion has been performed, younger-aged patients, and those given total body irradiation appear to be at greater risk [136, 137]. Currently, there is no known effective antiviral therapy. Cidofovir is active against adenovirus in vitro and case series suggest clinical activity, although there are no controlled clinical trials. Ribavirin also has some activity, but treatment responses have been inconstant. Since high-level viremia is often a harbinger of subsequent development of invasive disease, some centers monitor viremia in high-risk cord blood or haploidentical transplant recipients on a weekly basis and initiate cidofovir preemptively if high-titer viremia develops [138].

## 6 Intestinal Viruses

Outbreaks of a variety of enteric pathogens occur in the community with seasonal variation. Immunocompromised patients can become infected during these community outbreaks. Common pathogens include coxsackievirus, rotavirus, the Norwalk agent, caliciviruses, and astroviruses. The allogeneic HCT recipient is especially vulnerable to severe, even life-threatening, and diarrheal illness. There are no effective antiviral therapies. Electrolyte and fluid replacement are important adjunctive measures. Immunoglobulin given orally has been suggested as a treatment for these illnesses, but adequate clinical trials are lacking.

## 7 Community Respiratory Viruses

Respiratory syncytial virus (RSV), influenza, and parainfluenza viruses are frequent causes of upper- and lower-respiratory-tract illness. Transmission is frequent in the community and often is the source of infection in immunocompromised cancer patients. The degree of immune compromise (e.g., lymphopenia) is a risk factor for severe illness from the community respiratory viruses [139–142] (see chapter Respiratory Infections).

Inactivated influenza vaccine is available and may be potentially protective for immunocompromised patients [143], but severely immunocompromised patients, such as early convalescent allogeneic HCT recipients, unfortunately do not respond reliably or adequately. Neuraminidase inhibitors, such as oseltamivir or zanamivir, are preferred treatment options for influenza A and B and have largely replaced amantadine and rimantidine because of less toxicity and emergence of resistance to the latter class of drugs. Early start of therapy (less than 48 h after onset of symptoms) is quite important. An ominous note is the recent observation of some influenza strains exhibiting resistance to oseltamivir (but retaining susceptibility to zanamivir). Neurominidase inhibitors can also be used in highly immunosuppressed patients exposed to influenza to prevent symptomatic infection.

Ribavirin, a nucleoside analog, can be clinically useful for RSV infection [144, 145]. As with influenza, early initiation of therapy is important. Lymphopenia and respiratory failure are adverse factors for response. Immunoglobulin with high-titer antibody against RSV or palivizumab, a RSV-specific monoclonal antibody, may have additive effects when added to ribavirin, but controlled trials have not been conducted. A controversial issue is whether administration of therapy for upper-tract infection will prevent the progression to lower-tract disease. A retrospective review on the use of ribavirin for RSV upper-tract infection in leukemia and in HCT patients suggested a reduction in subsequent pneumonia [146]; however, a small randomized trial in HCT patients suggested a reduction in viral load with aerosolized ribavirin, but no substantial reduction in subsequent development of lower-tract disease was evident [147]. A study of palivizumab suggested no benefit in its use in HCT patients to prevent progression of upper-tract infection to pneumonia [148].

There are no effective treatment approaches established for parainfluenza infections. Human metapneumovirus is a recently discovered RNA paramyxovirus. It has been isolated from a small percent of HCT patients undergoing bronchoscopy, mostly for idiopathic pneumonitis [149]. There is no known effective therapy, but ribavirin is active as well as immunoglobulin in vitro.

Cautionary measures must be exercised to avoid nosocomial transmission of these airborne organisms during community outbreaks [150–152]. Infection control measures are paramount to prevent spread of infection among patients, patient families, and health care workers during community outbreaks. These include respiratory isolation of patients with documented and suspected infection, use of masks, and restricting contact of patients with family and health care workers with

respiratory infections. Chemoprophylaxis of HCT patients exposed to influenza has been shown to be useful and well-tolerated in HCT patients [153] whether there is a role for prophylaxis in other immunocompromised patient groups is unclear.

## 8 Papovaviruses (Polyomaviruses)

JC and BK viruses cause asymptomatic infection in children but establish a persistent infection in renal and urogenital epithelial cells. JC virus has been associated with progressive multifocal leukoencephalopathy. BK virus has been associated with hemorrhagic cystitis in allogeneic HCT recipients [154–158]. At present, there are no effective therapies.

Cidofovir is active against polyomaviruses in vitro, and there are case reports and series describing its use, but its efficacy has not been documented [159]. DNA gyrase inhibitors, such as ciprofloxacin, may have efficacy in prevention in high-risk HCT patients [160].

## 9 Retroviruses

Human T-cell lymphotrophic virus type-1 (HTLV-1) is an endemic retrovirus in some areas of the world. Transmission can occur by breast feeding, sexual contact, or blood transfusion. It has been associated with the development of the adult T-cell 1eukemia/lymphoma syndrome. Latency between infection and onset of disease is often more than a decade, and the risk of development of disease may be dependent on the age of infection, with early childhood being most risky.

HIV (formerly HTLV-3) is a retrovirus that is the causative agent of AIDS. Sexual transmission and transmission via blood transfusion or organ transplant are well established. The institution of routine screening tests for blood products and organ donors has reduced the risk of transmission substantially. Several nucleoside analogs are active inhibitors of reverse transcriptase, and protease inhibitors have recently been found to be useful in the suppression of viral replication, with corresponding clinical benefits. There are multiple effective combination regimens that are effective in long-term suppression of viral replication and decline in immunity. The emergence of antiviral resistance has plagued the development of effective and enduring antiviral strategies, however.

## 10 Conclusions

The increase in viral infections in immunocompromised patients and the increasing numbers of immunocompromised patients have given a sense of urgency to improve our diagnostic techniques and to develop an armamentarium of antiviral agents for use in the control of these prevalent and opportunistic

microorganisms. Recognition of the relevant protective immune responses is likely to lead to new biologic strategies to supplement pharmacologic measures to control serious morbidity from these pathogens in the future.

## References


1. Saral R (1988) Management of mucocutaneous herpes simplex virus infections in immunocompromised patients. Am J Med 85(2A):57–60
2. Saral R, Burns WH, Prentice HG (1984) Herpes virus infections: clinical manifestations and therapeutic strategies in immunocompromised patients. Clin Haematol 13(3):645–660
3. Khan SA, Wingard JR (2001) Infection and mucosal injury in cancer treatment. JNCI Monogr 29:31–36
4. Herget GW, Riede UN, Schmitt-Graff A et al (2005) Generalized herpes simplex virus infection in an immunocompromised patient: report of a case and review of the literature. Pathol Res Pract 201:123–129
5. Pruneda RC, Almanza I (1987) Centrifugation-shell vial technique for rapid detection of herpes simplex virus cytopathic effect in vitro cells. J Clin Microbiol 25:423
6. Schmidt NJ, Dennis J, Devlin V et al (1983) Comparison of direct immunofluorescence and direct immunoperoxidase procedures for detection of herpes simplex virus antigen in lesion specimens. J Clin Microbiol 18:445–448
7. Gonik B, Seibel M, Berkowitz A et al (1991) Comparison of two enzyme-linked immunosorbent assays for detection of herpes simplex virus antigen. J Clin Microbiol 29:436–438
8. Nahass GT, Goldstein BA, Zhu WY et al (1992) Comparison of Tzanck smear, viral culture, and DNA diagnosis methods in detection of herpes simplex and varicella-zoster infection. JAMA 268:2541–2544
9. Meyers JD, Wade JC, Mitchell CD et al (1982) Multicenter collaborative trial of intravenous acyclovir for the treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. Am J Med 73A:229
10. Mitchell CD, Gentry SR, Boen JR et al (1981) Acyclovir therapy for mucocutaneous herpes simplex infections in immunocompromised patients. Lancet 2:1389
11. Shepp DH, Newton BA, Dandliker PS et al (1985) Oral acyclovir therapy for mucocutaneous herpes simplex virus infection in immunocompromised marrow transplant recipients. Ann Intern Med 102:783
12. Wade JC, Newton B, McLaren C et al (1982) Treatment of mucocutaneous herpes simplex virus infection after marrow transplantation with intravenous acyclovir: a double blind trial. Ann Intern Med 96:265
13. Selby PJ, Jameson B, Watson JG et al (1980) Parenteral acyclovir therapy for herpes virus infections in man. Lancet 2:1267
14. Soul-Lawton J, Seaber E, On N et al (1995) Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother 39(12):2759–2764
15. Perry CM, Faulds D (1996) Valaciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in herpesvirus infections. Drugs 52(5):754–772
16. Weller S, Blum MR, Doucette M et al (1993) Pharmacokinetics of the acyclovir pro-drug valaciclovir after escalating single- and multiple-dose administration to normal volunteers. Clin Pharmacol Ther 54(6):595–605
17. Saral R, Burns WH, Laskin OL et al (1981) Acyclovir prophylaxis of herpes-simplex-virus infections: a randomized, double-blind, controlled trial in bone marrow transplant recipients. N Engl J Med 305:63

18. Saral R, Ambinder RF, Burns WH et al (1983) Acyclovir prophylaxis against recrudescent herpes simplex virus infections in leukemia patients: a randomized, double-blind placebo controlled study. Ann Intern Med 99:773
19. Anderson H, Scarfee JH, Sutton RNP et al (1984) Oral acyclovir prophylaxis against herpes simplex virus in non-Hodgkin lymphoma and acute lymphoblastic leukaemia patients receiving remission induction chemotherapy. A randomised double blind placebo controlled trial. Br J Cancer 50:45–49
20. Wade JC, Newton B, Flournoy N, Meyers JD (1984) Oral acyclovir prophylaxis of herpes simplex virus infection after marrow transplant. Ann Intern Med 100:823
21. Wade JC, Newton B, Flournoy N et al (1984) Acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. Ann Intern Med 99:773–776
22. Saral R (1990) Management of acute viral infections. NCI Monogr 9:107–110
23. Wingard JR (1993) Viral infections in leukemia and bone marrow transplant patients. Leuk Lymphom 11:115–125
24. Ambinder RF, Burns WH, Lietman PS et al (1984) Prophylaxis: a strategy to minimize antiviral resistance. Lancet 1:1154–1155
25. Saral R, Ambinder RF, Burns WH et al (1983) Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. A randomized, double-blind, placebo-controlled study. Ann Intern Med 99(6):773–776
26. Wade JC, McLaren C, Meyers JD (1983) Frequency and significance of acyclovir-resistant herpes simplex virus isolated from marrow transplant patients receiving multiple courses of treatment with acyclovir. J Infect Dis 148:1077–1082
27. Burns WH, Santos GW, Saral R et al (1982) Isolation and characterizations of resistant herpes simplex virus after acyclovir therapy. Lancet 2:421
28. McLaren C, Chen MS, Ghazzouli I et al (1985) Drug resistance patterns of herpes simplex virus isolates from patients treated with acyclovir. Antimicrob Agent Chemother 28:740–744
29. Safrin S, Assakeen T, Follansbee S, Mills J (1990) Foscarnet therapy for acyclovir-resistant mucocutaneous herpes simplex virus infection in 26 AIDS patients: preliminary data. J Infect Dis 161:1078
30. Safrin S, Crumpacker C, Chatis, et al (1991) A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. N Engl J Med 325:551–555
31. Randolph-Habecker J, Iwata M, Torok-Storb B (2002) Cytomegalovirus mediated myelosuppression. J Clin Virol 25(Suppl 2):S51–S56
32. Torok-Storb B, Boeckh M, Hoy C et al (1997) Association of specific cytomegalovirus genotypes with death from myelosuppression after marrow transplantation. Blood 90:2097–2102
33. Choi JH, Kim DW, Cho SG et al (1997) Pre-emptive ganciclovir treatment can play a role in restoration of hematopoiesis after allogeneic bone marrow transplantation. Bone Marrow Transplant 19:187–190
34. Leland DS, Hansing RL, French ML (1989) Clinical experiences with cytomegalovirus isolation using conventional cell cultures and early antigen detection in centrifugation-enhanced shell vial cultures. J Clin Microbiol 27:1159–1162
35. Gleaves CA, Smith TF, Shuster EA, Pearson GR (1985) Comparison of standard tube and shell vial cell culture techniques for the detection of cytomegalovirus in clinical specimens. J Clin Microbiol 21:217
36. Boeckh M, Bowden RA, Goodrich JM et al (1992) Cytomegalovirus antigen detection in peripheral blood leukocytes after allogeneic marrow transplantation. Blood 80:1358–1364
37. van der Bij W, Torensma R, van Son WJ et al (1988) Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leucocytes. J Med Virol 25:179–188

38. Jiwa NM, van de Rijke FM, Mulder A et al (1989) An improved immunocytochemical method for detection of human cytomegalovirus antigens in peripheral blood leucocytes. Histochemistry 91:345–349
39. Spector SA, Merrill R, Wolf D et al (1992) Detection of human cytomegalovirus in plasma of AIDS patients during acute visceral disease by DNA amplification. J Clin Microbiol 30:2359–2365
40. Brytting M, Xu W, Wahren B et al (1992) Cytomegalovirus DNA detection in sera from patients with active cytomegalovirus infections. J Clin Microbiol 30:1937–1941
41. Einsele H, Steidle M, Vallbracht A et al (1991) Early occurrence of human cytomegalovirus infection after bone marrow transplantation as demonstrated by the polymerase chain reaction technique. Blood 77:1104–1110
42. Nolte FS, Emmens RK, Thurmond C et al (1995) Early detection of human cytomegalovirus viremia in bone marrow transplant recipients by DNA amplification. J Clin Microbiol 33:1263–1266
43. Landry ML, Fergussen D (1993) Comparison of quantitative cytomegalovirus antigenemia assay with culture methods and correlation with clinical disease. J Clin Microbiol 31:2851–2856
44. Schmidt CA, Oettle H, Wilborn F et al (1994) Demonstration of cytomegalovirus after bone marrow transplantation by polymerase chain reaction, virus culture and antigen detection in buffy coat leukocytes. Bone Marrow Transplant 83:71–75
45. Shepp DH, Dandliker PS, deMiranda P, et al (1985) Activity of 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl] guanine in the treatment of cytomegalovirus pneumonia. Ann Intern Med 103:368
46. Emanuel D, Cunningham I, Jules-Elysee K et al (1988) Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Ann Intern Med 109:777–782
47. Reed EC, Bowden RA, Dandliker PS et al (1988) Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann Intern Med 109:783–788
48. Schmidt GM, Kovacs A, Zaia JA et al (1988) Ganciclovir/immunoglobulin combination therapy for the treatment of human cytomegalovirus-associated interstitial pneumonia in bone marrow allograft recipients. Transplantation 46:905–907
49. Reed EC, Wolford JL, Kopecky KJ et al (1990) Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo-controlled trial. Ann Intern Med 112(7):505–510
50. Ljungman P, Cordonnier C, Einsele H et al (1998) Use of intravenous immune globulin in addition to antiviral therapy in the treatment of CMV gastrointestinal disease in allogeneic bone marrow transplant patients: a report from the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 21:473–476
51. Goodrich JM, Bowden RA, Fisher L et al (1993) Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 118:173–178
52. Winston DJ, Ho WG, Bartoni K et al (1993) Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Ann Intern Med 118:179–184
53. Schmidt GM, Horak DA, Niland JC et al (1991) A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplant patients. N Engl J Med 324:1005–1011
54. Goodrich JM, Mori M, Gleaves CA et al (1991) Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplant. N Engl J Med 325:1601–1607
55. Drew WL, Ives D, Lalezari JP et al (1995) (for the Syntex Cooperative Oral Ganciclovir Study Group). Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. N Engl J Med 333:615–620

56. Drew WL, Miner RC, Busch DF et al (1991) Prevalence of resistance in patients receiving ganciclovir for serious cytomegalovirus infection. J Infect Dis 163:716–719
57. Ayala E, Greene J, Sandin R et al (2006) Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 37(9):851–856
58. Einsele H, Reusser P, Bornhäuser M et al (2006) Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. Blood 107(7):3002–3008
59. van der Heiden PL, Kalpoe JS, Barge RM et al (2006) Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. Bone Marrow Transplant 37(7):693–698
60. Busca A, de Fabritiis P, Ghisetti V et al (2007) Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. Transpl Infect Dis 9(2):102–107
61. Volin L, Barkholt L, Nihtinen A et al (2008) An open-label randomised study of oral valganciclovir versus intravenous ganciclovir for pre-emptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation [abstract]. In: 34th annual meeting of the European Group for Blood and Marrow Transplantation. Florence, Italy
62. Moretti S, Zikos P, Van Lint MT et al (1998) Forscarnet vs ganciclovir for cytomegalovirus (CMV) antigenemia after allogeneic hemopoietic stem cell transplantation (HSCT): a randomised study. Bone Marrow Transplant 22(2):175–180
63. Goodrich JM, Boeckh M, Bowden R (1994) Strategies for the prevention of cytomegalovirus disease after marrow transplantation. Clin Infect Dis 19:287–298
64. Forman SJ, Zaia JA (1994) Treatment and prevention of cytomegalovirus pneumonia after bone marrow transplantation: where do we stand? Blood 83:2392–2398
65. Devine SM, Wingard JR (1994) Viral infections in severely immunocompromised cancer patients. Support Care Cancer 2:355–368
66. Boeckh M, Nichols G, Papanicolaou G et al (2003) Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. Biol Blood Marrow Transplant 9(9):543–558
67. Ljungman P, Deliliers GL, Platzbecker U et al (2001) Cidofovir for cytomegalovirus infection and disease in allogeneic stem cell transplant recipients. The infectious diseases working party of the European Group for Blood and Marrow Transplantation. Blood 97:388–392
68. Chou S, Guentzel S, Michels R et al (1995) Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. J Infect Dis 172:239–242
69. Emery VC, Griffiths PD (2000) Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. Proc Natl AcadSc i USA 97:8039–8044
70. Razis E, Cook P, Mittelman A, Ahmed T (1994) Treatment of ganciclovir resistant cytomegalovirus with foscarnet: a report of two cases occurring after bone marrow transplantation. Leuk Lymphom 12:477–480
71. Meyers JD, Reed EC, Shepp DH et al (1988) Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 318:70–75
72. Prentice HG, Gluckman E, Powles RL et al (1994) Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. Lancet 343:749–753
73. Ljungman P, de La Camara R, Milpied N et al (2002) Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood 99(8):3050–3056

74. Bowden RA, Slichter SJ, Sayers MH et al (1991) Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for prevention of primary cytomegalovirus infection after marrow transplant. Blood 78:246–250
75. Bowden RA, Sayers M, Flournoy N et al (1986) Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. N Engl J Med 314:1006–1010
76. Mackinnon S, Burnett AK, Crawford RJ et al (1988) Seronegative blood products prevent primary cytomegalovirus infection after bone marrow transplantation. J Clin Pathol 41:948–950
77. Miller W, McCullough J, Balfour HH et al (1988) Prevention of CMV infection by blood products: a randomized trial (abstract K128). J Cell Biochem 12(Suppl. C):93
78. De Witte T, Schattenbereg A, Van Dijk BA et al (1990) Prevention of primary cytomegalovirus infection after allogeneic bone marrow transplantation by using leukocyte-poor random blood products from cytomegalovirus-unscreened blood-bank donors. Transplantation 50:964–968
79. Bowden RA, Slichter SJ, Sayers M et al (1995) A comparison of filtered leukocyte-reduced cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. Blood 85:3598–3603
80. Winston DJ, Ho WG, Lin CH et al (1987) Intravenous immune globulin for prevention of cytomegalovirus infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med 106:12–18
81. Bass EB, Powe NR, Goodman SN et al (1993) Efficacy of intravenous immune globulin in preventing complications of bone marrow transplantation: a meta analysis. Bone Marrow Transplant 12:273–282
82. Messori A, Rampazzo R, Scroccaro G, Martini N (1994) Efficacy of hyperimmune anti-cytomegalovirus immunoglobulins for the prevention of cytomegalovirus infection in recipients of allogeneic bone marrow transplantation: a meta-analysis. Bone Marrow Transplant 13:163–167
83. Bowden RA, Fisher LD. Rogers K et al (1991) Cytomegalovirus (CMV)-specific intravenous immunoglobulin for the prevention of primary CMV infection and disease after marrow transplant. J Infect Dis 164:483–487
84. Guglielmo BJ, Wong-Beringer A, Linkcr CA (1994) Immune globulin therapy in allogeneic bone marrow transplant: a critical review. Bone Marrow Transplant 13:499–510
85. Sullivan KM, Kopecky KJ, Jocum J et al (1990) Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med 323:705–712
86. Locksley RM, Flournoy N, Sullivan KM, Meyers JD (1985) Infection with varicella-zoster virus after marrow transplantation. J Infect Dis 152:1172–1181
87. Atkinson K, Meyers JD, Storb R et al (1980) Varicella-zoster virus infection after marrow transplantation for aplastic anemia or leukemia. Transplantation 29:47–50
88. Schiller GJ, Nimer SD. Gajewski JL, Golde D (1991) Abdominal presentation of varicella-zoster infection in recipients of allogeneic bone marrow transplantation. Bone Marrow Transplant 7:489–491
89. Balfour HH Jr, Bean B, Laskin OL et al and the Burroughs Wellcome Collaborative Acyclovir Study Group (1983) Acyclovir halts progression of herpes zoster in immunocompromised patients. N Engl J Med 308:1448–1453
90. Meyers JD, Wade JC, Shepp DH, Newton B (1984) Acyclovir treatment of varicella-zoster virus infection in the compromised host. Transplantation 37:571
91. Shepp DH, Dandliker PS, Meyers JD (1986) Treatment of varicella-zoster virus infection in severely immunocompromised patients: a randomized comparison of acyclovir and vidarabine. N Engl J Med 314:208–212
92. McKendrick MW, McGill JI, White JE, Wood MJ (1986) Oral acyclovir in acute herpes zoster. Br Med J 293:1529–1532

93. Ljungman P, Lönnqvist B, Ringdén O et al for the Nordic Bone Marrow Transplant Group (1989) A randomized trial of oral versus intravenous acyclovir for treatment of herpes zoster in bone marrow transplant recipients. Bone Marrow Transplant 4:613–615
94. Boivin G, Edleman CK, Pedneault L et al (1994) Phenotypic and genotypic characterization of acyclovir-resistant varicella-zoster viruses isolated from persons with AIDS. J Infect Dis 170:68–75
95. Safrin S, Berger TG, Gilson I et al (1991) Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. Ann Intern Med 115:19–21
96. Zaia JA, Levin MJ, Preblud SR et al (1983) Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. J Infect Dis 147:737
97. Gershon AA (1985) Live attenuated varicella vaccine: perspective. J Infect Dis 152:859
98. Gershon AA, Steinberg SP, and the Varicella Vaccine Collaborative Study Group of the NIAID (1989) Persistence of immunity of varicella in children with leukemia immunized with live attenuated varicella vaccine. N Engl J Med 320:892
99. Gershon AA, Steinberg SP, and the National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group (1990) Live attenuated varicella vaccine: protection in healthy adults compared with leukemic children. J Infect Dis 161:661
100. Lawrence R, Gershon AA, Holzman R et al (1988) The risk of zoster after varicella vaccination in children with leukemia. N Engl J Med 318:543
101. Ljungman P, Wang FZ, Nilsson C et al (2003) Vaccination of autologous stem cell transplant recipients with live varicella vaccine: a pilot study. Support Care Cancer 11:739–741
102. Hata A, Asanuma H, Rinki M et al (2002) Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. N Engl J Med 347:26–34
103. Ballerini P, Gaidano G, Inghirami G et al (1991) Multiple genetic alterations in AIDS-associated lymphomas. Blood 78:327
104. Knowles DM, Cesarman E, Chadburn A et al (1995) Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. Blood 85:552–565
105. Bakker NA, van Imhoff GW, Verschuuren EAM, van Son WJ (2007) Presentation and early detection of post-transplantation lymphoproliferative disorder after solid organ transplantation. Transpl Inter 20:207–218
106. Styczynski J, Einsele H, Gil L, Ljungman P (2009) Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. Transpl Infect Dis 11:383–392
107. Shapiro RS, McClain K, Frizzera G et al (1988) Epstein-Barr virus associated B cell lymphoproliferative disorders following bone marrow transplantation. Blood 71(5):1234–1243
108. Curtis RE, Travis LB, Rowlings PA et al (1999) Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood 94(7):2208–2216
109. Meerbach A, Wutzler P, Häfer R et al (2008) Monitoring of Epstein-Barr virus load after hematopoietic stem cell transplantation for early intervention in post-transplant lymphoproliferative disease. J Med Virol 80(3):441–454
110. Carrigan DR, Drobyski WR, Russler SK et al (1991) Interstitial pneumonitis associated with human herpesvirus six (HHV-6) infection in marrow transplant patients. Lancet 338:147
111. Cone RW, Hackman RC, Huang MW et al (1993) Human herpesvirus 6 in lung tissue from patients with pneumonitis after bone marrow transplantation. N Engl J Med 329:156
112. Drobyski WR, Knox KK, Majewski D, Carrigan DR (1994) Fatal encephalitis due to variant B human herpesvirus 6 infection in a bone marrow transplant recipient. N Engl J Med 330:1356

113. Drobyski WR, Dunne WM, Burd EM (1993) Human herpesvirus 6 (HHV-6) infection in allogeneic bone marrow transplant recipients: I. Evidence for a marrow suppressive role for HHV-6 in vivo. J Infect Dis 167:735
114. Carrigan DR, Knox KK (1994) Human herpesvirus 6 (HHV-6) isolation from bone marrow: HHV-6-associated bone marrow suppression in bone marrow transplant patients. Blood 84:3307–3310
115. Burns WH, Sandford GR (1990) Susceptibility of human herpesvirus 6 to antivirals in vitro. J Infect Dis 162:634–637
116. Zerr DM, Gupta D, Huang ML et al (2002) Effect of antivirals on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. Clin Infect Dis 34(3):309–317
117. Quinnan GV Jr, Kirmani N, Rook AH et al (1982) Cytotoxic cells in cytomegalovirus infections. HLA-restricted T-lymphocyte and non-T-lymphocyte cytotoxic responses correlate with recovery from cytomegalovirus infection in bone marrow transplant recipients. N Engl J Med 307:7
118. Reusser P, Riddel SR, Meyers SD, Greenberg PD (1991) Cytotoxic T-lymphocyte response to cytomegalovirus after human allogeneic bone marrow transplantation: pattern of recovery and correlation with cytomegalovirus infection and disease. Blood 78:1373–1380
119. Quinnan GV Jr, Burns WH, Kirmani N et al (1984) HLA-restricted cytotoxic T lymphocytes are an early immune response and important defense mechanism in infections. Rev Infect Dis 6:156–163
120. Riddel SR, Walter BA, Gilbert MJ, Greenberg PD (1994) Selective reconstitution of CD8 cytotoxic T lymphocyte responses in immunodeficient bone marrow transplant recipients by the adoptive transfer of T cell clones. Bone Marrow Transplant 14:S78–S84
121. Riddell SR, Watanabe KS, Goodrich JM et al (1992) Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T-cell clones. Science 257:238
122. Riddell SR, Reusser P, Greenberg PD (1991) Cytotoxic T-cells specific for cytomegalovirus: a potential therapy for immunocompromised hosts. Rev Infect Dis 13:966
123. Walter EA, Greenberg PD, Gilbert MJ et al (1995) Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow transplant by transfer of T-cell clones from the donor. N Engl J Med 333:1038–1044
124. Papadopoulos EB, Ladanyi M, Emanuel D et al (1994) Infusions of donor leukocytes to treat Epstein-Barr virus-associated lymphoproliferative disorders after allogeneic bone marrow transplantation. N Engl J Med 330:1185–1191
125. Rooney CM, Smith CA, Ng CY, Loftin SK et al (1998) Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus-induced lymphoma in allogeneic transplant recipients. Blood 92(5):1549–1555
126. Heslop HE, Perez M, Benaim E et al (1999) Transfer of EBV-specific CTL to prevent EBV lymphoma post bone marrow transplant. J Clin Apher 14(3):154–156
127. Lucas KG, Sun Q, Burton RL et al (2000) A phase I-II trial to examine the toxicity of CMV- and EBV-specific cytotoxic T lymphocytes when used for prophylaxis against EBV and CMV disease in recipients of CD34-selected/T cell-depleted stem cell transplants. Hum Gene Ther 11(10):1453–1463
128. Firpi RJ, Nelson DR (2008) Management of viral hepatitis in hematologic malignancies. Blood Rev 22(3):117–126
129. Martyak LA, Taqavi E, Saab S (2008) Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients: a meta-analysis. Liver Int 28(1):28–38
130. Lok AS, McMahon BJ (2007) Chronic hepatitis B. Hepatology 45(2):507–539
131. Liang R (2009) How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 113:3147–3153
132. Lok AS, Lai CL, Leung N et al (2003) Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 125:1714–1722

133. Peffault de Latour R, Lévy V, Asselah T et al (2004) Long-term outcome of hepatitis C infection after bone marrow transplantation. Blood 103:1618–1624
134. Shuhart MC, Myerson D, Childs BH (1994) Marrow transplantation from hepatitis C virus seropositive donors: transmission rate and clinical course. Blood 84:3229–3235
135. Ilan Y, Nagler A, Adler R et al (1993) Ablation of persistent hepatitis B by bone marrow transplantation from a hepatitis B-immune donor. Gastroenterology 104:1818–1821
136. Flomenberg P, Babbitt J, Drobyski WR et al (1994) Increasing incidence of adenovirus disease in bone marrow transplant recipients. J Infect Dis 169:775–781
137. Chakrabarti S, Mautner V, Osman H et al (2002) Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. Blood 100(5):1619–1627
138. Sivaprakasam P, Carr TF, Coussons M et al (2007) Improved outcome from invasive adenovirus infection in pediatric patients after hemopoietic stem cell transplantation using intensive clinical surveillance and early intervention. J Pediatr Hematol Oncol 29(2):81–85
139. Boeckh M (2008) The challenge of respiratory virus infections in hematopoietic cell transplant recipients. Br J Hematol 143:455–467
140. Bowden RA (1997) Respiratory virus infections after marrow transplant: the Fred Hutchinson Cancer Research Center experience. Am J Med 102:27–30
141. Hall CB, Powell KR, MacDonald NE et al (1986) Respiratory syncytial viral infection in children with compromised immune function. N Engl J Med 315:77–81
142. Rabella N, Rodriguez P, Labeaga R et al (1999) Conventional respiratory viruses recovered from immunocompromised patients: clinical considerations. Clin Infect Dis 28:1043–1048
143. Engelhard D, Nagler A, Hardan I et al (1993) Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell-depleted and autologous BMT recipients. Bone Marrow Transplant 11:1–5
144. Smith DW, Frankel LR. Mathers LH et al (1991) A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 325:24–29
145. Whimbey E, Champlin RE, Englund JA et al (1995) Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. Bone Marrow Transplant 16:393–399
146. Chemaly RF, Ghosh S, Bodey GP et al (2006) Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore) 85(5):278–287
147. Boeckh M, Englund J, Li Y, Miller C et al (2007) Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. Clin Infect Dis 44(2):245–249
148. de Fontbrune FS, Robin M, Porcher R et al (2007) Palivizumab treatment of respiratory syncytial virus infection after allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 45(8):1019–1024
149. Englund JA, Boeckh M, Kuypers J et al (2006) Fatal human metapneumovirus infection in stem-cell transplant recipients. Ann Intern Med 144(5):344–349
150. Englund JA, Anderson LJ, Rhame FS (1991) Nosocomial transmission of respiratory syncytial virus in immunocompromised adults. J Clin Microbiol 29:115–119
151. Whimbey E, Elting LS, Cough RB et al (1994) Influenza A virus infections among hospitalized adult bone marrow transplant recipients. Bone Marrow Transplant 13:437–440
152. Wingard JR (2008) Influenza: preparedness for an inevitable "Emergency" for the oncology and BMT unit. J Natl Compr Cancer Netw 6(2):215–222
153. Vu D, Peck AJ, Nichols WG et al (2007) Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 45(2):187–193
154. Arthur RR, Shah KV, Baust SJ et al (1986) Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. N Engl J Med 315:230–234

155. Russell SJ, Vowels MR, Vale T (1994) Haemorrhagic cystitis in paediatric bone marrow transplant patients: an association with infective agents. GVHD and prior cyclophosphamide. Bone Marrow Transplant 13:533–539
156. Azzi A, Fanci R, Bosi A et al (1994) Monitoring of polyomavirus BK viruria in bone marrow transplantation patients by DNA hybridization assay and by polymerase chain reaction: an approach to assess the relationship between BK viruria and hemorrhagic cystitis. Bone Marrow Transplant 14:235–240
157. Schneider EM, Dörries K (1983) High frequency of polyomavirus infection in lymphoid cell preparations after allogeneic bone marrow transplantation. Transplant Proc 25:1271–1273
158. Drummond JE, Shah KV, Saral R et al (1987) BK virus specific humoral and cell mediated immunity in allogeneic bone marrow transplant ($BM^T$) recipients. J Med Virol 23:331–344
159. Held TK, Biel SS, Nitsche A, Kurth A et al (2000) Treatment of BK virus-associated hemorrhagic cystitis and simultaneous CMV reactivation with cidofovir. Bone Marrow Transplant 26(3):347–350
160. Dropulic LK, Jones RJ (2008) Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant 41(1):11–18

# Neutropenic Fever and Sepsis: Evaluation and Management

Kenneth V. I. Rolston

**Abstract**

Neutropenia remains the predominant predisposing factor for infection in most cancer patients. Bacterial and fungal infections are common in this setting. Not all neutropenic patients have the same risk of developing severe infection or serious medical complications. Although all patients with neutropenia and fever should receive prompt, empiric antibiotic therapy, low-risk patients can be effectively managed without hospitalization—often with the administration of oral antibiotics. Other patients need hospital-based therapy. The emergence of resistant microorganisms has become a significant problem in neutropenic patients. Frequent epidemiologic surveys to detect the emergence of resistant organisms are recommended. Antibiotic stewardship and Infection Control Programs are important tools in combating resistant organisms.

**Keywords**

Neutropenic fever · Risk-assessment · Empiric therapy · Outpatient therapy · Antimicrobial stewardship

## Contents



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## 1 Introduction

Neutrophils provide protection against a multitude of bacterial and fungal pathogens. Neutropenia from any cause results in increased frequency and severity of infections caused by these organisms. Bodey and colleagues first described the association between neutropenia and infection in patients with hematologic malignancies in 1966 [1]. They demonstrated that the frequency and severity of infection was directly related to the degree and duration of neutropenia, once the absolute neutrophil count (ANC) dipped below 1,000/mm$^3$. The currently accepted definition of neutropenia is an ANC of $\leq$500/mm$^3$. It was traditional to admit all febrile neutropenic patients to the hospital for close monitoring and the administration of broad-spectrum, parenteral, antibiotic therapy for the entire duration of the febrile episode [2]. Our understanding of the syndrome of neutropenic fever has improved substantially in the ensuing years. The availability of truly broad-spectrum antimicrobial agents (extended spectrum cephalosporins, carbapenems) made it possible to administer monotherapy instead of always using two or three agents in combination [3]. The development of accurate risk prediction rules, improvement in infusion therapy and supportive care, and the increasing role played by home health care agencies has enabled clinicians to shift the site of care of febrile neutropenic patients from the hospital to the ambulatory clinic/home, for at least part of the duration of the febrile episode [4, 5]. The development of oral agents such as the fluoroquinolones, with potent activity against important gram-negative pathogens including *Pseudomonas aeruginosa,* has considerably improved the efficacy of infection prevention/prophylaxis for high-risk neutropenic patients. Improved diagnostic techniques have made the documentation of many infections (particularly fungal infections) quicker and more accurate [6, 7]. The frequent use (misuse?) of many antimicrobial agents in this setting has led to reduced susceptibility and/or the development of overt resistance among common bacterial and fungal pathogens [8, 9]. With new drug development almost at a standstill, antimicrobial stewardship and infection control have gained increasing importance in limiting the damage caused by multidrug-resistant organisms [10, 11]. The development of novel antineoplastic agents (e.g., purine analogs, various monoclonal antibodies, temozolamide) has altered the traditional spectrum of infection in patients receiving chemotherapy. These and other issues will continue to provide diagnostic and therapeutic challenges in the years to come.

**Table 1** Common causes of infection in neutropenic patients

| *Gram-positive bacteria* | *Fungal* |
|---|---|
| Coagulase-negative staphylococci | *Candida* species |
| *Staphylococcus aureus* | *Aspergillus* species |
| *Enterococcus* species | Zygomycetes |
| Viridans group streptococci | Other opportunistic fungi |
| *Bacillus* species | |
| *Corynebacterium* species | |
| *Streptococcus pneumoniae* | |
| Beta-hemolytic streptococci (groups A, B, C, G, F) | |
| *Stomatococcus mucilaginosus* | |
| *Gram-negative bacteria* | |
| *Escherichia coli* | |
| *Klebsiella* species | |
| Other *Enterobacteriaceae* | |
| *Pseudomonas aeruginosa* | |
| *Pseudomonas* (non-*aeruginosa*) species | |
| *Acinetobacter* species | |
| *Stenotrophomonas maltophilia* | |
| *Anaerobes* | |
| *Bacteroides* species | |
| *Clostridium* species | |

## 2 Epidemiology of Infection

Bacterial infections predominate during the initial phases of a neutropenic episode, whereas fungal infections are more common in patients with prolonged neutropenia. Bacterial and fungal pathogens that frequently cause infections in such patients are listed in Table 1. This list is by no means all inclusive, and it is important to remember that most microorganisms (even those with a low virulence potential) can cause opportunistic infection in neutropenic patients.

Additionally, the epidemiology of infection keeps changing, and institutional differences are not uncommon [12, 13]. Consequently, it is advisable to conduct local surveillance studies, at least in institutions that have been designated Comprehensive Cancer Centers, and treat large numbers of cancer patients [14, 15].

Most recent epidemiologic surveys have documented the predominance of gram-positive bacteria over gram-negative bacteria [14, 16, 17]. The proportion of infections caused by gram-positive bacteria has been reported to be as high as

75–80 % at some centers. These data, however, do not paint a complete picture, since both the European Organization for Research and Treatment of Cancer (EORTC) and the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) focus only on single-organism (monomicrobial) bacteremias [14, 16]. Although this is useful information, bacteremias cause only 20–30 % of infections in neutropenic patients [2, 3]. Other common sites of infection include the respiratory tract, the urinary tract, skin and skin structures, and the gastrointestinal tract [18]. Whereas gram-positive bacteria are the predominant organisms isolated from blood cultures, gram-negative organisms predominate at most other sites (e.g., pneumonias, urinary tract infections, peri-rectal infections, biliary tract infections, neutropenic enterocolitis). Another critical piece of information missing from the EORTC, SCOPE, and other surveys is the proportion of infections that are polymicrobial. Data from the M. D. Anderson Cancer Center indicate that polymicrobial infections have more than doubled in frequency since the early 1980s and currently account for 25–30 % of microbiologically documented infections [17–20]. Additionally, approximately 80 % of polymicrobial infections have a gram-negative component, and approximately 33 % are caused exclusively by multiple species of gram-negative bacilli [19, 21]. When all sites of infection as well as monomicrobial and polymicrobial infections are included in the overall spectrum, a substantially different picture emerges. The proportion of monomicrobial gram-positive infections falls sharply from approximately 80 to <50 % [17, 18]. This can have a significant impact on the choice of agents/regimens used for antimicrobial prophylaxis and for empiric therapy in this setting.

Gram-positive organisms colonizing the skin are isolated frequently. These include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus, Bacillus* species, and *Corynebacterium* species. Gram-positive organisms arising from the oropharynx and upper airways include viridans group *Streptococci* (VGE), *Streptococcus pneumoniae*, and *Stomatococcus mucilaginosus*, whereas the enterococci arise primarily from the lower gastrointestinal tract. Gram-negative organisms are represented most frequently by the Enterobacteriaceae (*Escherichia coli, Klebsiella* species, *Enterobacter* species) and *P. aeruginosa*, with *Acinetobacter* species and *Stenotrophomonas maltophilia* being reported as increasing frequently at some institutions [22–24]. Strict anaerobes are seldom isolated from neutropenic patients (<2 % of all bacterial infections), although *Clostridium difficile*-associated disease is becoming increasingly common [25, 26]. Rapidly growing mycobacteria are uncommon but occasionally cause catheter-related infections in neutropenic patients [27].

*Candida* species are still the most common fungi isolated from neutropenic patients and cause infections ranging from superficial lesions (thrush, esophagitis, vaginitis) to deep, systemic candidiasis [28]. Most cancer treatment centers have reported a decline in the proportions of infections caused by *Candida albicans* and an increase in the proportion caused by other *Candida* species (*C. tropicalis, C. glabrata, C. krusei*) [29]. *Candida parapsilosis* is the most common species associated with catheter-related candidemia [30]. This epidemiologic shift has been attributed largely to the use of fluconazole prophylaxis, although a similar

pattern has been described in patients who are fluconazole naïve [31, 32]. *Aspergillus* species are second in frequency among fungal pathogens in neutropenic patients [33]. They also cause a range of infections, including localized infections such as sinusitis, cutaneous aspergillosis, aspergilloma (fungus ball), and invasive/disseminated infections frequently involving the lungs and the central nervous system [34].

Many centers have reported an increase in the frequency of infections caused by the Zygomycetes, in part related to the use of voriconazole [35–37]. These infections are often indistinguishable from aspergillosis, with the rhino-cerebral form being particularly devastating [38]. A number of opportunistic fungal pathogens have emerged in recent years including *Fusarium* species, *Trichosporon beigelii, Blastoschizomyces capitus*, and *Scedosporium* species [33].

Viral infections are uncommon in neutropenic patients and are seen more often in patients with impaired cell-mediated immunity. It is important to remember that such patients do develop neutropenia, and viral infections may then need to be considered [2, 18]. Community respiratory viruses (influenza, parainfluenza, respiratory synsitial virus) do pose a significant threat to patients with hematologic malignancies and recipients of stem cell transplantation, particularly in the winter months [39, 40].

## 3 Initial Assessment of the Neutropenic Patient

One of the basic principles of the management of febrile neutropenic patients is to perform a quick but thorough evaluation before the administration of empiric antibiotic therapy. A complete history and physical examination is essential. Historical information of interest includes details of antineoplastic and immunosuppressive therapy, the use of antimicrobial prophylaxis, previous episodes of infection (or colonization with important pathogens) and their treatment, recent surgical/dental procedures, travel history, and potential exposure to sick contacts. Underlying comorbid conditions such as diabetes mellitus, chronic lung disease, cardiovascular, renal, and hepatic problems should also be noted as they might have an impact on the nature and severity of infection, the risk of complications, and the antimicrobial agents selected for therapy.

The inflammatory response is often blunted in neutropenic patients resulting in a paucity of symptoms and signs. Consequently, the physical examination should focus on detection of subtle signs especially at frequently infected sites such as the skin, oropharynx, gastrointestinal tract, and perineum. Although fever is the most consistent sign of infection in neutropenic patients, some patients may develop a serious infection without mounting a febrile response, particularly if they are receiving corticosteroids or other immunosuppressive agents.

Standard laboratory investigations include blood and urine cultures and cultures from other sites (e.g., respiratory specimens, CSF, wounds) when indicated. In patients with diarrhea, stool cultures are not very informative, but stool specimens for the detection of *Clostridium difficile* toxins should be obtained. Patients with

pulmonary symptoms or an infiltrate might require a bronchoscopy to obtain adequate specimens for microbiologic evaluation, as very few will have a productive cough. Nasal specimens are recommended for detecting the presence of community respiratory viruses, especially in the winter months.

Routine chest radiography is not recommended and should be done only in patients with respiratory signs and symptoms. Computerized tomography of the chest and other areas (sinuses, abdomen, pelvis) should be performed as clinically indicated and is far more informative than routine radiographic imaging. Other standard laboratory tests include complete blood cell and differential counts, a serum electrolyte panel, blood urea nitrogen and serum creatinine levels, and a hepatic panel (serum bilirubin and hepatic enzymes). These investigations should be repeated as clinically indicated.

## 4 Risk Assessment and Risk-Based Treatment Strategies

It has long been recognized that not all neutropenic patients have the same risk of developing serious infections and/or life-threatening complications. However, our ability to reliably identify low-risk and high-risk subgroups at the onset of a febrile episode was limited. This led to the practice of administering hospital-based empiric antibiotic therapy to all febrile neutropenic patients [2]. Although successful, this strategy was associated with prolonged hospital stay for many patients, leading to increased resource utilization and costs, and exposing patients to some of the iatrogenic hazards of hospitalization, as well as to the more resistant hospital microflora. With a greater understanding of the syndrome of febrile neutropenia, many investigators have developed reliable risk prediction rules. The most widely accepted of these, and the one used to identify low-risk patients for most antibiotic trials worldwide, is the risk index devised by the Multinational Association for Supportive Care in Cancer (MASCC). This risk index was derived (and subsequently validated) by assigning integer weights to seven characteristics to develop an index score—Table 2 [41]. A score of 21 identified low-risk patients with a positive predictive value of 91 %. Higher scores impart greater specificity with a corresponding loss in sensitivity. Separate but similar risk prediction rules have been developed for pediatric oncology patients [42]. Many investigators have developed simple clinical criteria to identify low-risk patients without having to calculate a risk index score [43–45]. This might be a simpler and more practical method of identifying such patients in a busy clinical practice setting.

There is uniform agreement that patients who are not classified as low risk should be hospitalized for the administration of empiric antibiotic therapy and close monitoring [2, 18]. Several different options for the treatment of low-risk patients have recently been evaluated. These include the nature of the empiric regimen (parenteral, sequential, i.e., IV → PO, oral) and the setting of therapy (initial hospitalization followed by early discharge, outpatient management of the entire febrile episode). These options constitute the entire scope of risk-based therapy.

**Table 2** The Multinational Association of Supportive Care in Cancer (MASCC). Risk index for the identification of low-risk febrile neutropenic patients

| Patient characteristics | Assigned score |
|---|---|
| Burden of illness | |
| No symptoms or mild symptoms | 5 |
| Moderate symptoms | 3 |
| No hypotension | 5 |
| No chronic lung disease | 4 |
| Solid tumor/no previous fungal infection | 4 |
| No dehydration | 3 |
| Outpatient status at onset of fever | 3 |
| Age <60 years | 2 |

Highest possible score = 26. A score of ≥21 indicates low-risk status [41]. Scores >21 increase specificity with corresponding loss of sensitivity

## 5 Empiric Antibiotic Therapy in Low-Risk Patients

The various strategies currently in use for the treatment of low-risk febrile neutropenic patients and the antimicrobial regimens used in this setting are listed in Tables 3 and 4. The first reports of oral therapy for documented bacterial infections in neutropenic patients focused on the therapeutic potential of trimethoprim/sulfamethoxazole, with a response rate of 54 % being reported in infections refractory to other regimens [46]. With the development of fluoroquinolones like ciprofloxacin with potent activity against most gram-negatives including *P. aeruginosa*, and moderate activity against many gram-positives, empiric oral therapy became a viable option [47]. With the development of accurate risk prediction rules, an appropriate population for such therapy was better defined [41, 48]. Despite these advances and the emergence of home healthcare agencies capable of safely delivering outpatient antibiotic therapy, many clinicians are still not comfortable with this approach [KR-personal observations]. Many prefer to admit low-risk patients to the hospital for a short (24–48 h) "stabilization" period, followed by early discharge on parenteral or oral antimicrobial agents. This conservative approach has been successfully evaluated in both adults and pediatric patients [49–52]. The results of these trials are summarized in Table 5. Talcott's pilot study produced disappointing results since 30 % of patients required readmission to the hospital for various reasons and 13.3 % developed serious medical complications. Patients with leukemia, some of whom were classified as low-risk patients but had prolonged neutropenia (up to 31 days), were included in this study and probably account for the high readmission rate [49]. Better results were achieved by investigators from Britain who only enrolled patient with solid tumors and lymphomas and excluded patients with hematologic malignancies [50]. Early

**Table 3** Treatment options for low-risk, febrile neutropenic patients

| |
|---|
| • Short (24–48 h) stabilization period in hospital, followed by early discharge on parenteral or oral regimens |
| • Outpatient (clinic/office/home) treatment of the entire febrile episode (parenteral, sequential, IV → PO, or oral regimen) |
| • Hospital-based parenteral or oral regimens |

Adapted from Refs. [4, 5, 43–45, 62]

**Table 4** Frequently used antibiotic regimens in low-risk patients

| Parenteral regimens | Oral regimens |
|---|---|
| Aztreonam + clindamycin | Cefuroxime |
| Ciprofloxacin + clindamycin | Ciprofloxacin + amoxicillin/clavulanate |
| Ceftriaxone (±) amikacin | Ciprofloxacin + clindamycin |
| Ertapenem (±) amikacin | Ciprofloxacin + azithromycin |
| Ceftazidime or cefepime | Moxifloxacin (±) agents used in combination with ciprofloxacin |

Adapted from Refs. [18, 45, 62, 63]

**Table 5** Outpatient management of low-risk febrile neutropenic patients after a short hospital stay

| Authors | Ref. no | Type of study and patient population | Antibiotic regimens | Response to initial regimen (±) no readmission % |
|---|---|---|---|---|
| Talcott et al. | [49] | Open-label, pilot study of 30 low-risk patients | IV mezlocillin + gentamicin or IV ceftazidime | 53 |
| Innes et al. | [50] | Randomized study comparing oral outpatient therapy ($n = 66$) to parenteral inpatient therapy ($n = 60$) after 24 h of hospitalization | IV gentamicin + piperacillin/tazobactam | 90 |
| | | | versus | |
| | | | PO ciprofloxacin + amoxicillin/clavulanate | 84.8 |
| Klastersky et al. | [51] | Open-label study of oral, outpatient antibiotics in 79 low-risk patients | Ciprofloxacin + amoxicillin/clavulanate | 96 |
| Santolaya et al. | [52] | Prospective, randomized comparisons of hospital-based ($n = 71$) and ambulatory ($n = 78$) antibiotic therapy in low-risk pediatric patients following 24–36 h of hospitalization | IV ceftriaxone + teicoplanin (hospital based treatment) | 94 |
| | | | PO cefuroxime (ambulatory treatment) | 95 |

discharge on oral ciprofloxacin + amoxicillin/clavulanate was associated with a much lower readmission rate (7.6 %). The oral regimen was well tolerated, and there were no deaths among patients enrolled on this study. Investigators from the Institute Jules Bordet (Brussels, Belgium) also used this approach (i.e., early discharge on oral ciprofloxacin + amoxicillin/clavulante) in 79 patients, most of whom had solid tumors [51]. The overall success rate was 96 % with only 3 patients needing readmission. No serious complications or deaths occurred in this cohort of patients. In a similar study conducted in Chile, children presenting with fever and neutropenia were assigned to receive oral cefuroxime 24–36 h after hospitalization if categorized as being low risk [52]. Seventy-four (95 %) of 78 patients treated in this manner had a positive response. These studies demonstrate the adaptability and success of this approach on a global scale.

A significant proportion of patients cared for at a comprehensive cancer center such as the M. D. Anderson Cancer Center come from other nations, are uninsured, or pay out-of-pocket. Even a short hospital stay can have a significant financial impact on these patients and their families. In the early 1980s, approximately 90 patients with solid tumors who developed fever during episodes of chemotherapy-induced neutropenia were treated with oral TMP/SMX + clindamycin or rifampin, having refused hospital admission [K. R. –unpublished data]. Most responded to this therapy with no serious complications or deaths, and considerable cost savings. This experience served as background data for formal trials of outpatient antibiotic therapy at this center. To date, 3 randomized trials at M. D. Anderson Cancer Center (2 in adult patients and 1 in pediatric patients) have evaluated this approach (i.e., outpatient treatment of the entire febrile episode [53–55]. Smaller pilot studies and institutional pathways in place at M. D. Anderson Cancer Center have added to this experience which is summarized in Table 6 [56–59]. Investigators from other institutions have also adopted this approach and reported their findings [60]. These studies demonstrate that both parenteral and oral regimens are safe and effective with response rates ranging from 80 to 95 %. Many patients not responding to the initial regimen did not require hospital admission, as they responded to alternative outpatient regimens. Among the few patients that needed hospitalization, none had serious complications, none required intensive care, and there were no infection-related deaths. A recently published systematic review concluded that “oral antibiotics may safely be offered to neutropenic patients with fever who are at low-risk for mortality” [61].

Outpatient management of febrile neutropenic patients does require institutional infrastructure that some institutions just cannot afford, particularly if they see small numbers of cancer patients—Table 7. Additionally, some medially low-risk patients may not have the psychosocial backup and support to be candidates for outpatient therapy [45, 58]. These patients can be treated in the hospital with the regimens listed in Table 3 [43, 44, 62].

**Table 6** Outpatient (parenteral and oral) antibiotic therapy of low-risk, febrile neutropenic patients. Experience from clinical trials and institutional pathways at the M. D. Anderson Cancer Center

| Authors | Reference no | Type of study and patient population | Antibiotic regimens | (%) Response to initial regimen |
|---|---|---|---|---|
| Rubenstein et al. | [53] | Randomized trial of IV versus PO outpatient regimen. 83 episodes, all adult | IV—aztrenonam + clindamycin | 95 |
| | | | PO—ciprofloxacin + clindamycin | 88 |
| Rolston et al. | [54] | Randomized trial of IV versus PO outpatient regimens, 179 episodes, all adults | IV aztreonam + clindamycin | 87 |
| | | | PO ciprofloxacin + amoxicillin/clavulanate | 90 |
| Mullen et al. | [55] | Randomized trial of IV versus PO regimens in pediatric patients, 75 episodes | IV ceftazidime | 94 |
| | | | PO ciprofloxacin | 80 |
| Rolston et al. | [56] | Open label, pilot study of oral quinolone monotherapy in adult, 40 episodes | PO gatifloxacin | 95 |
| Rolston et al. | [57] | Open-label, pilot study of oral quinolone monotherapy in adults, 21 episodes | PO moxifloxacin | 95 |
| Elting et al. | [58] | 529 episodes, adult patients enrolled on institutional outpatient pathways | PO ciprofloxacin + amoxicillin/clavulanate | 80 |
| Escalante et al. | [59] | 257 episodes, adult patients enrolled on institutional outpatient pathways | IV ceftazidime + clindamycin | 80[a] |
| | | | PO ciprofloxacin + amoxicillin/clavulanate | |

*IV* intravenous, *PO* oral
[a]Combined response rate for parenteral and oral regimens, as individual response rates were not mentioned

## 6 Empiric Therapy for Patients Not Categorized as Low Risk

The accepted standard of care for febrile neutropenic patients that do not fall into the low-risk category is the prompt administration of broad-spectrum antibiotic therapy (based on local susceptibility/resistance patterns) with close monitoring

**Table 7** Requirements for a successful program of outpatient antibiotic therapy in low-risk febrile neutropenic patients

| |
|---|
| Institutional support for necessary infrastructure |
| Dedicated, multidisciplinary teams of healthcare providers, (physicians, nurses, pharmacists, infusion therapists, etc.) |
| Local epidemiologic/microbiologic detail including current susceptibility/resistance patterns |
| Adequate monitoring and follow-up |
| 24-h access to healthcare team including "hotline" number |
| Adequate transport/communication for patients |

for response and the development of complications in the hospital [2, 18]. The various treatment options are listed in Table 8 and include combination antibiotic regimens (usually an antipseudomonal beta-lactam + an aminoglycoside, or an agent with gram-positive activity such as vancomycin or linezolid), or monotherapy with a single, broad-spectrum, antipseudomonal beta-lactam [2, 18]. Prior to the emergence of gram-positive organisms as the predominant bacterial pathogens in neutropenic patients, combinations of an aminoglycoside (e.g., gentamicin, amikacin, tobramycin) with an antipseudomonal beta-lactam were the

**Table 8** Antibiotic regimens commonly used in febrile neutropenic patients not classified as low risk

| |
|---|
| *Combination regimens with vancomycin*[a] |
| Vancomycin + cefepime or ceftazidime[b] |
| Piperacillin/tazobactam |
| Imipenem or meropenem |
| Aztreonam[c] |
| Ciprofloxacin (or other quinolone)[d] |
| *Combination regimens without vancomycin* |
| Aminoglycoside + cefepime or ceftazidime[b] |
| Piperacillin/tazobactam |
| Imipenem or meropenem |
| Quinolone[d] |
| *Monotherapy* |
| Cefepime or ceftazidime[b] |
| Piperacillin/tazobactam |
| Imipenem or meropenem |

[a]Vancomycin is occasionally replaced by linezolid
[b]Ceftazidime not useful at many institutions due to the emergence of resistant pathogens
[c]Aztreonam used primarily in patients with severe beta-lactam allergy
[d]Quinolones should not be used if patients have received prophylaxis with these agents

most frequently used regimens in this setting. Advantages associated with such combinations included broad coverage against most pathogens encountered in such patients, possible synergy resulting in rapid bactericidal activity (an important consideration in neutropenic patients), and the potential for reducing the development of resistant organisms [2, 18, 63]. The disadvantages of such combinations were an increase in adverse events and organ toxicity (oto- or nephrotoxicity), the need to monitor drug levels frequently particularly in patients with renal insufficiency and those receiving other nephrotoxic drugs, and suboptimal activity against many gram-positive pathogens (e.g., MRSA, viridans group streptococci, *Enterococcus* species). With the emergence of resistant gram-positive organisms as frequent pathogens in neutropenic patients, the inclusion of vancomycin (and teicoplanin in other countries) and later linezolid into the initial regimen became commonplace [2, 18, 64, 65]. Several studies, however, have demonstrated that the initial use of a narrow-spectrum gram-positive agent like vancomycin is not associated with superior outcomes when compared to the addition of such agents after isolation of a gram-positive organism [66–68]. These data, and the association of increased and prolonged vancomycin usage with the selection of VRE and staphylococci with reduced susceptibility to vancomycin (VISA), have led to the recommendation by most experts and societies that vancomycin (and similar agents) should only be included in the initial regimen at institutions that have a high rate of isolation of resistant gram-positive pathogens, or in patients with known colonization or a previous infection with such agents [2, 18, 69].

With the development of truly broad-spectrum agents (extended spectrum cephalosporins, carbapenems, piperacillin/tazobactam), empiric monotherapy became an option [70–72]. Many prospective, randomized trials have demonstrated that monotherapy with agents such as ceftazidime, cefepime, imipenem, meropenem, and piperacillin/tazobactam is associated with response rates similar to various comparator combination regimens [73–78]. A recently published systematic review showed that monotherapy was as effective as combination therapy with similar mortality rates, and similar rates of bacterial and fungal superinfection [79]. Monotherapy regimens were also associated with lower rates of treatment failure and fewer adverse events.

The same group has published an analysis linking cefepime monotherapy with a higher all-cause mortality than other agents used for monotherapy, including ceftazidime [80]. These data need to be interpreted with caution. Ceftazidime has limited activity against many gram-positive organisms, and many gram-negative pathogens have developed considerable resistance to it over the years [81, 82]. At least one recent meta-analysis has reported lower response rates with ceftazidime, and this agent has largely been replaced by cefepime in clinical practice [83]. Additionally, the FDA has just completed its own meta-analysis based on additional data beyond those in the aforementioned publication [84]. The FDA has determined that cefepime remains an appropriate therapy for its approved indications (including neutropenic fever). The decision of which cephalosporin to use should be based on local and current susceptibility data and not on studies conducted over two decades

ago [82]. The weight of current data/opinion supports the use of empiric monotherapy for most neutropenic patients with fever [2, 18, 79]. In today's tight economic environment, monotherapy may represent the most cost-effective option. Figure 1 provides an algorithm for the management of febrile neutropenic patients based on risk groups.

## 7 Evaluation of Response

The median time to defervescence in low-risk patients is 2 days and approximately 5 days in patients not classified as low risk [85–87]. Persistence of fever for 3–5 days in otherwise stable patients does not necessarily indicate failure of the initial regimen, particularly in patients with profound neutropenia. Approximately 70–80 % of patients will respond to the empiric regimen during this initial period [2, 18]. Persistence of fever beyond 3–5 days should lead to a full re-evaluation of the patient including a search for a drainable (abscess) or removable (infected medial device) focus, or development of a secondary or superinfection. A change in the initial regimen is recommended at this stage. This may consist of additional antibacterial agents if there were gaps in the original regimen, or the administration of antifungal or antiviral agents, if indicated [24].

In patients who remain febrile, imaging of various sites (paranasal sinuses, chest, abdomen), Doppler or venous flow studies, and various serologic tests may provide diagnostic clues. Occasionally, more invasive procedures (generally biopsy of various tissues) might be necessary but are often deferred as many neutropenic patients are severely thrombocytopenic as well. A small proportion of patients will have a non-infectious cause of fever, such as tumor fever or drug fever.

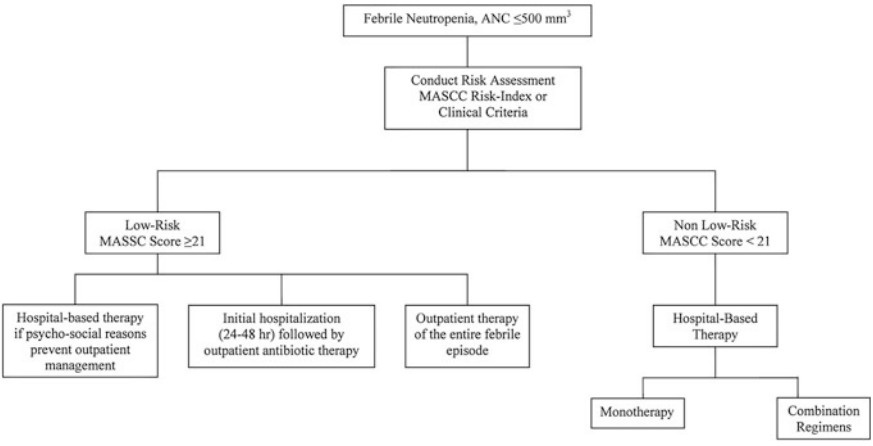


**Fig. 1** Algorithm for the management of febrile neutropenic patients (Adapted from Refs. [2, 5, 18, 24, 41, 45])

## 8 Duration of Therapy

The duration of therapy continues to be vigorously debated. One approach is to continue antibiotic therapy in all patients until the resolution of neutropenia (ANC $> 500/mm^3$ for 2 days) regardless of whether or not an infection was documented during the febrile episode [2, 18]. Another approach is the administration of therapy for approximately 3–4 days after resolution of all signs and symptoms of infection (including microbiologic or radiographic evidence if present initially), with a minimum of 7 days of treatment, regardless of whether or not the patients have persistent neutropenia. The former approach may result in needless administration of antibiotics to many patients, potentially increasing health care costs, toxicity, and the development of bacterial or fungal superinfections. The latter approach requires careful observation of the patient after discontinuation of therapy. The ultimate decision as to when to stop therapy often needs to be individualized and depends on various factors including (1) the patient's risk group, (2) the presence and nature of a documented infection, (bacteremia, pneumonia, urinary tract infection), (3) the nature of the underlying malignancy (solid tumor or hematologic malignancy), (4) the need for additional chemotherapy or immunosuppressive therapy or invasive procedures, and (5) the persistence of neutropenia. Some patients with documented infections and persistent neutropenia might benefit from the administration of hematopoietic growth factors (G-CSF; GM-CSF) and/or granulocyte transfusions, but their use remains controversial [88–90].

## 9 Antimicrobial Prophylaxis

A detailed discussion on antimicrobial prophylaxis is beyond the scope of this review. As already mentioned, the risk of developing severe infection is not uniform among all cancer patients, but is largely dependent on the underlying disease and the severity and duration of neutropenia. The benefit of antibacterial prophylaxis in reducing documented infections has only been established in patients with neutropenia exceeding 7 days. A recent meta-analysis showed increased survival in patients receiving antibacterial (quinolone) prophylaxis, especially patients with hematologic malignancies [91]. Routine antibacterial prophylaxis should not be given to patients in whom neutropenia is expected to last less than 7 days. This group includes most patients with solid organ malignancies [92]. The main drawback of antibacterial prophylaxis, even when it is clinically indicated, is the emergence of resistant organisms [93]. Consequently, local microbiological monitoring for the emergence of such organisms (primarily *E. coli* and *P. aeruginosa*) is recommended in institutions where prophylaxis is commonplace [94]. Trimethoprim–sulfamethoxazole is the agent of choice for the prevention of *Pneumocystis jivoreci* infection in patients at risk. Alternative agents include dapsone, pentamidine, and atovaquone [95]. Mold-active prophylaxis

(echinocandin, mold-active azole) is recommended in patients at high risk for developing invasive fungal infections, including recipients of allogeneic hematopoietic stem cell transplantation [96–99]. As always, the risks and benefits associated with antifungal prophylaxis need to be weighed before deciding on whether or not to administer prophylaxis [100].

## 10 Antimicrobial Stewardship

Antimicrobial agents are used with greater frequency and for a larger number of indications (prophylaxis, preemptive therapy, empiric therapy, targeted or specific therapy of a documented infection, and maintenance/suppressive therapy) in cancer patients than in most other patient populations [2]. Although justified, this has created pressures leading to the emergence of resistant organisms [93]. Traditionally, the development of novel antimicrobial agents has been an important tool in battling the problems caused by resistant organisms. However, the development of novel agents is at an all time low, mandating the judicious use of currently available agents—i.e., antimicrobial stewardship. The various strategies for antimicrobial stewardship program are listed in Table 9, and include a multidisciplinary antibiotic stewardship team (MAST), institutional pathways/

**Table 9** Recommendations for antimicrobial stewardship

| |
|---|
| *Baseline data/infrastructure* |
| Determine local epidemiology and resistance patterns |
| Know institutional formulary and prescribing habits |
| Develop multidisciplinary antimicrobial stewardship team (MAST) |
| *Recommendations for antimicrobial usage* |
| Limit antibacterial prophylaxis |
| Encourage targeted/specific therapy |
| Consider formulary restriction and/or preauthorization |
| Create guidelines and clinical pathways |
| Consider antimicrobial heterogeneity |
| Consider de-escalation (streamlining) of empiric regimen |
| Dose optimization |
| Parenteral to oral conversion |
| Optimization of duration of therapy |
| *Other strategies* |
| Prospective audits of antimicrobial usage with feedback to prescribers |
| Educational activities (grand rounds, in-services) |
| Strict adherence to infection control policies |

guidelines, formulary restrictions or preapproval requirements for certain agents, and de-escalation or streamlining of therapy when appropriate [10]. Antibiotic stewardship programs have been successfully implemented at several institutions (including ours) and in the opinion of this investigator will soon become mandatory at most institutions [11, 101–103].

## 11 Summary

Neutropenic patients continue to develop serious infections despite significant improvements in the supportive care of cancer patients, and the implementation of preventive and infection control strategies. The spectrum of infection undergoes periodic change with the emergence of newer opportunistic pathogens and/or the development of resistance among well-recognized pathogens. Prompt, empiric antibiotic therapy when a neutropenic patient becomes febrile remains the standard of care. However, not all neutropenic patients have the same risk of developing severe infections and associated complications. Low-risk patients can now be accurately identified at the onset of a febrile episode, and these patients can be treated with a short duration (24–48 h) of hospitalization followed by outpatient therapy, or can be managed entirely as outpatients. Very little change has occurred in the management of moderate-to-high-risk febrile neutropenic patients over the past decade. These patients are best managed in the hospital to facilitate close monitoring for the development of serious medical complications. Antimicrobial stewardship has become an important strategy in the overall management of neutropenic patients, especially since new drug development has declined appreciably. It is hoped that antimicrobial stewardship and strict adherence to infection control policies will reduce the emergence and spread of multidrug-resistant organisms, which are posing serious therapeutic challenges to clinicians caring for these high-risk patients. The development of less myelotoxic/immunosuppressive agents can mitigate this situation considerably, but remains a distant goal.

## References

1. Bodey GP, Buckley M, Sathe YS et al (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328–340
2. Freifeld AG, Bow EJ, Sepkowicz KA et al (2011) Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 52:e56–e93
3. Bodey GP, Fainstein V, Elting LS et al (1990) Beta-lactam regimens for the febrile neutropenic patient. Cancer 65:9–16
4. Rolston KVI (2003) Oral antibiotic administration and early hospital discharge is a safe and effective alternative for treatment of low-risk neutropenic fever. Cancer Treat Rev 29:551–554
5. Klastersky J (2004) Management of fever in neutropenic patients with different risks of complications. Clin Infect Dis 39:S32–S37

6. Greene RE, Schlamm HT, Oestmann JW et al (2007) Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 44:373–379
7. Wheat LJ, Walsh TJ (2008) Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. Eur J Clin Microbiol Infect Dis 27:245–251
8. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Speilberg B, Bartlett J (2009) Bad bugs, no drugs: no ESKAPE! An update from the infectious diseases society of America. Clin Infect Dis 48(1):1–12
9. Talbot GH, Bradley J, Edwards JE Jr et al (2006) Bad bugs need drugs: an update on the development pipeline from the antimicrobial availability task force of the infectious diseases society of America. Clin Infect Dis 42:657–668
10. Dellit TH, Owens RC, McGowan JE et al (2007) Infectious diseases society of America and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 44:159–177
11. Paskovaty A, Pflomm JM, Myke N et al (2005) A multidisciplinary approach to antimicrobial stewardship: evolution into the 21st century. Int J Antimicrob Agents 25:1–10
12. Diekema DJ, Jones RN, Rolston KVI (1999) Antimicrobial activity of gatifloxacin compared to seven other compounds tested against gram-positive organisms isolated at 10 cancer-treatment centers. Diagn Microbiol Infect Dis 34:37–43
13. Rolston KVI, Kontoyiannis DP, Yadegarynia D et al (2005) Nonfermentative gram-negative bacilli in cancer patients: increasing frequency of infection and antimicrobial susceptibility of clinical isolates to fluoroquinolones. Diag Microbiol Infect Dis 51:215–218
14. Zinner SH (1999) Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. Clin Infect Dis 29:490–494
15. Jacobson K, Rolston K, Elting L et al (1999) Susceptibility surveillance among gram-negative bacilli at a cancer center. Chemotherapy 45:325–334
16. Wisplinghoff H, Seifert H, Wenzel RP et al (2003) Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 36:1103–1110
17. Yadegarynia D, Tarrand J, Raad I (2003) Current spectrum of bacterial infections in cancer patients. Clin Infect Dis 37:1144–1145
18. Rolston KVI, Bodey GP (2006) Infections in patients with cancer. In: Kufe DW, Bast RC Jr, Hait WN, Hong WK, Pollock RE, Weichselbaum RR, Holland JF, Frei E III (eds) Cancer medicine, e7. BC Decker, Hamilton, Ontario, pp 2222–2245
19. Elting LS, Bodey GP, Fainstein V (1986) Polymicrobial septicemia in the cancer patient. Medicine 65:218–225
20. Rolston KVI, Bodey GP, Safdar A (2007) Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. Clin Infect Dis 45:228–233
21. Adachi JA, Yadegarynia D, Rolston K (2003) Spectrum of polymicrobial bacterial infection in patients with cancer, 1975–2002. (Abstract 4) In: American Society for Microbiology. Polymicrobial diseases, Lake Tahoe, NV, Oct. 19–23
22. Rolston KVI, Tarrand JJ (1999) *Pseudomonas aeruginosa*—Still a frequent pathogen in patients with cancer: 11-year experience from a comprehensive cancer center. Clin Infect Dis 29:463–464
23. Safdar A, Rolston KV (2007) *Stenotrophomonas maltophilia*: changing spectrum of a serious bacterial pathogen in patients with cancer. Clin Infect Dis 45:1602–1609
24. Sipsas NV, Bodey GP, Kontoyiannis DP (2005) Perspectives for the management of febrile neutropenic patients with cancer in the twentyfirst Century. Cancer 103:1103–1113
25. Fainstein V, Elting LS, Bodey GP (1989) Bacteremia caused by non-sporulating anaerobes in cancer patients A 12 year experience. Medicine 68:151–162
26. Gifford AH, Kirkland KB (2006) Risk factors for *Clostridium difficile*-associated diarrhea on an adult hematology-oncology ward. Eur J Clin Microbiol Infect Dis 25:751–755

27. Han XY, Dé I, Jacobson KL (2007) Rapidly growing mycobacteria clinical and microbiologic studies of 115 cases. Am J Clin Pathol 128:612–621
28. Abi-Said D, Anaissie E, Uzun O et al (1997) The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis 24:1122–1128
29. Hachem R, Hanna H, Kontoyiannis D et al (2008) The changing epidemiology of invasive candidiasis. *Candida glabrata* and *Candida krusei* as the leading causes of candidemia in hematologic malignancy. Cancer 112:2493–2499
30. Horn DL, Neofytos D, Anaissie E et al (2009) Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis 48:1695–1703
31. Wingard JR, Merz WG, Rinaldi MC et al (1991) Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 325:1274–1277
32. Mullen CA, Abd El-Baki H, Samir H et al (2003) Non-*albicans Candida* is the most common cause of candidemia in pediatric cancer patients. Support Care Cancer 11:321–325
33. Chamilos G, Luna M, Lewis RE et al (2006) Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica 91:986–989
34. Patterson TF, Kirkpatrick WR, White M et al (2000) Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. Medicine 79:250–260
35. Trifilio SM, Bennett CL, Yarnold PR et al (2007) Breakthrough zygomycosis after voriconazole administration among patients with hematolgic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. Bone Marrow Transplant 39:425–429
36. Marty FM, Cosimi LA, Baden LR (2004) Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med 350:950–952
37. Siwek GT, Dodgson KJ, de Magalhaes-Silverman M et al (2004) Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. Clin Infect DIs 39:584–587
38. Kontoyiannis DP, Wessel VC, Bodey GP et al (2000) Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis 30:851–856
39. Khanna N, Widmer AF, Decker M et al (2008) Respiratory syncytial virus infection in patients with hematological diseases: Single-center study and review of the literature. Clin Infect Dis 46:402–412
40. Cooksley CD, Avritscher EBC, Bekele BN et al (2005) Epidemiology and outcomes of serious influenza-related infections in the cancer population. Cancer 104:618–628
41. Klastersky J, Paesmans M, Rubenstein E et al (2000) The MASCC risk index: a multinational scoring system to predict low-risk febrile neutropenic cancer patients. J Clin Oncol 18:3038–3051
42. Santolaya ME, Alvarez AM, Avilés CL et al (2002) Prospective evaluation of a model of prediction of invasive bacterial infection risk among children with cancer, fever and neutropenia. Clin Infect Dis 35:678–683
43. Freifeld A, Marchigiani D, Walsh T et al (1999) A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. N Engl J Med 341:305–311
44. Kern WV, Cometta A, De Bock R et al (1999) Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. N Engl J Med 341:312–318 International antimicrobial therapy cooperative group of the European organization for research and treatment of cancer
45. Rolston K (1999) New trends in patient management: risk-based therapy for febrile patients with neutropenia. Clin Infect Dis 29:515–521
46. Bodey GP, Grose WE, Keating MJ (1982) Use of trimethoprim-sulfamethoxazole for treatment of infections in patients with cancer. Rev Infect Dis 4:579–585

47. Haron E, Rolston KVI, Cunningham C et al (1989) Oral ciprofloxacin therapy for infections in cancer patients. J Antimicrob Chemother 24:955–962
48. Talcott JA, Finberg R, Mayer RJ et al (1988) The medical course of cancer patients with fever and neutropenia: clinical identification of a low-risk subgroup at presentation. Arch Intern Med 148:2561–2568
49. Talcott JA, Whalen A, Clark J et al (1994) Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. J Clin Oncol 12:107–114
50. Innes HE, Smith DB, O'Reilly SM et al (2003) Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomized controlled single centre study. Br J Cancer 89:43–49
51. Klastersky J, Paesmans M, Georgala A et al (2006) Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. J Clin Oncol 24:4129–4134
52. Santolaya ME, Alvarez AM, Avilés CL et al (2004) Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. J Clin Oncol 22:3784–3789
53. Rubenstein EB, Rolston K, Benjamin RS et al (1993) Outpatient treatment of febrile episodes in low risk neutropenic cancer patients. Cancer 71:3640–3646
54. Rolston K, Rubenstein E, Elting L et al (1995) Ambulatory management of febrile episodes in low-risk neutropenic patients [abstract LM81]. In: program and abstract of the 35th interscience conference on antimicrobial agents and chemotherapy, American Society for Microbiology, Washington, DC
55. Mullen CA, Petropoulos D, Roberts WM et al (1999) Outpatient treatment of febrile neutropenia in low risk pediatric cancer patients. Cancer 86:126–134
56. Rolston KVI, Manzullo EF, Elting LS et al (2006) Once daily, oral, outpatient quinolone monotherapy for low-risk cancer patients with fever and neutropenia. Cancer 106:2489–2494
57. Rolston KVI, Frisbee-Hume SE, Patel S et al (2009) Oral moxifloxacin for outpatient treatment of low-risk, febrile neutropenic patients. Support Care Cancer 18(1):89–94
58. Elting LS, Lu C, Escalante CP et al (2008) Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. J Clin Oncol 26:606–611
59. Escalante CP, Weiser MA, Manzullo E et al (2004) Outcomes of treatment pathways in outpatient treatment of low risk febrile neutropenic cancer patients. Support Care Cancer 12:657–662
60. Hidalgo M, Hornedo J, Lumbreras JM et al (1999) Outpatient therapy with oral ofloxacin for patients with low risk neutropenia and fever. Cancer 85:213–219
61. Vidal L, Paul M, Ben dor I et al (2004) Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients: a systematic review and meta-analysis of randomized trials. J Antimicrob Chemother 54:29–37
62. Kern KV (2006) Risk assessment and treatment of low-risk patients with febrile neutropenia. Clin Infect Dis 15:533–540
63. Rolston KVI (2004) The infectious diseases society of America 2002 guidelines for the use of antimicrobial agents in patients with cancer and neutropenia: salient features and comments. Clin Infect Dis 39(Suppl 1):S44–S48
64. Rolston KVI, Nguyen H, Amos G et al (1994) A randomized double-blind trial of vancomycin versus teicoplanin for the treatment of gram-positive bacteremia in patients with cancer. J Infect Dis 69:350–355
65. Jaksic B, Martinelli G, Perez-Oteyza J et al (2006) Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis 42:597–607

66. Cinetta A, Kern WV, De Bock R et al (2003) Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. Clin Infect Dis 37:382–389
67. Rubin M, Hathorn JW, Marshall D et al (1988) Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. Ann Intern Med 108:30–35
68. Ramphal R, Bolger M, Oblon DJ et al (2003) Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. Antimicrob Agents Chemother 36:1062–1067
69. Segal BH, Freifeld AG, Baden LR et al (2008) Prevention and treatment of cancer-related infections. J Natl Compr Canc Netw 6:122–174
70. Pizzo PA, Hathorn JW, Hiemenez J et al (1986) A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N Engl J Med 315:552–558
71. Rolston K, Berkey P, Bodey GP et al (1992) A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. Arch Intern Med 152:283–291
72. Behre G, Link H, Maschmeyer G et al (1998) Meropenem monotherapy versus combination therapy with ceftazidime and amikacin for empirical treatment of febrile neutropenic patients. Ann Hematol 76:73–80
73. Cometta A, Calandra T, Gaya H et al (1996) Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The international antimicrobial therapy cooperative group of the European organization for research and treatment of cancer and the gruppo italiano malattie ematologiche maligne dell'adulto infection program. Antimicrob Agents Chemother 40:1108–1115
74. Akova M, Akan H, Korten V et al (1999) Comparison of meropenem with amikacin plus ceftazidime in the empirical treatment of febrile neutropenia: a prospective randomized multicentre trial in patients without previous prophylactic antibiotics. Meropenem study group of Turkey. Int J Antimicrob Agents 13:15–19
75. Yamamura D, Gucalp R, Carlisle P et al (1997) Open randomized study of cefepime versus piperacillin-gentamicin for treatment of febrile neutropenic cancer patients. Antimicrob Agents Chemother 41:1704–1708
76. Del Favero A, Menichette F, Martino P et al (2001) A multicenter, double-blind, placebo-controlled trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropenia. Clin Infect Dis 33:1295–1301
77. Raad II, Abi-Said D, Rolston KV et al (1998) How should imipenem-cilistatin be used in the treatment of fever and infection in neutropenic cancer patients? Cancer 82:2449–2458
78. Feld R, DePauw B, Berman S et al (2000) Meropenem versus ceftazidime in the treatment of cancer patients with febrile neutropenia: a randomized, double-blind trial. J Clin Oncol 18:3690–3698
79. Paul M, Soares-Weiser K, Leibovici L (2003) Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. Brit Med J 326:1111–1119
80. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L (2007) Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis 7:338–348
81. Rolston KVI, Kontoyiannis DP, Raad II, LeBlanc BJ, Streeter HL, Ho DH (2003) Susceptibility surveillance among gram-negative bacilli at a comprehensive cancer center (Abstract A-004). In: 103rd general meeting American Society of Microbiology. Washington, D.C., May 18–22

82. Rolston KVI, Bodey GP (2006) Comment on: empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother 58:478
83. Glasmacher A, von Lilienfled-Toal M, Schulte S et al (2005) An evidence-based evaluation of important aspects of empirical antibiotic therapy in febrile neutropenic patients. Clin Microbiol Infect 11(Suppl 5):17–23
84. Kim PW, Wu YT, Cooper C, Rochester G, Valappil T, Wang Y, Kornegay C, Nambiar S (2010) Meta-analysis of a possible signal of increased mortality associated with cefepime use. Clin Infect Dis 51(4):381–389
85. Elting LS, Rubenstein EB, Rolston K et al (2000) Time to clinical response: an outcome of antibiotic therapy of febrile neutropenia with implications for quality and cost of care. J Clin Oncol 18:3699–3706
86. Pizzo PA, Robichard KJ, Gill FA (1979) Duration of empiric antibiotic therapy in granulopenic patients with cancer. Am J Med 67:194–199
87. Corey L, Boeckh M (2002) Persistent fever in patients with neutropenia. N Engl J Med 346:222–224
88. Smith TH, Khatcheressian J, Lyman GH et al (2006) 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24:3187–3205
89. Hübel K, Carter RA, Liles WC et al (2002) Granulocyte transfusion therapy for infections in candidates and recipients of HPC transplantation: a comparative analysis of feasibility and outcome for community donors versus related donors. Transfusion 42:1414–1421
90. Price TH, Bowden RA, Boeckh M et al (2000) PhaseI/II trial of neutrophil transfusions from donors stimulated with G-CSF and dexamethasone for treatment of patients with infections in hematopoietic stem cell transplantation. Blood 95:3302–3309
91. Gafter-Gvili A, Fraser A, Paul M et al (2005) Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 142:979–995
92. Segal BH, Freifeld AG (2007) Antibacterial prophylaxis in patients with neutropenia. J Natl Compr Cancer Netw 5:235–242
93. Kern WV, Andriof E, Oethinger M et al (1994) Emergence of fluoroquinolone-resistant *Escherichia coli* at a cancer center. Antimicrob Agents Chemother 38:681–687
94. Baden LR (2005) Prophylactic antimicrobial agents and the importance of fitness. N Engl J Med 353:1052–1054
95. Green H, Paul M, Vidal L et al (2007) Prophylaxis for *Pneumocystis* pneumonia (PCP) in non-HIV immunocompromised patients (review). Cochrane Database Syst Rev 3, Art No.: CD005590
96. Hamza NS, Ghannoum MA, Lazarus HM (2004) Choices aplenty: antifungal prophylaxis in hematopoietic stem cell transplant recipients. Bone Marrow Transpl 34:377–389
97. van Burik JAH (2005) Role of new antifungal agents in prophylaxis of mycoses in high risk patients. Curr Opin Infect Dis 18:479–483
98. van Burik JAH, Ratanatharathorn V, Stepan DE et al (2004) Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 39:1407–1416
99. Cordonnier C, Maury S, Pautas C et al (2004) Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. Bone Marrow Transpl 33:943–948
100. DePauw BE, Donnelly JP (2007) Prophylaxis and aspergillosis—has the principle been proven? N Engl J Med 356:409–411

101. Metjian TA, Prasad PA, Kogon A et al (2008) Evaluation of an antimicrobial stewardship program at a pediatric teaching hospital. Pediatr Infect Dis J 27:106–111
102. Agwu A, Lee CKK, Jain SK et al (2008) A worldwide web-based antimicrobial stewardship program improves efficiency, communication, and user satisfaction and reduces cost in a tertiary care pediatric medical center. Clin Infect Dis 47:747–753
103. Mulanovich V, Chemaly R, Mihu C et al (2009) Antimicrobial stewardship program in the critical care unit (CcU) of a comprehensive cancer center. (Abst. 09-070). Multinational Association for Supportive Care in Cancer 2009 International MASCC/ISOO Symposium Rome, Italy, June 25–27

# Respiratory Infections

Evan J. Anderson

**Abstract**

The respiratory tract is a common site of infection in cancer patients and is associated with substantial moribidity and mortality in this population. Cancer, chemotherapy, and radiation can all cause noninfectious pulmonary infiltrates and respiratory symptoms that can masquerade as a respiratory tract infection. Cancer patients are at a particular risk for infection by a wide variety of different viruses, fungi, and bacteria that can be difficult to treat. Although noninvasive diagnostics have significantly improved recently, patients with severe pneumonia and those not responding to usual therapy should be candidates for aggressive diagnostic testing and tissue sampling. Initial therapy should be carefully chosen and individually tailored to account for the individual patient's underlying risk factors for multi-drug-resistant pathogens, viral pathogens, or fungi. Once diagnostic testing returns, therapy should be altered to appropriately narrow the spectrum of coverage.

**Keywords**

Pneumonia · Cancer · Stem cell transplant · Lower respiratory tract infections

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## Contents



## 1 Introduction

Respiratory tract infections are a common cause of illness among patients with cancer and are a substantial source of morbidity and mortality. Data regarding the incidence and epidemiology of respiratory tract infections in cancer patients are limited. In 2006, cancer was identified as the second leading cause of death in the United States (nearly 560,000 deaths), while influenza and pneumonia were listed at number 8 (comprising over 56,000 deaths) [1]. Mortality in the national vital statistics reports is listed as due to a single cause, while a substantial amount of mortality is due to the combination of cancer and pneumonia. Additionally, the fourth leading cause of death is chronic lower respiratory diseases (e.g., chronic obstructive pulmonary disease), which overlaps with lung cancer and pneumonia. Of documented infections in patients with febrile neutropenia, 15–30 % are eventually documented to be pneumonia [2]. Thus, although a detailed understanding of the morbidity and mortality associated with pneumonia in patients with malignancy is limited, the burden is substantial.

Respiratory tract infections are often divided into upper and lower respiratory tract infections. Upper respiratory tract infections primarily involve the nose, pharynx, and other adjacent structures. Lower respiratory tract infections are often defined as having evidence of infection, respiratory symptoms or physical examination findings suggesting lower respiratory tract disease, and abnormal chest imaging. Lower respiratory tract infections include bronchitis, bronchiolitis (e.g., in young children), and pneumonia.

A detailed discussion of upper respiratory tract infections is beyond the scope of this book chapter. Included within upper respiratory tract infections are pharyngitis, rhinitis, otitis media, and sinusitis. The majority of upper respiratory infections are due to viral etiologies [3]. Although pharyngitis may be due to viral etiologies (e.g., herpes simplex virus, cytomegalovirus, or Epstein Barr virus),

chemotherapy- or radiation-induced mucositis and bacterial etiologies (e.g., *Streptococcus pyogenes* most commonly) may also occur.

Rarely perioral infections that involve the floor of the mandible can rapidly dissect through the tissue planes of the neck to cause Ludwig's angina. In this disease process, a "bull neck" develops with potential airway narrowing and respiratory compromise, and risk of progression into the mediastinum. Lemierre's syndrome can also develop due to spread of infection from the perioral space into the soft tissues of the neck causing a septic thrombophlebitis of the jugular vein and septic emboli to the lungs. *Fusobacterium*, an oral anaerobe, is most commonly responsible. These infections are uncommon, but potentially life threatening.

Otitis media and sinusitis can occur in patients with underlying malignancies. In healthy patients infections are most commonly due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [4]. In patients with more chronic disease, *Staphylococcus aureus*, enteric gram-negative bacteria, and anaerobes can also occur. In the setting of neutropenia or chronic graft versus host disease (GVHD), the possibility of invasive fungal sinusitis should be entertained and aggressively evaluated for if the patient develops symptoms potentially consistent with sinusitis. Rapid development of ocular findings, cranial nerve palsies, or mental status changes in the setting of sinusitis should prompt emergent sinus imaging and evaluation by an otolaryngologist for possible surgical debridement and biopsy. Failure to respond to usual empiric antibiotic therapy should also prompt additional imaging and possibly more invasive strategies to identify a pathogen and to evaluate for complications.

Lower respiratory tract infections classically include bronchitis, bronchiolitis, pneumonitis, and pneumonia. These terms are poorly defined, substantial overlap exists, and differentiation between these entities in an individual patient may be difficult. This chapter will refer to lower tract respiratory disease as pneumonia unless otherwise specified. Most epidemiological studies and clinical trials of pneumonia have required patients to have evidence of acute illness (e.g., fever, leukocytosis, or severe leukopenia), evidence of acute respiratory symptoms (e.g., cough, dyspnea, tachypnea, abnormal breath sounds), and abnormal imaging of the chest suggesting pulmonary abnormality (e.g., lobar consolidation) [5–8]. Unfortunately, many clinical trials of pneumonia have excluded most or all patients with underlying malignancies, and guidelines do not adequately address the issues in this patient population [9–14].

## 2 Differential Diagnosis of Pneumonia

The differential diagnosis of pulmonary infiltrates is broad and is outlined in Table 1. Considerations include cardiac, pulmonary, malignant, inflammatory, and infectious processes. Notably, cardiac or pulmonary toxicity from comorbid medical conditions (e.g., rheumatoid arthritis) or medications (e.g., amiodarone) can occur in the setting of cancer management. Cardiotoxic chemotherapeutic

**Table 1** Common causes of respiratory symptoms or disease in cancer patients

| |
|---|
| ***Infectious*** |
| Lower respiratory tract illness (e.g., pneumonia) |
| Septic emboli from bacteremia |
| Sepsis |
| Aspiration pneumonia |
| Aspiration pneumonitis |
| Post-obstructive pneumonia (particulary in setting of an obstructing malignancy) |
| ***Cardiac*** |
| Acute myocardial infarction (AMI) |
| Congestive heart failure (CHF) with pulmonary edema |
| Chronic |
| Acute e.g., due to AMI or acute valvular insufficiency |
| Cardiac toxicity from prior therapy, including |
| Cyclophosphamide |
| Mitoxantrone |
| Anthracyclines |
| Paclitaxel and docetaxel |
| Trastuzumab |
| Mediastinal or total body irradiation |
| ***Pulmonary*** |
| Noncardiogenic pulmonary edema |
| Volume overload |
| Capillary leak (e.g., sepsis) |
| Pulmonary embolism (particularly with infarction) |
| Fat embolism |
| Transfusion-related lung injury |
| Alveolar hemorrhage |
| Idiopathic eosinophilic pneumonia |
| ARDS |
| Preexisting pulmonary disease (e.g., COPD, bronchiectasis) |
| Preexisting medical disease (e.g., rheumatoid arthritis) |
| Medication related (e.g., amiodarone) |

(continued)

**Table 1** (continued)

| ***Oncological*** |
|---|
| Metatstatic malignancy |
| Primary lung malignancy |
| Leukemic infiltrates |
| ***Treatment-Related Pulmonary Toxicity*** |
| Radiation-induced pneumonitis and fibrosis |
| Medication related, including |
| Bleomycin |
| Busulfan |
| Chorambucil |
| Cyclophosphamide |
| Gefitinib |
| Methotrexate |
| Nitrosoureas |
| Procarbazine |
| Rituximab |
| Taxanes |
| mTor inhibitor-associated pneumonitis |
| Others |
| Cryptogenic organizing pneumonia (COP) (bronchiolitis obliterans organizing pneumonia, BOOP) |
| ***After stem cell or bone marrow transplantation*** |
| Idiopathic pneumonia syndrome (idiopathic interstitial pneumonitis) |
| Graft versus host disease (GVHD) |

agents such as cyclophosphamide, anthracyclines, mitoxantrone, paclitaxel, docetaxel, and trastuzumab or mediastinal radiation should always be considered as a potential cause of cardiovascular dysfunction, which may present with primarily respiratory symptoms [15, 16]. Similarly, interstitial pneumonitis may result from treatment with bleomycin, cyclophosphamide, gemcitabine, cytarabine, fluorouracil, procarbazine, gefitinib, rituximab, and many other agents [15, 17, 18]. In addition, inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus, everolimus, and temsirolimus, can cause a progressive noninfectious pneumonitis [19, 20].

Other complications of cancer treatment such as volume overload, acute lung injury after blood transfusion, pulmonary embolism, and diffuse alveolar hemorrhage should also be considered. Primary lung cancer or metastatic disease can

also result in pulmonary opacities. Sometimes, malignancies, particularly primary lung cancer, can obstruct or impede air flow into or out of the lung, resulting in a post-obstructive pneumonia or a lung abscess. Radiation pneumonitis, particularly if associated with fever and an elevation in white blood cell count [21], is often difficult to distinguish from an infectious pneumonitis [22]. The infiltrates with radiation pneumonitis can have a perivascular haziness which can progress to patchy alveolar filling infiltrates [21]. In addition, multiple disease processes can simultaneously occur in the lungs, and this possibility should be entertained.

Indwelling catheter infections must also be considered in patients with symptoms of infection and pulmonary infiltrates on chest imaging. Indwelling catheters dramatically increase the risk of bloodstream infections and endocarditis. Bacteremia or right-sided endocarditis can result in embolic pulmonary infiltrates (typically peripheral) and respiratory distress. Bacteremia and sepsis can also result in capillary leak with associated diffuse patchy infiltrates or acute respiratory distress syndrome (ARDS).

## 3 Epidemiological Risk Factors for Pneumonia

Certain epidemiological risk factors exist for pneumonia, and ascertainment of such factors in an individual patient can be helpful in expanding or altering the differential diagnosis. A history of cigarette smoking has been identified as the strongest epidemiological risk factor for invasive pneumococcal disease in immunocompetent, nonelderly adults [23]. The season of the year should be considered as many respiratory viral infections occur predominantly in the winter and spring (e.g., influenza, respiratory syncytial virus (RSV), and human metapneumovirus). Children, particularly those in daycare, may transmit respiratory viruses such as RSV and influenza which are risk factors for invasive pneumococcal disease [23]. Sick contacts also may be a source for less commonly observed infections such as tuberculosis or measles. A history of exposure to tuberculosis is important since it may remain in a latent state for years before reactivating with increasing age or immune depletion. It is very important to consider that approximately 60 % of tuberculosis cases diagnosed in the United States occur in individuals who were born outside the United States [24]. Geographic factors are also helpful in considering endemic fungi such as histoplasmosis (the Mississippi and Ohio River valleys) and coccidioidomycosis (desert southwest, particularly the San Joaquin valley) which are more frequently observed in cancer patients. Although blastomycosis is frequently mistaken for lung cancer or a metastatic malignancy, symptomatic disease is uncommon in those with cancer but may occur more frequently in those with defects in cell-mediated immunity [25]. Exposure to certain pets such as parakeets or parrots (a cause of psittacosis) or other animals such as birthing livestock (resulting in risk of infection with *Coxiella burnetti* or Q-fever) can suggest other uncommon causes of pneumonia. Ongoing construction at a medical center without appropriate

protective measures or exposure to aerosolized soil can result in an increased risk of *Aspergillus* pneumonia [26]. These and other nosocomial risk factors for *Aspergillus* and also for *Legionella* infections are outlined elsewhere in this volume (Chapter Infection Control and Prevention Considerations).

Recent history of a preceding or current viral illness should be obtained. It has been known that coinfections or mixed infections can be identified in community-acquired pneumonia (CAP) [12, 27]. Improved diagnostic testing, particularly the recent application of PCR testing for respiratory viral pathogens, has resulted in a greater appreciation for the interaction that can occur between bacterial and viral pathogens. In previously healthy children and adults who are admitted with pneumonia, 5–30 % have both viruses and bacteria identified using molecular techniques [10, 28–33]. Additionally, viruses (e.g., influenza, RSV, and human metapneumovirus) have an important role in predisposing patients to invasive bacterial pneumonia. In a case-controlled study, prior influenza infection, 1–4 weeks before, predisposed children to subsequent severe pneumococcal pneumonia requiring hospitalization with an odds ratio of 12.4 [34]. Influenza infection is also a risk factor for severe *S. aureus* pneumonia (particularly methicillin-resistant *S. aureus* or MRSA) [35, 36]. A recent review of autopsies of patients who died during the 1918 influenza pandemic suggested that much of the mortality was actually due to bacterial superinfection [37]. Others have also identified *S. pneumoniae* more frequently in nasopharyngeal secretions in those with severe novel 2009 H1N1 disease than in those with mild cases [38]. Additional pediatric data suggest that invasive pneumococcal disease correlates with a preceding RSV infection (up to 4 weeks later) and with a preceding human metapneumovirus or influenza infection (up to 2 weeks later) [38]. It should be noted that pneumococcal vaccination of children has been associated with a decrease in lower respiratory tract infections caused by influenza, parainfluenza, RSV, and human metapneumovirus [39, 40]. Thus, although data are lacking specifically in the cancer patient population, recent data suggest that viruses may predispose to subsequent bacterial infection and that bacteria and viruses are commonly coidentified in pneumonia.

Additional baseline epidemiological risk factors related to the underlying malignancy should be assessed. For example, a lung cancer patient with underlying chronic obstructive pulmonary disease (COPD) with multiple prior COPD exacerbations is at risk for different pulmonary pathogens than are hematological malignancy patients. In addition to the specific tumor, the stage of the malignancy can also be helpful in suggesting potential oncology-related risk factors. For example, a patient with known brain metastases is at a higher risk of aspiration pneumonia than a patient without metastatic disease. Other risk factors for aspiration include impaired swallowing (especially with head and neck cancer), altered mental status, and procedures requiring sedation [41, 42].

Several points bear particular emphasis. First, immune deficits can occur from the underlying hematological malignancy (e.g., multiple myeloma) which can result in a deficit in humoral immunity which increases the risk of encapsulated organisms *S. pneumoniae* and *H. influenzae*. Second, strategies used to diagnose or

treat the underlying malignancy can also increase the risk of pneumonia due to certain pathogens. For example, although uncommonly performed, splenectomy is strongly associated with an increased risk of infection with encapsulated organisms. Prolonged administration of steroids can increase the risk of invasive fungal pathogens and *Pneumocystis jiroveci* pneumonia (PCP). Administration of antilymphocyte antibodies can result in severe depletion of CD4 cells, placing patients at risk of cell-mediated infections and reactivation of latent infections. It is increasingly being recognized that delayed lymphocyte reconstitution (perhaps as a marker of delayed reconstitution of certain lymphocyte populations) can significantly impact recovery from certain viral infections such as adenovirus [43]. The depth and duration of neutropenia that occurs during chemotherapy directly increases the risk of bacterial and fungal infections—*Aspergillus* most notably. Finally, the impairment of mucosal defenses due to the cytotoxicity of chemotherapy can also increase the risk of invasive bacterial pathogens and impair mucous clearance from the respiratory tract, further increasing the risk of invasive respiratory tract infections.

## 4 Stem Cell Transplant Risk Factors

Engraftment, particularly CD4+ cell engraftment, is better with peripheral blood stem cell transplantation (SCT) than with bone marrow transplantation (BMT) with fewer fungal, bacterial, and viral infections occurring after transplantation [44]. Despite these improvements, pneumonia frequently complicates SCT. The two most important factors impacting the risk of infection after transplantation are the presence or absence of GVHD and the time from transplantation [45]. Classically, during the pre-engraftment period (usually less than 2–6 weeks), bacterial infections, *Candida*, *Aspergillus*, and HSV are among the most common pathogens [45]. After engraftment until about 100 days from SCT, the impact of deficient cell-mediated immunity results in an increased risk of CMV, PCP, and *Aspergillus* infections [45–48]. In the late phase (after about 100 days), reactivation of CMV and VZV, and infections with encapsulated bacteria (e.g., pneumococcus) are most common and the risk correlates with the severity of prior GVHD [45]. Additionally, development of invasive *Aspergillus* infections >6 months after transplantation has been associated with chronic GVHD and prior CMV disease [46]. Notably, the risk of serious illness from respiratory viruses remains elevated throughout transplantation [45].

There are also other important factors impacting the risk of infection after transplantation. Allogeneic SCT recipients are at a higher risk of infectious complications than are autologous SCT recipients [45]. It is uncommon for autologous SCT recipients to have infectious complications after 3 months, while allogeneic SCT recipients continue to have measurable humoral, cell-mediated, and reticuloendothelial system deficits [49, 50]. Receipt of HLA-mismatched or unrelated donor transplants are also independent risk factors for latent viral

reactivation and invasive fungal disease [45, 48]. The impact of T-cell depletion with a monoclonal anti-CD52 antibody (alemtuzumab) upon subsequent risk of reactivation of latent infections such as CMV and development of new infections should not be underestimated [46, 47, 51, 52]. Prior CMV is a major risk factor for subsequent invasive fungal disease [46, 53, 54]. Other important risk factors for invasive aspergillosis after engraftment include GVHD, receipt of corticosteroids, neutropenia, lymphopenia, and respiratory virus infections [45, 46]. While hospitalized, patients remain at risk of nosocomial acquisition of respiratory viruses such as influenza, parainfluenza, RSV, and adenovirus, which have been known to cause large outbreaks in transplant centers [55–58]. The seasonality of these viruses appears to closely approximate that of the healthy population [59].

## 5 Organisms Causing Pneumonia in Cancer Patients

Common and uncommon organisms responsible for pneumonia in cancer patients are outlined in Table 2. Cancer patients are a heterogeneous group of individuals who may have pathogens that may closely resemble the organisms observed in patients with CAP [14], hospital-acquired pneumonia (HAP) [13], or pneumonia in immunosuppressed patients [60]. For example, a prostate cancer patient on hormonal therapy or an outpatient with colon cancer on 5-fluorouracil with no prior bone marrow suppression is likely to have pathogens that mirror those of CAP. In contrast, a surgically complicated colon cancer patient requiring a prolonged stay in the surgical intensive care unit and mechanical ventilation will be predisposed to pathogens that are commonly observed in HAP. A SCT recipient who develops pneumonia while neutropenic can be infected by pathogens observed in immunosuppressed patients, but could have pathogens more like a patient with HAP if the pneumonia develops during hospitalization or even CAP if the patient is $>1$ year out from SCT with immune reconstitution with no underlying GVHD. As well, the organisms causing aspiration pneumonia should be considered in patients with cancer for whom either comorbid conditions or medication use places them at a heightened risk of aspiration (e.g., alterations in mental status, mucositis, narcotic, and benzodiazepine use). One recent study documented that 15 % of cancer patients who underwent bronchoalveolar lavage (BAL) had multiple pathogens identified [2]. Thus, physicians caring for cancer patients with pneumonia should carefully consider potential pathogens.

Of particular importance is the consideration of prior microbiological isolates identified in a patient and prior anti-infective therapy. Adherence to trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis greatly decreases the risk of PCP. Other prophylactic regimens for PCP are generally not as effective and also lack the protection that TMP-SMX provides against some bacteria and *Nocardia* [45, 61]. Prior antibiotic administration with broad-spectrum agents places patients at risk of infection with a drug-resistant pathogen. For example, prior levofloxacin administration has been previously associated with acquisition of fluoroquinolone-

**Table 2** Respiratory tract pathogens of importance in cancer patients

| ***Common viral pathogens*** | ***Common bacterial pathogens*** | ***Common fungal pathogens*** |
|---|---|---|
| Influenza | *Streptococcus pneumoniae* | Molds |
| A (H3N2 endemic) | *Haemophilus influenzae* | *Aspergillus* spp. |
| A (H1N1 endemic) | *Moraxella catarrhalis* | Mucormycoses |
| B | *Staphylococcus aureus* | *Alternaria* |
| 2009 H1N1 (epidemic) | Methicillin susceptible | *Cladosporium* |
| Respiratory syncytial virus | Methicillin resistant | *Scedosporium* |
| Human metapneumovirus | *Streptococcus pyogenes* | *Fusarium* |
| Parainfluenza, types 1-3 | Other *Streptococcus* spp. | *Penicillium* |
| Adenovirus | Group B streptococci | Yeasts |
| Rhinovirus | Group G streptococci | *Candida* spp. (almost always embolic) |
| Herpes simplex virus, types 1 and 2 | Viridans group streptococci | *Cryptococcus* |
| Cytomegalovirus | Enterobacteriaceae | *Pneumocystis jerovechi* (PCP, PJP) |
| Varicella zoster virus | *Escherichia coli* | Dimorphic fungi |
| Ebstein-Barr virus (as a cause of PTLD) | *Klebsiella pneumoniae* | *Histoplasma capsulatum* |
| Human herpesvirus 6 | *Pseudomonas aeruginosa* | *Coccidioides immitis* |
| Human coronaviruses (e.g., NL63, HKU-1) | *Acinetobacter baumannii* | |
| | *Mycoplasma pneumoniae* | ***Uncommon other pathogens*** |
| | *Chlamydiophila pneumoniae* | Severe acute respiratory syndrome (SARS) |
| | *Legionella* spp. | Avian influenza |
| | Oral anaerobes (especially with aspiration) | Rubeola (measles) |

(continued)

**Table 2** (continued)

| | | |
|---|---|---|
| | *Prevotella spp.* | Hantavirus |
| | *Fusobacterium* spp. | *Mycobacterium kansasii* |
| | Polymicrobial | *Mycobacterium avium intracellulare* (MAC) |
| | | *Actinomyces* |
| | ***Common acid fast pathogens*** | *Blastomyces dermatidis* |
| | *Mycobacterium tuberculosis* | *Strongyloides stercoralis* |
| | *Nocardia* spp. | *Toxoplasma gondii* |
| | | |
| | ***Uncommon bacterial pathogens*** | |
| | *Neisseria meningitidis* (especially serogroup Y) | |
| | *Bordetella pertussis* | |
| | *Chlamydia psittaci* | |
| | *Coxiella burnetti* (Q-fever) | |
| | *Yersinia pestis* | |

resistant *S. pneumoniae* infections [62, 63]. Prior administration of an antiviral such as acyclovir, ganciclovir, or oseltamivir may substantially decrease the risk of infection, but if infection occurs, it may be due to a drug-resistant viral pathogen [48, 64]. Multiple authors have documented that prior administration of voriconazole in SCT recipients is a risk factor for breakthrough fungal infections due to mucormycosis (*Rhizopus*) [65–67].

Herpes simplex virus (HSV) infections can occasionally involve the lung. Since HSV can reactivate in up to 70 % of BMT recipients [68], it is recommended that acyclovir prophylaxis be administered to all SCT recipients until engraftment occurs and mucositis resolves [49]. It is important to consider HSV as a potential pathogen of the lungs, particularly in patients with perioral lesions or mucositis. Although HSV can be identified from bronchial fluid by PCR, it is not routinely tested for by most molecular laboratories. Viral culture, rapid shell vial, and DFA tests all can easily identify HSV. Treatment is with high-dose acyclovir. Resistance to acyclovir can occur through mutations in the thymidine kinase gene and rarely through mutations in the HSV DNA polymerase [48]. Alternatives include the nephrotoxic medications foscarnet and cidofovir, although occasionally resistance to these can develop [69, 70] (See Chapter Antimicrobial Agents, Drug Adverse Reactions and Interactions, and Cancer).

CMV, and particularly CMV pneumonitis, had previously been the most common cause of death in BMT recipients [71], but has declined with aggressive monitoring and treatment of CMV reactivations. Consistently identified risk factors for CMV disease include CMV seropositivity, GVHD, lymphopenia, and use of alemtuzumab [47, 72–74]. CMV establishes latency; thus, isolation of CMV by viral culture from peripheral sites (e.g., nasopharyngeal, urine, and stool) is poorly predictive in identifying patients who will develop subsequent invasive CMV disease, and some patients who developed disease before peripheral cultures had enough time to grow [75, 76]. Although CMV pp65 antigen testing of blood resulted in more rapid identification, it was limited by the need for large blood volumes and could not be used in neutropenic patients [43]. The advent of PCR testing of the blood has further improved the detection of CMV in neutropenic patients and has been associated with improved survival over viral culture [43]. After treatment of patients for CMV, the physician should remain aware that the risk of subsequent bacterial and fungal infections is substantially increased [53, 54, 77, 78].

The epidemic of 2009 novel H1N1 dramatically impacted hospital admissions during the spring and fall of 2009. It has the capacity to replicate within human lung tissue and can cause a diffuse viral pneumonitis that can be associated with severe hypoxemia, ARDS, and sometimes multisystem organ failure [79–81]. Very few cases of severe illness occurred in patients >60 years of age [81, 82], but underlying immunosuppression was present in about 15 % of patients with 2009 H1N1 disease requiring hospitalization [82]. A retrospective single cancer-center study conducted on May–June 2009 noted that 2009 H1N1 occurred more commonly among patients with an underlying hematological malignancy than among those with solid tumors [83]. Over 90 % of patients presented with cough and

fever [83]. Thirty-seven percentage of patients required hospitalization, and 27 % of those that were assessed with radiographs had lower respiratory tract disease [83]. Almost all of these patients received neuraminidase therapy, 86 % received this on clinical presentation, and none of these patients required mechanical ventilation or died due to 2009 H1N1 disease [83]. Early administration of oseltamivir to patients who have 2009 H1N1 influenza has been associated with better outcomes and lower risk of death [81, 82]. Thus, when influenza is occurring in the community, empiric therapy for influenza should be instituted in patients with compatible symptoms awaiting results of testing [81]. Additionally, therapy should be continued in patients with negative testing if severe or progressive disease exists until an alternative diagnosis is established due to PCR being falsely negative in $\sim$10 % of specimens [81]. Notably, >1/3 of healthy patients will continue to shed 2009 H1N1 or seasonal influenza by PCR for >7 days after onset of illness; viral shedding may be even more prolonged in hospitalized patients or patients with underlying immunosuppression [81, 84–86]. It is uncertain whether detectable influenza genetic material represents viable replicating virus [84]. Delayed viral clearance has been associated with late initiation of oseltamivir [81, 84, 85] and has been associated with comorbidities and with prolonged hospital stays [85].

## 6 Imaging

Chest radiography (chest X-ray) is necessary for the routine evaluation of patients suspected of having pneumonia due to its superior sensitivity and specificity over that of physical examination [14]. It is recommended in cancer patients that are febrile, neutropenic, and have any respiratory signs or symptoms [87]. It can be useful in suggesting other potential etiologies (e.g., congestive heart failure) and pathogens. Interstitial or peribronchial infiltrates are classically associated with viral pathogens, while lobar or alveolar infiltrates are more frequently seen with bacterial pathogens; however, substantial overlap exists. About 70 % of children with documented bacterial pneumonia will have airspace disease [8]. In children with influenza that have pulmonary infiltrates, up to 50 % may have an alveolar component to their infiltrate [88]. With 2009 H1N1 influenza, radiographic findings commonly included diffuse mixed interstitial and alveolar infiltrates [81]. In patients with bacterial superinfection of 2009 H1N1, lobar and a multilobar distribution can occur [81]. Chest radiography can also help identify a complicated pneumonia—usually defined as necrotizing pneumonia, lung abscess, loculated pleural fluid, or empyema. Presence of an effusion suggests a bacterial process—particularly *S. pneumoniae*, *S. aureus*, or *S. pyogenes*. Lateral decubitus films are useful in determining whether an effusion associated with pneumonia is free-flowing or loculated (suggested by failure of the fluid to move to the dependent region of the chest with changes in position). Chest X-rays are particularly limited in the early detection of pneumonia in patients with cancer, particularly when

obtained in the supine position [89]. It is also well known that a delay in chest X-ray appearance of pneumonia can occur; thus, patients who have a high clinical suspicion of pneumonia should be treated presumptively for 24–48 h before repeating the chest X-ray [14].

High-resolution CT scanning has improved sensitivity and specificity for pneumonia over that of chest X-ray in patients without underlying cancer [90]. The sensitivity of chest X-ray in comparison with CT scan has been shown to be about 50 % [89]. In one study, the use of high-resolution CT scanning resulted in a median increase of 5 days in the time of detection of a pulmonary infiltrate over that of using chest X-rays alone [91]. Importantly, in those with a negative high-resolution CT scan, no individuals developed an inflammatory lung lesion within the next 5 days and <10 % developed an inflammatory lung lesion within the next 20 days [91]. CT angiography can help in the evaluation of pulmonary embolism which is also common in oncology patients while still proving substantial information about the lung parenchyma and mediastinal lymphadenopathy. Although classic findings on CT imaging include consolidation with bacterial disease, nodules with fungal disease, a perihilar ground glass opacity with PCP, and a mosaic pattern of ground glass opacities with viral disease, these findings are nonspecific and not diagnostic [89]. CT can be helpful in suggesting noninfectious etiologies (e.g., radiation pneumonitis, drug toxicity, malignancy) and in providing precise localization of the infiltrate for subsequent diagnostic procedures [89].

Certain characteristics are strongly associated with invasive *Aspergillus* in the setting of neutropenia. These findings include the presence of a halo sign, which is an area of hemorrhage around a nodular lesion, or the presence of an air-crescent sign [92, 93]. These findings are strongly suggestive of *Aspergillus*, but can also occur in infections with *Pseudomonas aeruginosa*, *Nocardia*, zygomycetes, *Fusarium*, and scedosporium [92, 94]. These classic findings are not the most sensitive findings observed with invasive pulmonary aspergillosis. In a large multicentered study of invasive *Aspergillus*, 95 % had at least one macronodule (defined as ≥1 cm), 61 % had a halo sign, 30 % had consolidation, 27 % had an infarct-shaped macronodule, 20 % had cavitation, and only 10 % had an air-crescent sign [94]. Interestingly, a good prognostic sign is the finding of a halo sign, which correlated with improved response to therapy and survival [94].

Other imaging tests may be appropriate depending on the clinical setting to exclude other diagnoses. For example, brain natriuretic peptides (BNP) or echocardiography may be beneficial in individual patients in excluding congestive heart failure. Transesophageal echocardiography is more sensitive than transthoracic echocardiography for endocarditis and should be used in adult patients in whom endocarditis is being strongly considered in the differential diagnosis [95].

## 7 Diagnostic Strategies

The gold standard for the diagnosis of pneumonia requires sampling of respiratory tract tissue and identifying pathogens by tissue culture or on histopathological examination. However, an invasive diagnostic strategy is usually unnecessary or not feasible due to its attendant risks in cancer patients (e.g., risk of infection and bleeding). It should be recognized that *S. pneumoniae* is considered the predominant pathogen in CAP; it is identified in about 2/3 of bacteremic pneumonia [3, 96]. A recent study using transthoracic lung aspiration has confirmed this finding [97]. Some evidence suggests that although *Mycoplasma pneumoniae* and *Chlamydiophila pneumoniae* are relatively common causes of pneumonia in outpatients, they are infrequently observed in patients with severe disease in whom *S. aureus*, *Legionella* species, and gram-negative bacilli are more frequently observed [3]. This may be even truer in patients with underlying cancer who require hospitalization for pneumonia.

In general, more aggressive diagnostic strategies are necessary in patients with cancer than in patients without cancer who present with a routine pneumonia. This is due to the higher likelihood of alternative diagnostic possibilities (e.g., metastatic malignancy). As well, unusual pathogens (e.g., PCP, tuberculosis) and multidrug-resistant pathogens occur with a higher frequency. A higher rate of clinical failure and mortality has been observed in patients with pneumonia that are not initiated on appropriate antimicrobial therapy [13, 14, 98–101]. In another study of 200 immunocompromised patients (140 of which had either hematological malignancy or SCT), mortality was associated with SCT (53 % vs. 33 %), requirement of mechanical ventilation (odds ratio [OR] of 28), an APACHE II score of >20 (OR 5.5), and a delay of >5 days in establishing a specific diagnosis (OR 3.4) [102].

### 7.1 Noninvasive Testing Modalities

Tables 3 and 4 outline routine and supplemental testing that may be of potential benefit in patients with underlying malignancies who present with pneumonia. Although blood cultures identify a pathogen in 5–14 % of patients with CAP [3, 14], these are particularly important in patients with underlying malignancies in whom other etiologies (e.g., central line infection with embolic lung lesions) must be considered. Sputum cultures, although not universally recommended [3], are likely to be of higher benefit in patients with underlying malignancies in whom common pathogens are less frequently observed. Obtaining sputum for culture prior to antibiotic administration increases the yield. In particular, they can be helpful in identifying pathogens that empiric coverage may not have adequately covered (e.g., MRSA, a drug-resistant gram-negative rod).

A number of tests for the presence of antigens have been developed for identifying fungal and bacterial pathogens. Several important caveats exist for antigen

**Table 3** Assays used in viral detection

| Assay | Sensitivity | Specificity | Time | Cost | Expertise required | Pathogens commonly tested | Important limitations |
|---|---|---|---|---|---|---|---|
| Viral culture | +++ | ++++ | − − − | + | − − | HSV, CMV, VZV, influenza, RSV, parainfluenza | This will routinely miss human metapneumovirus and many rhinoviruses |
| Rapid shell vial | + | +++ | + | + | − − | HSV, CMV, VZV, influenza, RSV, parainfluenza | This will routinely miss human metapneumovirus and many rhinoviruses |
| Rapid antigen | – | +++ | ++++ | +++ | ++++ | Influenza, RSV | This assay will only detect the virus for which antigen is specifically tested. Recent literature suggests less sensitive in adults as they are in children and poor sensitivity in detecting 2009 H1N1 influenza |
| DFA | ++ | +++ | +++ | ++ | − | HSV, VZV | This assay will only detect the virus for which antigen is specifically tested |
| ELISA/EIA | +++ | ++++ | +++ | + | − − | Any respiratory virus | Rarely used |
| CMV pp65 antigenemia | ++ | +++ | +++ | + | − − | CMV | Extensive supportive literature correlation with active disease. It is limited by requiring that the patient not be neutropenic |
| PCR/RT-PCR | ++++ | ++ ± | ++ ± | − − − | − − − | Testing for all viruses is possible | Each virus requires molecular amplification (if not specifically tested for, it will be missed). Correlation of a positive test with active disease may be lacking (nucleic acid may remain longer than infectious or actively replicating virus). This is the current gold standard test, but laboratory contamination is always a possibility |

*DFA* direct fluorescent antibody, *ELISA/EIA* enzyme-linked immunosorbent assay/enzyme immnoassay, *CMV* cytomegalovirus, *PCR/RT-PCR* polymerase chain reaction/reverse transcription–polymerase chain reaction, *HSV* herpes simplex virus, *VZV* varicella zoster virus, and *RSV* respiratory syncytial virus
Modified from Anderson EJ. Viral diagnostics and antiviral therapy in hematopoietic stem cell transplantation. Current pharmaceutical design 2008; 14:1997–2010. With permission from Bentham Science Publishers

**Table 4** Diagnostic tests for oncology patients with possible pneumonia

| *Initial laboratory testing* | *Additional baseline laboratory tests to consider* |
|---|---|
| CBC with manual differential | Nasal or naspopharyngeal specimen for extended viral testing for human metapneumovirus, adenovirus, rhinovirus, parainfluenzavirus |
| Comprehensive metabolic panel | Sputum fungal stain and culture |
| Blood cultures | Sputum AFB stain and mycobacterial culture |
| Minimum of 2, more if endocarditis is suspected | Urinary *Histoplasma* antigen |
| Urinalysis and urine culture | Urinary *Blastomyces* antigen |
| Chest XRAY (PA and lateral views) | Urinary *Coccidioides* antigen |
| Sputum culture for bacterial culture | Fungal serologies (lower yield than urinary antigens) |
| Useful specimen if >25 WBC/hpf and <10 epithelial cells/hpf observed | Serum cryptococcal antigen |
| Nasal or nasopharyngeal specimen for viral PCR testing (for influenza and RSV) | *Strongyloides* serology and stool examination for ova and parasites |
| *Streptococcus pneumoniae* urinary antigen | |
| *Legionella* urinary antigen (serogroup 1) | |
| *Aspergillus* galactomannan assay | |
| CMV pp65 or CMV PCR from blood[a] | |
| *If bronchoalveolar lavage or lung tissue is obtained* | *If pleural fluid is obtained* |
| Gram stain and quantitative bacterial culture | pH[c] |
| *Legionella* DFA and culture | LDH[c] |
| KOH stain and fungal culture | Protein[c] |
| AFB stain and mycobacterial culture | Glucose[c] |
| Viral culture (rapid shell vial culture) or | Cell count with differential |
| Extended viral PCR testing | Gram stain with quantitative bacterial culture |
| PCP DFA assay | KOH stain and fungal culture |
| Aspergillus galactomannan assay | AFB stain and mycobacterial culture |
| 16S ribosomal RNA sequencing[b] | *Legionella* DFA and culture |

(continued)

**Table 4** (continued)

| | |
|---|---|
| Cytology ± histology depending on specimen | PCP DFA assay |
| | 16S ribosomal RNA sequencing[b] |
| | Cytology (+Histology if tissue obtained) |
| | Aspergillus galactomannan assay |

[a]Send in stem cell transplant recipients
[b]Limited availability, primarily a research tool
[c]Determine whether pleural fluid is transudate or exudate
*CBC* complete blood count, *PA* posteroanterior, *hpf* high-power field, *PCR* polymerase chain reaction; *RSV* respiratory syncytial virus, *DFA* direct fluorescent antibody, *KOH* potassium hydroxide, *AFB* acid fast bacilli, *PCP Pneumocystis jerovechi*, and *RNA* ribonucleic acid

tests. First, all of the antigen tests have sensitivities that are <90 % and some much less than this. Thus, they should not be viewed as tests that can "rule out" the presence of a pathogen. Second, the antigen tests are most sensitive before or shortly after initiation of treatment with an agent that has activity against the specific pathogen. These tests generally become negative fairly quickly and in some cases (e.g., histoplasmosis) can be used to gauge response to therapy. Finally, these tests are more sensitive in the setting of disseminated disease than in pneumonia alone.

Urinary antigen assays *for Legionella* (70 % sensitivity, >90 % specificity for serogroup 1) and *S. pneumoniae* (60–90 % sensitivity with approaching 100 % specificity) should be obtained from patients who have failed outpatient antibiotic therapy, those with pleural effusions, and those requiring intensive care admission for pneumonia [3, 14]. It should be recognized that many other *Legionella* species can cause pneumonia but are not detected by the urinary antigen; to diagnose these species, culture or PCR of respiratory specimens is necessary. In patients at risk of endemic fungal disease, urinary antigen tests exist for histoplasmosis, blastomycosis, and coccidiodiomycosis that have excellent sensitivities but some risk of cross-reaction with other fungal pathogens including other endemic fungi and *Penicillium* [103–107]. Response to therapy can be followed by obtaining serial specimens for some of these urinary antigen tests [103].

Serum antigen tests also exist but are limited to evaluation for certain invasive fungal pathogens. First, the cryptococcal latex antigen test is widely available and should be considered in patients with cell-mediated immunity deficits. An antigen test (Fungitell BG, Associates of Cape Cod, East Falmouth, Mass.) was developed to detect (1→3)-$\beta$-D-glucan which is a cell wall component of *Aspergillus* and most other fungi [108]. Thus, it is not specific for *Aspergillus* and has been found to be positive in patients with candidemia and with cyptococcosis, fusariosis, PCP, and histoplasmosis [109–112]. The sensitivity of this test for *Aspergillus* has ranged from 50 to 100 % with a specificity that ranges from 44 to 98 % [108, 111]. In clinical practice, the (1→3)-$\beta$-D-glucan assay was not found to be helpful in discriminating fungal from bacterial infections in the intensive care unit setting

[113]. Even in healthy populations, a false-positive rate of 7–20 % has been observed, which may be even higher in populations at risk for invasive fungal infections [108]. False positives have also been observed with certain medications, following hemodialysis, with use of IV tubing filters, with administration of albumin or immunoglobulin, and after exposure to gauze [108, 111]. Additionally, echinocandins interfere with (1→3)-$\beta$-D-glucan synthesis and administration of an echinocandin (e.g., caspofungin, micafungin, anidulafungin) may be associated with a falsely negative assay [110].

Another antigen test, the Platelia (BioRad Laboratories, Redmond, WA) *Aspergillus* enzyme immunoassay has a sensitivity of 79–96 % and specificity of 74–99 % for invasive aspergillosis when performed on blood specimens [108]. The best cutoff for the *Aspergillus* galactomannan test to optimize sensitivity while maintaining a high degree of specificity has been an area of intensive investigation. Obtaining the *Aspergillus* EIA twice weekly with ≥2 samples ≥0.5 to 1.0 can result in earlier diagnosis of invasive pulmonary aspergillosis [114, 115]. Unfortunately, false-negative and false-positive results can occur with the *Aspergillus* galactomannan test. Administration of piperacillin–tazobactam is associated with false-positive tests, which may be due to galactomannan being carried through the drug production processing stages from *Penicillium* [116, 117]. False-positive tests have also occurred after receipt of other *Penicillium*-derived antibiotics including amoxicillin and ticarcillin both with and without a beta-lactamase inhibitor [108]. Additionally, false-positive tests have occurred in patients infected with all of the endemic fungi, and with *Fusarium*, *Rhodotorula*, *Trichophyton*, *Penicillium*, *Paecilomyces*, and *Alternaria* species [108, 116, 118]. Plasmalyte (Baxter Healthcare Corporation), an electrolyte replacement solution containing sodium gluconate produced by *Aspergillus flavus*, has also been associated with false-positive *Aspergillus* galactomannan tests [108, 119]. Probably the most frequent cause of a false-negative *Aspergillus* galactomannan test is the administration of mold-active antifungal therapy. Marr et al. demonstrated that the sensitivity of the galactomannan test fell from 89 to 52 % in patients receiving mold-active antifungal therapy [120]. False-negative results have also been noted in patients who have localized *Aspergillus* infections [108].

The diagnosis of invasive fungal infections is difficult in patients with cancer or SCT, resulting in the European Organization for Research and Treatment of Cancer and Mycoses Study Group setting guidelines for definitive, probable, and possible invasive fungal infections [121]. In part, this is due to the difficulty that exists in obtaining a tissue diagnosis which would prove invasive fungal disease. In general, host factors predisposing the patient to fungal infection (e.g., neutropenia, GVHD), clinical features of fungal infection (e.g., CT imaging showing a halo sign or an air-crescent sign, sinusitis), and mycological evidence of infection (e.g., positive antigen test, positive culture) all must be present to demonstrate a probable case of invasive fungal disease [121]. In clinical practice, many cases are possible cases and this should not dissuade the clinician from treating for invasive fungal disease since these guidelines were primarily written to help develop common research definitions [121].

In a retrospective study from M.D. Anderson, clinical characteristics and risk factors were able to separate pulmonary zygomycosis from invasive pulmonary aspergillosis. Risk factors for zygomycosis infection included voriconazole prophylaxis (OR 7.76), concomitant sinusitis (OR, 25.7), ≥10 pulmonary nodules (OR, 19.8) and pleural effusion (OR, 5.07) on initial CT scan [66]. The authors did not observe a difference on CT scan in other findings commonly associated with pulmonary mold infections such as masses, cavities, halo signs, or an air-crescent sign [66]. In another study from the same group, sinus involvement alone or in combination with pulmonary disease strongly suggested invasive zygomycosis in comparison with *Aspergillus* [67].

Commonly performed viral testing strategies are outlined in Table 3. In the past several years, there has been increasing realization of the poor sensitivity of most rapid antigen tests in identifying viral pathogens [29, 81] and an increased reliance upon the use of PCR [43, 59, 122, 123]. In the past, many "home-brew" PCR-based assays were used at various centers [43]. In many centers, PCR is available for testing for the most common respiratory pathogens (e.g., influenza and RSV) and for CMV. Some centers also have access to the FDA-approved XTAG Respiratory Viral Panel (Luminex Corp, Austin, TX) which has the ability to test for influenza A, B, RSV A and B, parainfluenza types 1–3, adenovirus, human metapneumovirus, and rhinovirus [43]. Real-time PCR provides more rapid results that are quantitative and can also detect multiple viruses simultaneously [43]. In a recent retrospective study of SCT recipients, quantitative PCR viral load of respiratory virus RNA from BAL specimens did not correlate with subsequent mechanical ventilation or death [124]. In contrast, 5/6 patients from the same study, who had viral RNA detected in serum specimens, died. In a multivariate analysis, detection of viral RNA in serum was associated with an adjusted relative risk of death within 30 days of 1.8 in comparison with those who were not viremic [124]. These results remain to be confirmed, but could provide useful prognostic information in the future. Several caveats to PCR testing for viral pathogens should be emphasized. PCR identification of a virus may indicate recent infection but not active disease. Data for this are lacking in cancer patients, but in healthy infants, prolonged shedding of RSV by real-time PCR has been observed (20–30 days after symptoms begin) [43, 125]. Although PCR is considered the gold standard for the diagnosis of 2009 H1N1, PCR specimens from both the upper and lower respiratory tracts have been falsely negative in about 10 % of patients [81]. In addition, cross-contamination of samples can easily occur with PCR, resulting in false-positive tests. Thus, PCR results should always be viewed in the context of the clinical scenario of the patient and additional respiratory specimen types should be obtained in a patient in whom the clinical impression is discordant with the test results [81].

Finally, screening for tuberculosis can now be performed either with PPD skin test or through a new blood test called the interferon-gamma release assay (IGRA). In the test, the patient's blood is mixed in vitro with tuberculosis-specific antigen that then results in the release of interferon gamma from any T cells that have previously been exposed to tuberculosis. The benefit of this test is that there is not

the potential for cross-reaction in patients who have previously been exposed to BCG vaccine (administered routinely in countries of the world in which tuberculosis is endemic). It should be recognized that a PPD is least sensitive for detecting prior tuberculosis disease when the patient is actively infected with tuberculosis. For example, in a study from Africa of TB and HIV-infected patients, the IGRA was 65 % sensitive, while the PPD was 31 % sensitive [126]. Both PPD and IGRA were least sensitive in those with CD4 counts <200 [126]. Data regarding use of the IGRA are lacking in patients with active tuberculosis and cancer. Thus, neither a negative PPD nor a negative IGRA rules out the possibility of active tuberculosis. Instead, anyone suspected of having active pulmonary tuberculosis should immediately be placed in negative pressure isolation and undergo sputum evaluation for tuberculosis.

## 7.2 Invasive Diagnostic Testing

Obtaining an etiological diagnosis can also be helpful in avoiding prolonged broad-spectrum antibiotic administration, avoiding antibiotic toxicity, and decreasing the risk of bacterial superinfections (e.g., *Clostridium difficile*). Thus, an unusual clinical presentation, particularly severe pneumonia (e.g., necessitating ICU admission or intubation with mechanical ventilation), and failure to respond to initial empiric antimicrobial therapy within 48–72 h should all prompt aggressive diagnostic measures with attempts to obtain deep specimens or tissue early in the clinical course of pneumonia.

Several issues are frequently raised as objections to diagnostic procedures in this population. First, patients frequently have coagulopathies due to their underlying malignancy or chemotherapy. Second, concern may exist about risk of introducing infection in those who are immunosuppressed. Third, many patients are clinically unstable and at risk for needing more substantial respiratory support (either noninvasive mechanical ventilation or routine mechanical ventilation) after a procedure. Fourth, those in whom a diagnostic procedure is considered often have been pretreated with broad-spectrum empiric coverage. Thus, the yield from the procedure is often low. Finally, the procedures with the best yield are the most invasive and the most likely to result in complications.

Despite these frequent potential issues, obtaining a deep specimen or tissue can often be quite helpful. If all the cultures return negative, this can sometimes provide support for stopping empiric antibiotic escalation in a patient who is not doing well. It may also provide support for narrowing antibiotic administration (e.g., stopping empiric MRSA coverage or PCP coverage). It can also identify other noninfectious causes of fever and pulmonary infiltrates such as malignancy or pulmonary hemorrhage.

Unfortunately, no standard approach exists in the management of cancer patients needing a diagnostic procedure. A great deal of center-to-center variability exists in the way in which these patients are managed. Some centers have very

little experience with certain techniques, limiting their diagnostic options. The location of the patient's infiltrate must also be considered. A peripheral, pleural-based nodule will not be very amenable to BAL but is likely to be easily reached by either an imaging-guided needle biopsy, or a video-assisted thoracoscopic (VAT) biopsy. In contrast, a perihilar or very medial lesion will be more amenable to BAL and less easily accessed by an imaging-guided needle biopsy or VATS.

Bronchoscopy with BAL is probably least invasive and can be combined with a protected sampling, but this does not increase yield [127]. Yield can approach 50 % using BAL [127]. The combination of BAL with a transbronchial biopsy will improve the yield due to the tissue that is available for pathological review but requires a specially trained bronchoscopist and is associated with a higher risk of bleeding and pneumothorax [128]. BAL fluid can be tested for *Aspergillus* galactomannan where it has 91 % sensitivity and 88 % specificity when a cutoff of $\geq$1.0 was used [129]. It should be noted that like all antigen tests, its sensitivity may be impacted by effective treatment (patients receiving antimold therapy) [129].

In one study of open thoracotomies in patients with malignancies, a specific diagnosis was reached in 62 % of those that underwent biopsies with a change in management made in 57 % of patients after the procedure [130]. Infections, inflammatory disease (primarily cryptogenic organizing pneumonia), and malignancy had a similar contribution to those in which a specific diagnosis was reached [130]. Yield was better in those with a focal infiltrate, who were not on a ventilator, and who were not neutropenic [130]. Complications were seen in 13 % of individuals [130]. An additional benefit to this approach is opportunity to directly visualize the lesion, send larger pieces for pathology, and drain any coexistent effusion for diagnostic and therapeutic purposes. A recent study of patients with a history of hematological malignancy that were found to have lung lesions that subsequently underwent CT-guided needle biopsy had a 60 % diagnostic yield [131]. Since this study included a number of patients without evidence of infection, the yield of CT-guided needle biopsy may be lower in the setting of infectious pulmonary infiltrates.

In patients with severe pneumonia who require intubation, aspiration from the endotracheal tube shortly after intubation can provide important information in which it does not require patient cooperation and bypasses the upper airway-colonizing agents [14]. A regular bronchoscopy can be considered, or a technique available at some institutions is nonbronchoscopic BAL which appears to have a higher yield with less contamination than endotracheal aspiration [132, 133]. Such a specimen should be sent for all of the same studies that are routinely sent with bronchoscopy including viral testing, *Legionella* testing, PCP DFA, fungal testing, and cytology (see Table 4).

Pleural effusion has been associated with early nonresponsiveness to antimicrobial therapy and with ultimate clinical failure [100, 101]. Thus, the current CAP guideline recommendations are to perform a thoracentesis in all individuals in whom a pleural effusion is >5 cm in size on imaging [14]. In cancer patients, a thoracentesis can provide both diagnostic benefits by potentially identifying

pathogens and alternative diagnoses (e.g., metastasis) and therapeutic benefit by improving the lung–chest wall interaction. Risks include bleeding and pneumothorax.

Careful examination of the skin should be performed to identify any new or changing skin lesions. The skin can provide important information about some systemic infections. Infections due to *Cryptococcus, Nocardia*, *Aspergillus*, *Pseudomonas*, *Fusarium*, and mycobacteria can all spread to the skin from a pulmonary source. A skin biopsy which is minimally invasive can sometimes provide diagnostic information that would be difficult to obtain from the lungs.

Other sites that can sometimes also be helpful are the eyes and the sinuses. Endopthalmitis or retinal lesions can be suggestive of fungal disease. In addition to usual bacterial pathogens, both *Aspergillus* and mucormycosis can cause sinus disease. It should be noted, however, that sinusitis is much more strongly associated with zygomycosis infection than is *Aspergillus* [66].

## 8 Need for Hospital Admission

The approach to management of lower respiratory tract infections includes the decision whether hospitalization is necessary in an individual patient. Several severity scores have been developed for deciding which individuals with CAP should be admitted. The most common severity scores are the CURB-65 and the PORT score/pneumonia severity index (PSI). The CURB-65 scale does not take into account any underlying comorbidities, but instead gives a single point for each factor noted in clinical assessment: *C*onfusion, elevated *U*rea Nitrogen, *R*espiratory rate ($\geq$30 breaths/min), low *B*lood pressure, and age >65 years. The points for each of these factors are then added together and are validated with 30-day mortality data. For patients with a score of 0, mortality is 0.7 %, 1 = 2.1 %, 2 = 9.2 %, 3 = 14.5 %, 4 = 40 %, and 5 = 57 % [3, 14]. Thus, patients with scores of 0–1 are often treated as outpatients, 2 is recommended to be admitted to the general medical wards, and $\geq$3 should be admitted to the intensive care unit [14]. It is important to realize that CURB-65 does not take into account patients with underlying malignancy in which mortality would be expected to be even higher. The PORT score or PSI is more complicated and requires addition of additional variables, but does take into account underlying renal disease, liver disease, and malignancy [14, 134]. Again, higher scores correlate with higher mortality. Forms for calculating both CURB-65 and the PSI are widely available both on the Internet and also as applications for PDAs. It is recommended that scoring systems should contribute to and not supersede clinical judgment [3]. Both severity scoring systems underestimate the mortality in patients with underlying malignancy and severity scoring system is validated neither in HAP/VAP nor in patients with neutropenia nor those who are severely immunocompromised.

## 9 Treatment

Appropriate empiric antimicrobial coverage is crucial to optimizing outcomes in patients with cancer and pneumonia. Prior recent antibiotic administration should be taken into account when choosing an empiric antibiotic regimen for pneumonia. Patients receiving fluoroquinolone prophylaxis should not be treated empirically with a fluoroquinolone if they become ill [87]. In addition, prior colonization with multi-drug-resistant pathogens should be taken into account in empiric coverage. For example, prior colonization with MRSA should prompt empiric coverage with an agent known to be active this pathogen (e.g., vancomycin, linezolid). It should be noted that daptomycin is not effective in the treatment of pneumonia which may be due to binding of the drug by surfactant in the lungs [135]. Additionally, recent drug-resistant microbiological isolates (e.g., carbapenem-resistant *Acinetobacter baumannii* or carbapenem-resistant *Klebsiella pneumoniae*) identified from a patient should prompt the physician to modify empiric antibiotics to include drugs that will include the drug-resistant pathogen(s).

In those patients that have had minimal antimicrobial exposure and health care contact, empiric coverage with a regimen to cover CAP in a patient being admitted may be appropriate (e.g., respiratory fluoroquinolone **or** an intravenous $\beta$-lactam **plus** a macrolide) [14]. Outpatient therapy options would be the same choice of a respiratory fluoroquinolone **or** of an oral $\beta$-lactam **plus** a macrolide [14]. In those who meet criteria for HCAP, HAP, or VAP, risk factors for drug resistance usually exist. Empiric coverage with an antipseudomonal $\beta$-lactam **or** carbapenem **plus** either an antipseudomonal fluoroquinolone **or** aminoglycoside **plus** an agent active against MRSA (vancomycin or linezolid) is warranted [13]. In the setting of neutropenic fever, empiric coverage will usually appear fairly similar to that of the HAP/VAP guidelines although coverage with an agent active against atypical organisms is important for those being admitted from home (e.g., levofloxacin or a macrolide). Empiric coverage for aspiration may also be necessary or for influenza, depending on the time of year. In the setting of MDR pathogens such as carbapenem-resistant *A. baumannii* or carbapenem-resistant *K. pneumoniae*, consultation with a local infectious disease specialist is encouraged to help make recommendations based on the local antibiotic sensitivity patterns.

As previously discussed, failure to respond to empiric therapy should lead to a reconsideration of the diagnosis and more aggressive invasive diagnostic testing. When possible, it is important to narrow the antibiotic coverage to avoid placing the patient at risk for colonization with new MDR pathogens or infection with *C. difficile*. In those in whom a reduction in immunosuppression can be achieved, this should be considered when appropriate. Administration of chemotherapy may need to be delayed until the acute infection resolves.

In the treatment of CMV pneumonitis, induction doses of IV ganciclovir are recommended. Some use the combination of high-titer CMV-IVIG with ganciclovir since an improvement was noted in comparison with historical controls in outcomes [43].

In cancer patients with influenza (who are usually immunosuppressed), duration of administration should be 10 days instead of 5 [81]. In patients with pneumonia or progressive disease, a higher dose (150 mg given twice daily) should be considered [81]. Additionally, patients should be monitored for viral clearance and the development of oseltamivir resistance should be considered if the time to viral clearance is delayed [81]. Intravenous formulations of zanamivir and peramivir exist for patients with severe disease [81]. Development of oseltamivir resistance in 2009 H1N1 has been associated with immunosuppression, failed post-exposure oseltamivir prophylaxis, and prolonged administration of oseltamivir [81, 136]. Currently, almost all 2009 H1N1 disease that has accumulated oseltamivir resistance has remained susceptible to zanamivir which is more active than is peramivir against these oseltamivir-resistant isolates [81]. Notably, in the 2008–2009 season, almost all seasonal H3N2 disease was resistant to the adamantanes (amantadine and rimantadine). It is certain that the resistance in 2009 H1N1 and seasonal influenza will continue to change, and current recommendations should be reviewed prior to each influenza season (see www.cdc.gov/flu/).

Classically, empiric administration of antimold therapy has been recommended for patients with persistent neutropenic fever. This was driven by a number of older studies that suggested an increased mortality in patients in whom antifungal therapy was withheld [137]. Data demonstrating benefit with the early use of CT scan of the chest and the *Aspergillus* galactomannan test have resulted in some recent authors challenging the dogma of routine administration of mold-active antifungals to all patients with prolonged neutropenic fever [115, 137–140]. Limited data suggest that in those with a negative high-resolution CT scan, this strategy of withholding empiric antifungal therapy was not associated with an increased risk of invasive fungal infections or death [140]. This approach is not considered the current standard of practice as defined in the 2011 guidelines for the management of febrile neutropenia but is an interesting approach and an active area of research [87]. Empiric coverage with a mold-active agent such as liposomal amphotericin or an echinocandin is recommended [87]. Among those with neutropenia who actually have invasive fungal disease, a subset will get clinically worse usually as the neutropenia resolves and an acute inflammatory response occurs at the site of preexisting fungal infection. Usual therapy for fungal infections is otherwise outlined in Chapter Fungal Infections in Cancer Patients.

There is increasing recognition that prior treatment regimens for CAP of 7–14-day duration may not be necessary and may be associated with an increased risk of complications such as *C. difficile* [14, 141, 142]. Data for courses as short as 3 days with azithromycin or 5 days with a fluoroquinolone exist [6, 14, 141]. For ventilator-associated pneumonia randomized controlled trial data suggest that, for most pathogens, 8 days is sufficient, although patients with neutropenia, immunosuppressant, and long-term steroids were excluded from the trial [13, 143]. Notably, patients with nonfermenting gram-negative rods such as *P. aeruginosa* and *A. baumanni* had a higher risk of relapse with this approach [143]. Others

suggest that use of additional noninvasive tests such as procalcitonin, which is elevated in bacterial infections but not viral disease, may allow physicians to greatly shorten the duration of therapy for pneumonia [142]. Data for shortening the antimicrobial course are lacking in oncology patients. Guidelines recommend 7–14 days as appropriate for the infection or longer until the absolute neutrophil count is 500 cells and rising [87].

## 10 Outcomes

Evidence suggests 1-year mortality rates of 20–40 % in elderly patients without cancer admitted with CAP [144]. One would expect that the 1-year mortality rates would be higher in patients with underlying malignancy. As previously described, mortality is increased in patients with pneumonia that are not initiated on appropriate antimicrobial therapy [13, 14, 98, 99, 101]. In viral infections, delayed lymphocyte reconstitution and development of end-organ disease have been associated with worse outcomes [43, 51, 145–147]. In a prior study of severe CAP requiring ICU admission, being immunosuppressed (which included patients that had received radiation, chronic steroids, and those receiving cytotoxic therapy) was associated with a 2.25-fold increased risk of mortality on multivariate analysis [7]. Mortality has been 3.2-fold higher in those with cancer who develop VAP on multivariate analysis [98]. In a study of cancer patients who developed acute respiratory failure, almost 50 % died, and survival was associated with cardiogenic pulmonary edema and was very poor in anyone in whom mechanical ventilation was required [148]. Goals of care should be revisited in anyone not responding after the first 48–72 h of ICU care, particularly in the setting of progressive malignancy and need for mechanical ventilation since mortality is exceedingly high [148].

## 11 Conclusions

Respiratory tract infections occur commonly in cancer patients and contribute substantially to morbidity and mortality. Noninfectious infiltrates occur commonly in these patients and should be considered in the differential diagnosis. Recent molecular methods have improved our capacity to diagnose the pathogens responsible for pneumonia, but frequently empiric therapy is still necessary and should take into account the patient's underlying risk factors for multi-drug-resistant pathogens, viruses, and fungi. Since many pathogens can cause disease in this population, in those not responding to empiric therapy, aggressive diagnostic testing and tissue sampling is necessary to help focus treatment modalities.

## References


1. Heron M, Hoyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B (2009) Deaths: final data for 2006. Natl Vital Stat Rep 57:1–134
2. Rolston KV, Bodey GP, Safdar A (2007) Polymicrobial infection in patients with cancer: an underappreciated and underreported entity. Clin Infect Dis 45:228–233 (An official publication of the Infectious Diseases Society of America)
3. File TM (2003) Community-acquired pneumonia. Lancet 362:1991–2001
4. Piccirillo JF (2004) Clinical practice. Acute bacterial sinusitis. New England J Med 351:902–910
5. McIntosh K (2002) Community-acquired pneumonia in children. New England J Med 346:429–437
6. Dunbar LM, Wunderink RG, Habib MP et al (2003) High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin. Infect Dis 37:752–760 (An official publication of the infectious diseases society of America)
7. Bodi M, Rodriguez A, Sole-Violan J et al (2005) Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to infectious diseases society of America guidelines on survival. Clin Infect Dis 41:1709–1716 (An official publication of the Infectious Diseases Society of America)
8. Bradley JS, McCracken GH (2008) Unique considerations in the evaluation of antibacterials in clinical trials for pediatric community-acquired pneumonia. Clin Infect Dis 47(3):S241–S248 (An official publication of the Infectious Diseases Society of America)
9. Johansson N, Kalin M, Giske CG, Hedlund J (2008) Quantitative detection of *Streptococcus pneumoniae* from sputum samples with real-time quantitative polymerase chain reaction for etiologic diagnosis of community-acquired pneumonia. Diagn Microbiol Infect Dis 60:255–261
10. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J (2010) Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 50:202–209
11. Ruiz M, Ewig S, Marcos MA et al (1999) Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. Am J Respir Crit Care Med 160:397–405
12. Lim WS, Macfarlane JT, Boswell TC et al (2001) Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 56:296–301
13. Niederman MS, Craven DE, Bonten MJ, Chastre J, Craig WA, Fagon JY, Wunderink RG (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 71:388–416
14. Mandell LA, Wunderink RG, Anzueto A et al (2007) Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72
15. Yahalom J, Portlock CS (2008) Long-term cardiac and pulmonary complications of cancer therapy. Hematol Oncol Clin North Am 22:305–318
16. Katayama M, Imai Y, Hashimoto H et al (2009) Fulminant fatal cardiotoxicity following cyclophosphamide therapy. J Cardiol 54:330–334
17. Wagner SA, Mehta AC, Laber DA (2007) Rituximab-induced interstitial lung disease. Am J Hematol 82:916–919
18. Danson S, Blackhall F, Hulse P, Ranson M (2005) Interstitial lung disease in lung cancer: separating disease progression from treatment effects. Drug Saf 28:103–113
19. Everolimus and pazopanib: two new drugs for renal cell cancer (2010). Med Lett Drugs Ther 52:33–34
20. Rodriguez-Pascual J, Cheng E, Maroto P, Duran I (2010) Emergent toxicities associated with the use of mTOR inhibitors in patients with advanced renal carcinoma. Anti-cancer Drugs 21:478–486

21. Crawford SW (1999) Noninfectious lung disease in the immunocompromised host. Respiration 66:385–395
22. Salinas FV, Winterbauer RH (1995) Radiation pneumonitis: a mimic of infectious pneumonitis. Semin Respir Infect 10:143–153
23. Nuorti JP, Butler JC, Farley MM et al (2000) Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. New Engl J Med 342:681–689
24. Centers for Disease Control and Prevention (CDC) (2010) Trends in tuberculosis–United States. MMWR Morbidity and mortality weekly report 2011; 60:333–337
25. Smith JA, Kauffman CA (2010) Blastomycosis. Proc Am Thorac Soc 7:173–180
26. Maschmeyer G, Haas A, Cornely OA (2007) Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 67:1567–1601
27. Jokinen C, Heiskanen L, Juvonen H et al (2001) Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland. Clin Infect Dis 32:1141–1154
28. Juven T, Mertsola J, Waris M et al (2000) Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J 19:293–298
29. Centers for Disease Control and Prevention (CDC) (2009) Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus—United States. Mmwr 2009, 58:826–829
30. Michelow IC, Olsen K, Lozano J et al (2004) Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 113:701–707
31. de Roux A, Marcos MA, Garcia E et al (2004) Viral community-acquired pneumonia in nonimmunocompromised adults. Chest 125:1343–1351
32. Angeles Marcos M, Camps M, Pumarola T et al (2006) The role of viruses in the aetiology of community-acquired pneumonia in adults. Antivir Ther 11:351
33. Jennings LC, Anderson TP, Beynon KA et al (2008) Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 63:42–48
34. O'Brien KL, Walters MI, Sellman J et al (2000) Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 30:784–789
35. Centers for Disease Control and Prevention (CDC) (2007) Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza—Louisiana and Georgia, December 2006–January 2007. Mmwr 2007, 56:325–329
36. Hageman JC, Uyeki TM, Francis JS et al (2006) Severe community-acquired pneumonia due to *Staphylococcus aureus*, 2003–04 influenza season. Emerg Infect Dis 12:894–899
37. von Linstow ML, Eugen-Olsen J, Koch A, Winther TN, Westh H, Hogh B (2006) Excretion patterns of human metapneumovirus and respiratory syncytial virus among young children. Eur J Med Res 11:329–335
38. Palacios G, Hornig M, Cisterna D et al (2009) *Streptococcus pneumoniae* coinfection is correlated with the severity of H1N1 pandemic influenza. PLoS ONE 4:e8540
39. Madhi SA, Ludewick H, Kuwanda L et al (2006) Pneumococcal coinfection with human metapneumovirus. J Infect Dis 193:1236–1243
40. Madhi SA, Klugman KP (2004) A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med 10:811–813
41. Petroianni A, Ceccarelli D, Conti V, Terzano C (2006) Aspiration pneumonia. Pathophysiological aspects, prevention and management: a review. Panminerva Med 48:231–239
42. Langerman A, Maccracken E, Kasza K, Haraf DJ, Vokes EE, Stenson KM (2007) Aspiration in chemoradiated patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 133:1289–1295
43. Anderson EJ (2008) Viral diagnostics and antiviral therapy in hematopoietic stem cell transplantation. Curr Pharm Des 14:1997–2010

44. Storek J, Dawson MA, Storer B et al (2001) Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. Blood 97:3380–3389
45. Tomblyn M, Chiller T, Einsele H et al. (2009) Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant 15:1143–1238
46. Marr KA, Carter RA, Boeckh M, Martin P, Corey L (2002) Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 100:4358–4366
47. Chakrabarti S, Mackinnon S, Chopra R et al (2002) High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. Blood 99:4357–4363
48. Anderson EJ, Ison MG (2008) Adenoviral Infections in transplant recipients. In: Scheld WM, Hammer SM, Hughes JM (eds) Emerging infections, vol 8. ASM Press, Washington, pp 75–91
49. Dykewicz CA (2001) Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 33:139–144
50. Lum LG (1987) The kinetics of immune reconstitution after human marrow transplantation. Blood 69:369–380
51. Chakrabarti S, Mautner V, Osman H et al (2002) Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. Blood 100:1619–1627
52. Lion T, Baumgartinger R, Watzinger F et al (2003) Molecular monitoring of adenovirus in peripheral blood after allogeneic bone marrow transplantation permits early diagnosis of disseminated disease. Blood 102:1114–1120
53. Grow WB, Moreb JS, Roque D et al (2002) Late onset of invasive *Aspergillus* infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant 29:15–19
54. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M (2002) High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. J Infect Dis 185:273–282
55. Nichols WG, Erdman DD, Han A, Zukerman C, Corey L, Boeckh M (2004) Prolonged outbreak of human parainfluenza virus 3 infection in a stem cell transplant outpatient department: insights from molecular epidemiologic analysis. Biol Blood Marrow Transplant 10:58–64
56. Leruez-Ville M, Chardin-Ouachee M, Neven B et al (2006) Description of an adenovirus A31 outbreak in a paediatric haematology unit. Bone Marrow Transplant 38:23–28
57. Taylor GS, Vipond IB, Caul EO (2001) Molecular epidemiology of outbreak of respiratory syncytial virus within bone marrow transplantation unit. J Clin Microbiol 39:801–803
58. Harrington RD, Hooton TM, Hackman RC et al (1992) An outbreak of respiratory syncytial virus in a bone marrow transplant center. J Infect Dis 165:987–993
59. Ison MG (2007) Respiratory viral infections in transplant recipients. Antivir Ther 12:627–638
60. Ewig S, Welte T, Chastre J, Torres A (2010) Rethinking the concepts of community-acquired and health-care-associated pneumonia. Lancet Infect Dis 10:279–287
61. Green H, Paul M, Vidal L, Leibovici L (2007) Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 82:1052–1059
62. Davidson R, Cavalcanti R, Brunton JL et al (2002) Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. New Engl J Med 346:747–750
63. Low DE (2004) Quinolone resistance among pneumococci: therapeutic and diagnostic implications. Clin Infect Dis 38(4):S357–S362

64. Baz M, Abed Y, Papenburg J, Bouhy X, Hamelin ME, Boivin G (2009) Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. New Engl J Med 361:2296–2297
65. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA (2004) Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis 39:743–746
66. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP (2005) Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41:60–66
67. Kontoyiannis DP, Lionakis MS, Lewis RE et al (2005) Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 191:1350–1360
68. Wade JC, Newton B, Flournoy N, Meyers JD (1984) Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. Ann Intern Med 100:823–828
69. Chakrabarti S, Pillay D, Ratcliffe D, Cane PA, Collingham KE, Milligan DW (2000) Resistance to antiviral drugs in herpes simplex virus infections among allogeneic stem cell transplant recipients: risk factors and prognostic significance. J Infect Dis 181:2055–2058
70. Frangoul H, Wills M, Crossno C, Engel M, Domm J (2007) Acyclovir-resistant herpes simplex virus pneumonia post-unrelated stem cell transplantation: a word of caution. Pediatr Transplant 11:942–944
71. Wingard JR, Chen DY, Burns WH et al (1988) Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. Blood 71:1432–1437
72. Einsele H, Ehninger G, Steidle M et al (1993) Lymphocytopenia as an unfavorable prognostic factor in patients with cytomegalovirus infection after bone marrow transplantation. Blood 82:1672–1678
73. Meyers JD, Flournoy N, Thomas ED (1986) Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis 153:478–488
74. Castagnola E, Cappelli B, Erba D, Rabagliati A, Lanino E, Dini G (2004) Cytomegalovirus infection after bone marrow transplantation in children. Hum Immunol 65:416–422
75. Einsele H, Ehninger G, Hebart H et al (1995) Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. Blood 86:2815–2820
76. Goodrich JM, Mori M, Gleaves CA et al (1991) Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. New Engl J Med 325:1601–1607
77. Broers AE, van Der Holt R, van Esser JW et al (2000) Increased transplant-related morbidity and mortality in CMV-seropositive patients despite highly effective prevention of CMV disease after allogeneic T-cell-depleted stem cell transplantation. Blood 95:2240–2245
78. Craddock C, Szydlo RM, Dazzi F et al (2001) Cytomegalovirus seropositivity adversely influences outcome after T-depleted unrelated donor transplant in patients with chronic myeloid leukaemia: the case for tailored graft-versus-host disease prophylaxis. Br J Haematol 112:228–236
79. Zhang J, Zhang Z, Fan X et al (2009) Pandemic H1N1 influenza virus replicates in human lung tissues. J Infect Dis 201:1522–1526
80. Webb SA, Pettila V, Seppelt I et al (2009) Critical care services and 2009 H1N1 influenza in Australia and New Zealand. New Engl J Med 361:1925–1934
81. Bautista E, Chotpitayasunondh T, Gao Z et al (2010) Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. New Engl J Med 362:1708–1719
82. Jain S, Kamimoto L, Bramley AM et al (2009) Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. New Engl J Med 361:1935–1944

83. Redelman-Sidi G, Sepkowitz KA, Huang CK et al (2009) H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. J Infect 60:257–263
84. Ling LM, Chow AL, Lye DC et al (2010) Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. Clin Infect Dis 50:963–969
85. Lee N, Chan PK, Hui DS et al (2009) Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 200:492–500
86. Leekha S, Zitterkopf NL, Espy MJ, Smith TF, Thompson RL, Sampathkumar P (2007) Duration of influenza A virus shedding in hospitalized patients and implications for infection control. Infect Control Hosp Epidemiol 28:1071–1076
87. Freifeld AG, Bow EJ, Sepkowitz KA et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis 52:e56–e93 (An official publication of the Infectious Diseases Society of America)
88. Lahti E, Peltola V, Virkki R, Ruuskanen O (2006) Influenza pneumonia. Pediatr Infect Dis J 25:160–164
89. Heussel CP, Kauczor HU, Ullmann AJ (2004) Pneumonia in neutropenic patients. Eur Radiol 14:256–271
90. Syrjala H, Broas M, Suramo I, Ojala A, Lahde S (1998) High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clin Infect Dis 27:358–363 (An official publication of the Infectious Diseases Society of America)
91. Heussel CP, Kauczor HU, Heussel GE et al (1999) Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. J Clin Oncol 17:796–805
92. Walsh TJ, Anaissie EJ, Denning DW et al (2008) Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46:327–360 (An official publication of the Infectious Diseases Society of America)
93. Vento S, Cainelli F, Temesgen Z (2008) Lung infections after cancer chemotherapy. Lancet Oncol 9:982–992
94. Greene RE, Schlamm HT, Oestmann JW et al (2007) Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 44:373–379 (An official publication of the Infectious Diseases Society of America)
95. Baddour LM, Wilson WR, Bayer AS et al (2005) Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 111:e394–e434
96. Fine MJ, Smith MA, Carson CA et al (1996) Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA 275:134–141
97. Ruiz-Gonzalez A, Falguera M, Nogues A, Rubio-Caballero M (1999) Is *Streptococcus pneumoniae* the leading cause of pneumonia of unknown etiology? A microbiologic study of lung aspirates in consecutive patients with community-acquired pneumonia. Am J Med 106:385–390
98. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH (2002) Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122:262–268
99. Kollef MH, Sherman G, Ward S, Fraser VJ (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115:462–474
100. Roson B, Carratala J, Fernandez-Sabe N, Tubau F, Manresa F, Gudiol F (2004) Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 164:502–508

101. Arancibia F, Ewig S, Martinez JA et al (2000) Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med 162:154–160
102. Rano A, Agusti C, Benito N et al (2002) Prognostic factors of non-HIV immunocompromised patients with pulmonary infiltrates. Chest 122:253–261
103. Wheat LJ, Freifeld AG, Kleiman MB et al (2007) Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 45:807–825 (An official publication of the Infectious Diseases Society of America)
104. Mongkolrattanothai K, Peev M, Wheat LJ, Marcinak J (2006) Urine antigen detection of blastomycosis in pediatric patients. Pediatr Infect Dis J 25:1076–1078
105. Chapman SW, Dismukes WE, Proia LA et al (2008) Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 46:1801–1812 (An official publication of the Infectious Diseases Society of America)
106. Durkin M, Connolly P, Kuberski T et al (2008) Diagnosis of coccidioidomycosis with use of the Coccidioides antigen enzyme immunoassay. Clin Infect Dis 47:e69–e73
107. Durkin M, Witt J, Lemonte A, Wheat B, Connolly P (2004) Antigen assay with the potential to aid in diagnosis of blastomycosis. J Clin Microbiol 42:4873–4875
108. Wheat LJ (2009) Approach to the diagnosis of invasive aspergillosis and candidiasis. Clin Chest Med 30:367–377 (viii)
109. Egan L, Connolly P, Wheat LJ et al (2008) Histoplasmosis as a cause for a positive Fungitell (1→3)-beta-D-glucan test. Med Mycol 46:93–95
110. Persat F, Ranque S, Derouin F, Michel-Nguyen A, Picot S, Sulahian A (2008) Contribution of the (1→3)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol 46:1009–1013
111. Ostrosky-Zeichner L, Alexander BD, Kett DH et al (2005) Multicenter clinical evaluation of the (1→3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis 41:654–659
112. Tasaka S, Hasegawa N, Kobayashi S et al (2007) Serum indicators for the diagnosis of pneumocystis pneumonia. Chest 131:1173–1180
113. Digby J, Kalbfleisch J, Glenn A, Larsen A, Browder W, Williams D (2003) Serum glucan levels are not specific for presence of fungal infections in intensive care unit patients. Clin Diagn Lab Immunol 10:882–885
114. Maertens J, Theunissen K, Verbeken E et al (2004) Prospective clinical evaluation of lower cut-offs for galactomannan detection in adult neutropenic cancer patients and haematological stem cell transplant recipients. Br J Haematol 126:852–860
115. Busca A, Locatelli F, Barbui A et al (2006) Usefulness of sequential *Aspergillus* galactomannan antigen detection combined with early radiologic evaluation for diagnosis of invasive pulmonary aspergillosis in patients undergoing allogeneic stem cell transplantation. Transplant Proc 38:1610–1613
116. Viscoli C, Machetti M, Cappellano P et al (2004) False-positive galactomannan platelia *Aspergillus* test results for patients receiving piperacillin-tazobactam. Clin Infect Dis 38:913–916
117. Adam O, Auperin A, Wilquin F, Bourhis JH, Gachot B, Chachaty E (2004) Treatment with piperacillin-tazobactam and false-positive *Aspergillus* galactomannan antigen test results for patients with hematological malignancies. Clin Infect Dis 38:917–920
118. Wheat LJ, Hackett E, Durkin M et al (2007) Histoplasmosis-associated cross-reactivity in the BioRad Platelia *Aspergillus* enzyme immunoassay. Clin Vaccine Immunol 14:638–640
119. Racil Z, Kocmanova I, Lengerova M, Winterova J, Mayer J (2007) Intravenous PLASMA-LYTE as a major cause of false-positive results of platelia *Aspergillus* test for galactomannan detection in serum. J Clin Microbiol 45:3141–3142

120. Marr KA, Laverdiere M, Gugel A, Leisenring W (2005) Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. Clin Infect Dis 40:1762–1769
121. Ascioglu S, Rex JH, de Pauw B et al (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clinical Infect Dis 34:7–14 (An official publication of the Infectious Diseases Society of America)
122. Roghmann M, Ball K, Erdman D, Lovchik J, Anderson LJ, Edelman R (2003) Active surveillance for respiratory virus infections in adults who have undergone bone marrow and peripheral blood stem cell transplantation. Bone Marrow Transplant 32:1085–1088
123. Ison MG, Hayden FG (2002) Viral infections in immunocompromised patients: what's new with respiratory viruses? Curr Opin Infect Dis 15:355–367
124. Campbell AP, Chien JW, Kuypers J et al (2010) Respiratory virus pneumonia after hematopoietic cell transplantation (HCT): associations between viral load in bronchoalveolar lavage samples, viral RNA detection in serum samples, and clinical outcomes of HCT. J Infect Dis 201:1404–1413
125. Gerna G, Campanini G, Rognoni V et al (2008) Correlation of viral load as determined by real-time RT-PCR and clinical characteristics of respiratory syncytial virus lower respiratory tract infections in early infancy. J Clin Virol 41:45–48
126. Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, Raja A (2009) Role of interferon gamma release assay in active TB diagnosis among HIV infected individuals. PloS one 4:e5718
127. Boersma WG, Erjavec Z, van der Werf TS, de Vries-Hosper HG, Gouw AS, Manson WL (2007) Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL. Respir Med 101:317–325
128. Ninane V (2001) Bronchoscopic invasive diagnostic techniques in the cancer patient. Curr Opin Oncol 13:236–241
129. Maertens J, Maertens V, Theunissen K et al (2009) Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis 49:1688–1693 (An official publication of the Infectious Diseases Society of America)
130. White DA, Wong PW, Downey R (2000) The utility of open lung biopsy in patients with hematologic malignancies. Am J Respir Crit Care Med 161:723–729
131. Gupta S, Sultenfuss M, Romaguera JE et al (2010) CT-guided percutaneous lung biopsies in patients with haematologic malignancies and undiagnosed pulmonary lesions. Hematol Oncol 28:75–81
132. Arora SC, Mudaliar YM, Lee C, Mitchell D, Iredell J, Lazarus R (2002) Non-bronchoscopic bronchoalveolar lavage in the microbiological diagnosis of pneumonia in mechanically ventilated patients. Anaesth Intensive Care 30:11–20
133. Fujitani S, Cohen-Melamed MH, Tuttle RP, Delgado E, Taira Y, Darby JM (2009) Comparison of semi-quantitative endotracheal aspirates to quantitative non-bronchoscopic bronchoalveolar lavage in diagnosing ventilator-associated pneumonia. Respir Care 54:1453–1461
134. Fine MJ, Auble TE, Yealy DM et al (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. New Engl J Med 336:243–250
135. Pertel PE, Bernardo P, Fogarty C et al (2008) Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 46:1142–1151 (An official publication of the Infectious Diseases Society of America)
136. Update on oseltamivir-resistant pandemic A (H1N1) 2009 influenza virus: January 2010. Wkly Epidemiol Rec 2009;85:37-40

137. Segal BH, Almyroudis NG, Battiwalla M et al (2007) Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis 44:402–409 (An official publication of the Infectious Diseases Society of America)
138. Maertens J, Theunissen K, Verhoef G et al (2005) Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 41:1242–1250
139. de Pauw BE (2005) Between over- and undertreatment of invasive fungal disease. Clin Infect Dis 41:1251–1253
140. Dignan FL, Evans SO, Ethell ME et al (2009) An early CT-diagnosis-based treatment strategy for invasive fungal infection in allogeneic transplant recipients using caspofungin first line: an effective strategy with low mortality. Bone Marrow Transplant 44:51–56
141. Scalera NM, File TM Jr (2007) How long should we treat community-acquired pneumonia? Current Opin Infect Dis 20:177–181
142. Wunderink RG (2006) A CAP on antibiotic duration. Am J Respir Crit Care Med 174:3–5
143. Chastre J, Wolff M, Fagon JY et al (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA J Am Med Assoc 290:2588–2598
144. Yende S, Angus DC, Ali IS et al (2007) Influence of comorbid conditions on long-term mortality after pneumonia in older people. J Am Geriatr Soc 55:518–525
145. Kampmann B, Cubitt D, Walls T et al (2005) Improved outcome for children with disseminated adenoviral infection following allogeneic stem cell transplantation. Br J Haematol 130:595–603
146. Chakrabarti S, Collingham KE, Fegan CD, Pillay D, Milligan DW (2000) Adenovirus infections following haematopoietic cell transplantation: is there a role for adoptive immunotherapy? Bone Marrow Transplant 26:305–307
147. Heemskerk B, Lankester AC, van Vreeswijk T et al (2005) Immune reconstitution and clearance of human adenovirus viremia in pediatric stem-cell recipients. J Infect Dis 191:520–530
148. Azoulay E, Thiery G, Chevret S et al (2004) The prognosis of acute respiratory failure in critically ill cancer patients. Medicine (Baltimore) 83:360–370

# Enteric Infections

Michael Wang and Stuart Johnson

**Abstract**

Cancer patients, particularly those with neutropenia, are at risk for enteric and intra-abdominal infections. Specific infections and infectious syndromes in this setting include neutropenic enterocolitis, bacterial infections such as *Clostridium difficile* infection (CDI), viral infections such as CMV colitis, and parasitic infections such as strongyloidiasis. Diagnosing and gauging the severity of CDI presents challenges, as chemotherapy may produce symptoms that mimic CDI and laboratory findings such as leukocytosis are not reliable in this population. Treatment for enteric infections should be pathogen specific, although broad-spectrum antibiotics are often required as initial empiric therapy in patients with neutropenia.

**Keywords**

Intra-abdominal infections · Neutropenic enterocolitis · *Clostridium difficile*

## Contents



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## 1 Introduction

Treatment for cancer often involves potent chemotherapeutic agents with resultant neutropenia for which prophylactic antibiotics are often prescribed [1, 2]. These chemotherapeutic regimens may result in abdominal complications, many of which are infectious in nature [1]. Abdominal infections in the setting of neutropenia carry significant mortality risks, particularly in hematologic malignancies, and 72–92 % of these neutropenia-associated infections occur in patients with hematologic malignancies [1, 3].

The differential diagnosis for cancer-related abdominal infection is broad and includes entities that also occur in patients without cancer. Non-infectious etiologies that may mimic abdominal infections include small bowel obstruction, cholecystitis, colonic pseudo-obstruction, and splenic rupture [3]. Infections not unique to cancer patients, but which are common in this setting, include appendicitis, diverticulitis, and *Clostridium difficile* infection (CDI). Enteritis due to Salmonella, Shigella, Yersinia, and Campylobacter are rare in the cancer population [4]. These pathogens are normally contracted via contaminated food products and are uncommon in hospitals. The enteric infectious syndrome most directly related to malignancy is neutropenic enterocolitis [1].

## 2 Neutropenic Enterocolitis

Neutropenic enterocolitis is a life-threatening complication of chemotherapy in patients with leukemia or solid tumors [5, 6]. It also occurs in individuals with aplastic anemia or cyclic neutropenia who have not received cytotoxic therapies. However, neutropenic enterocolitis most frequently occurs after intensive chemotherapy for leukemia [7]. The reported incidence of neutropenic enterocolitis varies from 0.8 to 26 %. Pooled data from 21 studies gave an incidence of 5.3 % in patients hospitalized for hematologic malignancies, high-dose chemotherapy in solid tumors, and aplastic anemia [7].

Currently, there is no standard clinical definition for neutropenic enterocolitis [7]. The traditional clinical triad includes fever, abdominal pain, and diarrhea [5, 7, 8]. Ultrasound and computed tomography (CT) have been established as useful diagnostic tools [5, 7, 9]. Bowel wall thickening has been proposed as an indicator of neutropenic enterocolitis, but there is no agreement to the degree of thickness

required for this diagnosis. One study proposed a cutoff of 4 mm as suggestive of the diagnosis [7], whereas another study proposed mural thickening of 10 mm as indicative of a poorer outcome [9]. Neutropenic enterocolitis usually involves the cecum and has also been referred to as typhilitis [10]. In addition, neutropenic enterocolitis is frequently complicated by bacteremia or fungemia [5, 11]. Fungemia, bacteremia, and hypotension are all associated with increased morbidity and mortality [11].

Clinically distinguishing neutropenic enterocolitis from CDI may be difficult [12]. Pathological findings in neutropenic enterocolitis include diffuse dilatation and edema of the bowel wall, prominently involving the cecum and ascending colon. There may be different degrees of mucosal and submucosal necrosis, hemorrhage, and ulceration [5]. Obtaining a pathologic diagnosis may be difficult, especially given patients' degrees of neutropenia and thrombocytopenia. In addition, similar pathologic and radiographic findings are seen in CDI and CDI may be limited to the ascending colon as well [13]. Pseudomembranes suggest CDI. Bloody stools, often seen in neutropenic enterocolitis, are not characteristic of CDI. A positive stool *C. difficile* toxin assay is usually present in CDI.

There is no universal consensus regarding specific treatment for neutropenic enterocolitis, but antibiotic treatment should target the likely pathogens involved in the disease. Commonly implicated organisms include *Enterococcus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Bacteroides fragilis*, viridans group *Streptococcus*, and alpha-hemolytic *Streptococcus* [5, 11]. The guidelines from the Infectious Disease Society of America (IDSA) for treatment for neutropenic fever suggest a carbapenem, such as imipenem or meropenem, or ceftazidime or cefepime [14]. An antipseudomonal beta-lactam antibiotic may also be combined with an aminoglycoside as dual therapy [7, 14]. However, cefepime and ceftazidime as monotherapy may not provide adequate anaerobic coverage. In this instance, metronidazole should be added [7]. The IDSA guidelines for treatment for intra-abdominal infections also include meropenem or imipenem or cephalosporins plus metronidazole [15]. In the case of cephalopsorins, an antipseudomonal agent such as ceftazidime or cefepime would be consistent with neutropenic fever guidelines. Other acceptable regimens may include piperacillin/tazobactam or aztreonam plus metronidazole [15].

The role of antifungal therapy for neutropenic enterocolitis has not been firmly established, but pooled data from one meta-analysis reported the frequency of fungal involvement of 6.2 % [16]. *Candida* species are most frequently implicated, including *C. albicans, C. glabrata*, and *C. krusei* [5, 16]. There is currently no consensus on the choice of antifungal agents. Fluconazole may be considered in select patients, particularly those with *C. albicans* and those not previously on fluconazole prophylaxis. Other therapeutic options include caspofungin, voriconazole, and amphotericin B [16, 17]. Fungemia and fungal infections in neutropenic enterocolitis carry a high mortality, ranging from 81.8–100 % [3, 5, 11]. The decision to include antifungal therapy must be made on an individual basis.

Surgical therapy for neutropenic enterocolitis carries significant morbidity and mortality. Abdominal surgery in neutropenic patients carries a 30-day and 90-day mortality risk of 30 and 52 %, respectively [3]. If possible, conservative management is preferable [1, 3, 5], with surgery delayed until after recovery of neutrophil counts [3]. Surgery should be considered in those cases with perforation [6]. Non-surgical management options that may be helpful include bowel rest, bowel decompression, antibiotics, and nutritional support [1].

## 3 *Clostridium Difficile* Infection

*Clostridium difficile* is the most common infectious cause of hospital-acquired diarrhea and colitis in general and the most common cause among cancer patients as well [18, 19]. The major risk factors for CDI overall, antibiotics, hospitalization, and advanced age [20] are also common among cancer patients. Cancer patients have additional factors, which may increase their risk of CDI. In particular, neutropenia secondary to hematologic malignancy or chemotherapeutic agents appears to increase CDI risk [19, 21]. CDI occurred at a median of 10 days of neutropenia and was complicated by bacteremia due to other enteric organisms in 21 % of the neutropenic episodes in one study of patients on a leukemia ward with CDI [19]. Other potential risk factors in cancer patients include hypoalbuminemia, treatment with proton pump inhibitors, histamine-2 blockers, intravenous vancomycin, fluoroquinolones, and cephalosporins [21]. Antibiotic use is of particular concern in this patient population. Antibiotics often have profound effects on the indigenous bowel flora, which normally provide resistance to infection with *C. difficile*. In addition, some antibiotics may select for specific antibiotic-resistant *C. difficile* strains [22]. Antibiotic duration is also an important factor as evidenced by one case–control study of outpatients at a cancer hospital where case patients that developed CDI received longer courses of antibiotics than control patients [23]. Historically, cephalosporins and clindamycin have carried the highest risk for CDI [24]. However, fluoroquinolones have been increasingly associated with CDI [24–27] and this class of antibiotics is often used for prophylaxis in patients with hematologic malignancies and neutropenia [2]. Fluoroquinolones have been implicated in the recent North American epidemic of CDI due the BI/NAP1/027 strain of *C. difficile*, which has developed high-level fluoroquinolone resistance [18]. During this epidemic in Quebec, fluoroquinolones were the single biggest risk factor for developing CDI [25]. Other outbreaks have implicated levofloxacin [26] or a formulary switch from levofloxacin to gatifloxacin [28].

Chemotherapy may also be an inciting agent for CDI, even in the absence of antibiotics. One potential explanation for this finding is chemotherapy-induced alteration of bowel flora [29]. Regimens containing high-dose paclitaxel had a rate of CDI as high as 20 %, compared with standard regimens with an incidence of 2 % [30]. Similarly, a study of ovarian cancer patients reported a CDI rate of 6.4 % in those receiving cisplatin-based regimens [31]. Other chemotherapy

agents that have been implicated include methotrexate, bleomycin, vinblastine, 5-FU, cyclophosphamide, doxorubicin, and cytarabine [32]. Unfortunately, gastrointestinal side effects, including nausea, vomiting, and diarrhea, are commonly associated with chemotherapy, particularly platinum-based regimens, and these side effects may be difficult to differentiate from CDI [30].

Diagnosis of CDI among cancer patients can be challenging because of the frequency of diarrhea and other gastrointestinal symptoms in this population as well as the high rate of asymptomatic carriage of *C. difficile* in the hospital setting. The stool cytotoxicity cell assay using tissue culture has traditionally been used for diagnosis [33]. However, toxin testing has been replaced in most clinical laboratories by enzyme immunoassays (EIA) for toxin A and toxin B [33–35]. This assay has a quick turnaround time and is reasonably specific, but it has an estimated sensitivity of ~80 % [34]. The lack of sensitivity is not overcome by repeating EIA testing [33–35], and in general, the test should not be repeated within a seven-day period [33–35]. However, with the understanding that *C. difficile* is primarily acquired in the hospital setting, repeating the toxin assay days or weeks later in patients with prolonged hospital stays who have new or additional gastrointestinal symptoms is appropriate. Culture has high sensitivity, but has a three- to four-day reporting delay and is not widely available [33]. Newer testing strategies include screening with a test for glutamate dehydrogenase (GDH) followed by toxin assay for GDH-positive specimens and PCR [36, 37], but stool toxin testing remains the most widely used strategy at the present time.

Other laboratory findings that may suggest CDI include leukocytosis, elevated serum creatinine, and hypoalbuminemia. Leukocytosis may not be as useful in this population, given the frequency of neutropenia [38]. Radiographically, bowel wall thickening on CT scan may be useful, although this test is relatively insensitive [13, 33]. Pseudomembranous colitis demonstrated by endoscopy is specific, but it is also not a sensitive test for the diagnosis and endoscopy may not be practical or advisable in the setting of neutropenia [33].

Given the increasing severity of CDI, treatment regimens have been increasingly scrutinized. Prior recommendations have included metronidazole as first-line therapy for all patients with CDI. However, several recent studies have documented increased rates of treatment failure with metronidazole [39, 40]. There is now good evidence supporting improved outcomes of treatment for severe CDI with oral vancomycin over treatment with metronidazole [41]. However, mild to moderate CDI usually responds to treatment with metronidazole [41] and metronidazole has been effective for CDI in the setting of chemotherapy-induced neutropenia [19]. Appropriate regimens with these agents include metronidazole 500 mg orally three times daily for 10–14 days or vancomycin 125 mg orally four times daily for 10–14 days [42]. In addition, fidaxomicin, a non-absorbed macrocyclic agent, has also been approved for treatment for CDI [43]. Fidaxomicin 200 mg twice daily for 10 days was not inferior to vancomycin for cure and was superior for sustained response at 25 days after treatment completion.

Recurrent CDI has been increasingly problematic and may occur in one-third of all cases after successful recovery from the first episode [44]. First recurrences can be treated with the same agent used in the initial treatment regimen [42, 44]. However, if a relapse is noted to be severe, then oral vancomycin should be used. In addition, repeated or prolonged metronidazole courses should be avoided because of the risk of neurotoxicity. For patients with multiple recurrences, vancomycin in tapered and pulsed dose regimens is often effective in stopping subsequent recurrences [42]. There has been limited experience with other regimens for managing recurrent CDI, including vancomycin plus *Saccharomyces boulardii* [45], a post-vancomycin chaser regimen of rifaximin for 2 weeks [46], nitazoxanide [47], intravenous immunoglobulin [42], and fecal transplantation [48]. However, caution is advised in immunocompromised patients as cases of fungemia secondary to saccharomyces containing probiotics have been reported [49]. There are no data on stool transplants in immunocompromised patients, and they are not recommended in this setting [48].

## 4 Other Bacterial Infections

### 4.1 *Clostridium* Infections Other than CDI

*Clostridium* species, particularly bacteremia, have been associated with occult malignancy, most commonly a gastrointestinal source [50, 51]. One of these studies documented malignancy in 48 % of clostridial bacteremia, while another documented a relative risk of 40 for malignancy in patients with clostridial bacteremia. The *Clostridium* species most commonly associated with malignancy is *Clostridium septicum* [51, 52].

*C. septicum* has a particularly high association with hematologic malignancies and colon cancer. Approximately 24 % of patients with *C. septicum* infection will have hematologic malignancies and 75 % will have colon cancer [53]. *C. septicum* can be found in the gastrointestinal tract in humans [53]. It is possible that the acidic and hypoxic environment provided by anaerobic glycolysis of the tumor results in spore germination [52]. In the absence of a hematologic malignancy, a screening colonoscopy should strongly be considered [52].

Clinical syndromes seen with *C. septicum* infection include gas gangrene, myonecrosis, and septicemia. In distinction to disease associated with *C. perfringens*, gas gangrene associated with *C. septicum* typically develops in the absence of trauma and is spread hematogenously [54]. The α-toxin produced by *C. septicum* can induce hemolysis and cause tissue necrosis and is likely a key virulence factor of the organism [50–53]. Clinically, lesions may begin innocuously, but may evolve into overt gas gangrene within hours. Systemic toxicity then ensues with tachycardia, fever, diaphoresis, shock, and multiple organ failure [54].

In general, clostridial infections carry a high mortality [50–53] and often require surgical debridement [50, 53]. Effective treatment regimens include

penicillin plus clindamycin, although tetracycline and chloramphenicol have also been used effectively [54].

### 4.2 *Streptococcus bovis* Infection

*Streptococcus bovis* is classified as a non-enterococcal group D Streptococcus and is found among the normal flora of the human intestinal tract in 5–16 % of adults. As with *C. septicum*, *S. bovis* bacteremia carries a high association with colorectal cancer [55–57]. It is hypothesized that *S. bovis* may stimulate an overexpression of cyclo-oxygenase-2 (COX-2), which is also overexpressed in human colorectal cancers. COX-2 can inhibit apoptosis or stimulate angiogenesis, which may promote a carcinogenic process [56]. There is also considerable debate whether *S. bovis* is specifically involved in the pathogenesis of colon cancer or whether ulcerating colorectal carcinomas allow for increased growth of *S. bovis* with subsequent bacteremia [56].

Patients with *S. bovis* infection often present with bacteremia or endocarditis. *S. bovis* endocarditis was first discovered in 1951, but at the time, it was not distinguished from enterococcal endocarditis [55–57]. A review of studies among patients with *S. bovis* bacteremia demonstrated colon cancer incidences ranging from 6 to 71 % [57, 58]. Thus, colorectal screening is recommended in patients with *S. bovis* bacteremia or endocarditis [55–57].

## 5 Parasitic Infections

### 5.1 *Cryptosporidium* Infection

*Cryptosporidium* (*C. parvum* or *C. hominis*) is an intestinal protozoan parasite that is recognized as a cause of sporadic, self-limiting diarrhea in normal individuals. However, in immunocompromised patients, it may be associated with prolonged or life-threatening gastroenteritis [58]. While patients with AIDS are the most common immunocompromised risk group, cancer patients may also be at increased risk. While patients with solid tumors receiving chemotherapy are at risk for *Cryptosporidium* infection, those with hematologic malignancies such as acute leukemia are at considerably higher risk [58, 59]. Although not frequently diagnosed in immunocompetent patients in the United States, there have been outbreaks of cryptosporidiosis related to contaminated drinking water [59].

The clinical course of cryptosporidiosis can range from asymptomatic to severe or mild diarrhea. Gastroenteritis is characterized by watery diarrhea and malabsorption. Fever is also commonly present. Ingested oocysts release sporozoites, which attach to intestinal epithelium [60]. Extraintestinal disease, including pulmonary cryptosporidiosis, has rarely been reported in hematologic malignancy.

Biliary tract involvement has been reported in AIDS patients, but not in cancer patients [61].

Diagnosis of cryptosporidiosis first requires consideration of the pathogen when ordering diagnostic testing. Specimens should be sent specifically for microscopic examination of *Cryptosporidium* oocysts. The most commonly employed methods for detection include modified acid fast staining and direct fluorescent antibody staining [61, 62]. These tests must be specifically ordered because they are not part of the routine ova and parasite screening in most clinical laboratories. ELISA kits for antigen detection are also increasingly available [60].

Treatment options currently include supportive therapy and possibly antiparasitic therapy [58, 59]. Most cases, particularly in immunocompetent persons, are self-limiting [60]. Nitazoxanide 500 mg orally every 12 h has been shown to be efficacious in resolution of cryptosporidiosis in immunocompetent and moderately immunocompromised patients [63]. Treatment for three to seven days is recommended for immunocompetent adults with prolonged diarrhea or for pediatric patients. A longer course is typically recommended for AIDS patients or for patients with hematologic malignancies, although prior studies have had mixed results [64]. In addition, paromomycin is also noted to have in vitro activity and may have some clinical usefulness [64]. Correcting the underlying immune dysfunction is critical to eradicating the illness in HIV-infected patients [61, 64].

## 5.2 *Strongyloides* Infection

*Strongyloides stercoralis* is an intestinal helminth that is endemic in many developing countries, particularly tropical and subtropical regions, and in some parts of Europe and the southern United States [65–67]. A large number of infections are subclinical, but immunocompromised patients may have potentially fatal infections [65, 66, 68]. In patients with hematologic malignancies [66, 67], use of systemic corticosteroids [66] and allogeneic hematopoietic stem cell transplantation are important risk factors for strongyloidiasis [66]. In addition, prior gastric surgery and gastrointestinal cancer are also reported risk factors [67, 69].

The larvae of *Strongyloides* can penetrate the skin of the human host during the filariform stage. These larvae normally then migrate through circulation to the lungs, airway, and then are swallowed into the intestine [65]. Symptoms can range from asymptomatic to life-threatening hyperinfection [65–69]. Non-disseminated symptoms may include pruritic rash, particularly in the buttocks, groin, and trunk. Abdominal symptoms may include chronic diarrhea, nausea, and abdominal bloating [65, 66]. Pulmonary involvement can present as Loeffler's syndrome (dry cough, dyspnea, and transient pulmonary infiltrates with eosinophils) [66].

Immunocompromised patients may have life-threatening complications of strongyloidiasis, particularly those with impaired cellular immunity [65–67]. This is due to exaggeration of the autoinfection cycle, which occurs when the number of organisms increases rapidly and is present in extraintestinal regions [65].

Pulmonary hyperinfection can result in pneumonia or intra-alveolar hemorrhage. In addition, bacterial infections can result from translocation of gastrointestinal flora from damaged bowel mucosa, resulting in septicemia, pneumonia, meningitis, or disseminated disease [65, 66].

Diagnosis of strongyloidiasis should be considered in patients from endemic areas, even if they moved from the endemic region many years ago. The diagnosis is most frequently made on microscopic examination of stool for larvae [65]. Bronchial specimens may also be diagnostic in pulmonary disease [66]. Peripheral eosinophilia may or may not be present in strongyloidiasis [65, 66]. Pulmonary infiltrates on chest radiographs may also vary, including alveolar or interstitial, diffuse or local, unilateral or bilateral [65]. Ivermectin is currently first-line therapy for chronic strongyloidiasis. It is given orally at 200 μg/kg daily for 2 days, with consideration of repeat dosing after 2 weeks. Alternative regimens include albendazole 400 mg twice a day for 3 days. Longer courses may be necessary for disseminated strongyloidiasis or hyperinfection syndrome [70]. Screening for asymptomatic strongyloidiasis should be strongly considered in high-risk patients from endemic areas who are diagnosed with hematologic malignancies or who are to receive steroid or stem cell transplantation [66, 69].

## 5.3 Cytomegalovirus Infection

Cytomegalovirus (CMV) colitis is common in immunocompromised patients, particularly those with AIDS, solid organ transplants, and bone marrow allogeneic transplants. Bone marrow patients may be susceptible due to T-cell immunodeficiency, particularly during episodes of graft-versus-host disease (GVHD) [71]. Infections can be asymptomatic or cause disease in the gastrointestinal tract, liver, lungs, or eyes [72]. CMV can present as enterocolitis, specifically in those who have impaired T-cell function [73]. CMV colitis may follow administration of standard chemotherapy regimens [73–75]. Cases have been reported following administration of cisplatin and etoposide for lung cancer [75], docetaxel, 5-FU, and cisplatin for hypopharyngeal cancer [74], and a regimen of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) for non-Hodgkin's lymphoma [67].

CMV gastrointestinal disease has been increasing in frequency among patients with hematologic malignancy over the last several decades following conventional chemotherapy, aggressive therapy, and bone marrow transplantation [76, 77]. Gastrointestinal manifestations may include anorexia, nausea, vomiting, and diarrhea [77]. CMV risk appears to increase with the use of T-cell-depleting agents and aggressive chemotherapy [72]. Re-activation of CMV disease has occurred with the use of the immunomodulating antibody, rituximab [78], and CMV colitis has been reported with alemtuzumab [79].

Nucleic acid-based assays and antigen assays have been employed for the detection of CMV [80–82]. These assays allow both the diagnosis of active

infections and surveillance for incipient clinical disease in patients at risk. The CMV pp65 antigenemia assay is an indirect immunofluorescence stain with monoclonal antibodies to the CMV protein pp65 [81]. However, this test has been reported to be labor-intensive and subjective, particularly to less fresh specimens [80]. Other assays to detect CMV have included CMV DNA PCR and mRNA pp67 assays [80]. More recently, a real-time CMV PCR assay has been developed to diagnose and monitor CMV infections [82]. In a trial of HIV patients, break points of $3.0 \times 10^3$ copies/mL in whole blood had a sensitivity of 93 % and specificity of 86 %, while $1.0 \times 10^3$ copies/mL in plasma had a sensitivity of 89 % and specificity of 85 % [82]. The advantages of real-time PCR include improved accuracy and speed, and they are less time-consuming than traditional PCR [82]. CMV colitis is also diagnosed by intestinal biopsy and identification of cells with typical cytomegalic inclusions. However, sampling error may result in false-negative biopsies [83]. Stool PCR has also been proposed as a test for CMV colitis [83, 84]. However, studies supporting this method were small studies and need to be further evaluated on a larger scale.

Treatment for CMV infections includes ganciclovir, foscarnet, and/or cidofovir [76]. Intravenous (IV) ganciclovir has been considered first-line therapy, but CMV resistance has been reported. Ganciclovir treatment recommendations in patients with normal renal function normally include an induction dose, 5 mg/kg every 12 h, followed by a maintenance dose of 5 mg/kg daily, intravenously. Oral ganciclovir, however, may not be clinically efficacious because of poor absorption [72]. Intravenous foscarnet or cidofovir may be considered for treatment for infection with ganciclovir-resistant isolates [76, 84]. Foscarnet has been associated with renal and neural toxicity. Cidofovir has previously been used for treatment for CMV retinitis and also can be nephrotoxic [84]. CMV hyperimmunoglobulin (CMVIG) may also have benefit, but appears to more beneficial for CMV pneumonia rather than CMV colitis [76]. Treatment efficacy may be monitored by serial antigen or nucleic acid assays.

Prophylaxis of CMV may be beneficial in stem cell transplant patients. Ganciclovir or foscarnet are administered at induction doses for 1–2 weeks or until CMV load and/or antigenemia decreases [85]. Maintenance dosing may then commence for a total of 6 weeks to 3 months, or when immunosuppression resolves [71, 85]. An oral agent, oral valganciclovir, may be given for prophylaxis or preemptive therapy. It is dosed 900 mg every 12 h for induction, and 900 mg daily for maintenance [84]. Late CMV infection, or cases presenting after 100 days, may be associated with prior CMV antigenemia, graft-versus-host disease, CD4 cell counts of $<50$ cells/mm$^3$, or post-engraftment absolute lymphopenia of $<100$ lymphocytes/mm$^3$ [71]. These findings may support long-term prophylaxis of at-risk stem cell transplant patients.

## References


1. Wade DS, Douglass H Jr, Nava HR, Piedmonte M (1990) Abdominal pain in neutropenic patients. Arch Surg 125:1119–1127
2. Reuter S, Kern WV, Sigge A et al (2005) Impact of fluoroquinolone prophylaxis on reduced infection-related mortality among patients with neutropenia and hematologic malignancies. Clin Infect Dis 40:1087–1093
3. Badgwell BD, Cormier JN, Wray CJ et al (2008) Challenges in surgical management of abdominal pain in the neutropenic cancer patient. Ann Surg 248:104–109
4. Gorschluter M, Hahn C, Ziske C et al (2002) Low frequency of enteric infections by Salmonella, Shigella, Yersinia and Campylobacter in patients with acute leukemia. Infection 30:22–25
5. Gomez L, Martino R, Rolston KV (1998) Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. Clin Infect Dis 27:695–699
6. Wade DS, Nava HR, Douglass HO Jr (1992) Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer 69:17–23
7. Gorschluter M, Mey U, Strehl J et al (2005) Neutropenic enterocolitis in adults: systematic analysis of evidence quality. Eur J Haematol 75:1–13
8. Aksoy DY, Tanriover MD, Uzun O et al (2007) Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis. Ann Oncol 18:183–189
9. Cartoni C, Dragoni F, Micozzi A et al (2001) Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol 19:756–761
10. Picardi M, Camera A, Pane F, Rotoli B (2007) Improved management of neutropenic enterocolitis using early ultrasound scan and vigorous medical treatment. Clin Infect Dis 45:403–404
11. Starnes HF Jr, Moore FD Jr, Mentzer S, Osteen RT, Steele GD Jr, Wilson RE (1986) Abdominal pain in neutropenic cancer patients. Cancer 57:616–621
12. Gorbach S (1998) Editorial response: neutropenic enterocolitis. Clin Infect Dis 27(4):700–701
13. Boland GW, Lee MJ, Cats AM, Gaa JA, Saini S, Mueller PR (1994) Antibiotic-induced diarrhea: specificity of abdominal CT for the diagnosis of *Clostridium difficile* disease. Radiology 191:103–106
14. Hughes WT, Armstrong D, Bodey GP et al (2002) 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34:730–751
15. Solomkin JS, Mazuski JE, Bradley JS et al (2010) Diagnosis and management of complicated intra-abdominal infections in adults and children: guidelines by the surgical infectious society and the infectious diseases society of America. Clin Infect Dis 50:133–164
16. Gorschluter M, Mey U, Strehl J et al (2006) Invasive fungal infections in neutropenic enterocolitis: a systematic analysis of pathogens, incidence, treatment and mortality in adult patients. BMC Infect Dis 6:35
17. Walsh TJ, Teppler H, Donowitz GR et al (2004) Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 351:1391–1402
18. McDonald LC, Killgore GE, Thompson A et al (2005) An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 353:2433–2441
19. Gorschluter M, Glasmacher A, Hahn C et al (2001) *Clostridium difficile* infection in patients with neutropenia. Clin Infect Dis 33:786–791
20. McDonald LC (2005) *Clostridium difficile*: responding to a new threat from an old enemy. Infect Control Hosp Epidemiol 26:672–675
21. Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ (2007) *Clostridium difficile*–associated disease in a setting of endemicity: identification of novel risk factors. Clin Infect Dis 45:1543–1549

22. Johnson S, Samore MH, Farrow KA et al (1999) Epidemics of diarrhea caused by a clindamycin-resistant strain of *Clostridium difficile* in four hospitals. N Engl J Med 341:1645–1651
23. Palmore TN, Sohn S, Malak SF, Eagan J, Sepkowitz KA (2005) Risk factors for acquisition of *Clostridium difficile*-associated diarrhea among outpatients at a cancer hospital. Infect Control Hosp Epidemiol 26:680–684
24. Gerding DN (2004) Clindamycin, cephalosporins, fluoroquinolones, and *Clostridium difficile*-associated diarrhea: this is an antimicrobial resistance problem. Clin Infect Dis 38:646–648
25. Pepin J, Saheb N, Coulombe MA et al (2005) Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 41:1254–1260
26. Muto CA, Pokrywka M, Shutt K et al (2005) A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 26:273–280
27. Biller P, Shank B, Lind L et al (2007) Moxifloxacin therapy as a risk factor for *Clostridium difficile*-associated disease during an outbreak: attempts to control a new epidemic strain. Infect Control Hosp Epidemiol 28:198–201
28. Gaynes R, Rimland D, Killum E et al (2004) Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis 38:640–645
29. Blot E, Escande MC, Besson D et al (2003) Outbreak of *Clostridium difficile*-related diarrhoea in an adult oncology unit: risk factors and microbiological characteristics. J Hosp Infect 53:187–192
30. Husain A, Aptaker L, Spriggs DR, Barakat RR (1998) Gastrointestinal toxicity and *Clostridium difficile* diarrhea in patients treated with paclitaxel-containing chemotherapy regimens. Gynecol Oncol 71:104–107
31. Emoto M, Kawarabayashi T, Hachisuga MD, Eguchi F, Shirakawa K (1996) *Clostridium difficile* colitis associated with cisplatin-based chemotherapy in ovarian cancer patients. Gynecol Oncol 61:369–372
32. Anand A, Glatt AE (1993) *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis 17:109–113
33. Bartlett JG (2002) Clinical practice. Antibiotic-associated diarrhea. N Engl J Med 346:334–339
34. Mohan SS, McDermott BP, Parchuri S, Cunha BA (2006) Lack of value of repeat stool testing for *Clostridium difficile* toxin. Am J Med 119(356):e7–e8
35. Aichinger E, Schleck CD, Harmsen WS, Nyre LM, Patel R (2008) Nonutility of repeat laboratory testing for detection of *Clostridium difficile* by use of PCR or enzyme immunoassay. J Clin Microbiol 46:3795–3797
36. Ticehurst JR, Aird DZ, Dam LM, Borek AP, Hargrove JT, Carroll KC (2006) Effective detection of toxigenic *Clostridium difficile* by a two-step algorithm including tests for antigen and cytotoxin. J Clin Microbiol 44:1145–1149
37. Peterson LR, Manson RU, Paule SM et al (2007) Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. Clin Infect Dis 45:1152–1160
38. Wang M, Evans CT, Rodriguez T, Gerding DN, Johnson S (2013) *Clostridium difficile* infection (CDI) and limitations of markers for severity in patients with hematologic malignancy. Infect Cont Hosp Epidemiol 34:127–132
39. Pepin J, Alary ME, Valiquette L et al (2005) Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. Clin Infect Dis 40:1591–1597
40. Musher DM, Aslam S, Logan N et al (2005) Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. Clin Infect Dis 40:1586–1590
41. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB (2007) A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 45:302–307

42. Kelly CP, LaMont JT (2008) *Clostridium difficile*–more difficult than ever. N Engl J Med 359:1932–1940
43. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y et al (2011) Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 364:422–431
44. Pepin J, Routhier S, Gagnon S, Brazeau I (2006) Management and outcomes of a first recurrence of *Clostridium difficile*-associated disease in Quebec, Canada. Clin Infect Dis 42:758–764
45. Surawicz CM, McFarland LV, Greenberg RN et al (2000) The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. Clin Infect Dis 31:1012–1017
46. Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN (2007) Interruption of recurrent *Clostridium difficile*-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. Clin Infect Dis 44:846–848
47. Musher DM, Logan N, Hamill RJ et al (2006) Nitazoxanide for the treatment of *Clostridium difficile* colitis. Clin Infect Dis 43:421–427
48. Aas J, Gessert CE, Bakken JS (2003) Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. Clin Infect Dis 36:580–585
49. Munoz P, Bouza E, Cuenca-Estrella M et al (2005) Saccharomyces cerevisiae fungemia: an emerging infectious disease. Clin Infect Dis 40:1625–1634
50. Rechner PM, Agger WA, Mruz K, Cogbill TH (2001) Clinical features of clostridial bacteremia: a review from a rural area. Clin Infect Dis 33:349–353
51. Leal J, Gregson DB, Ross T, Church DL, Laupland KB (2008) Epidemiology of *Clostridium* species bacteremia in Calgary, Canada, 2000–2006. J Infect 57:198–203
52. Chew SS, Lubowski DZ (2001) *Clostridium septicum* and malignancy. ANZ J Surg 71:647–649
53. Larson CM, Bubrick MP, Jacobs DM, West MA (1995) Malignancy, mortality, and medicosurgical management of *Clostridium septicum* infection. Surgery 118:592–597; discussion 7–8
54. Stevens DL, Bisno AL, Chambers HF et al (2005) Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 41:1373–1406
55. Gold JS, Bayar S, Salem RR (2004) Association of S*treptococcus bovis* bacteremia with colonic neoplasia and extracolonic malignancy. Arch Surg 139:760–765
56. Burnett-Hartman AN, Newcomb PA, Potter JD (2008) Infectious agents and colorectal cancer: a review of *Helicobacter pylori*, *Streptococcus bovis*, JC virus, and human papillomavirus. Cancer Epidemiol Biomarkers Prev 17:2970–2979
57. Klein RS, Recco RA, Catalano MT, Edberg SC, Casey JI, Steigbigel NH (1977) Association of *Streptococcus bovis* with carcinoma of the colon. N Engl J Med 297:800–802
58. Mead GM, Sweetenham JW, Ewins DL, Furlong M, Lowes JA (1986) Intestinal cryptosporidiosis: a complication of cancer treatment. Cancer Treat Rep 70:769–770
59. Hunter PR, Nichols G (2002) Epidemiology and clinical features of *Cryptosporidium* infection in immunocompromised patients. Clin Microbiol Rev 15:145–154
60. Leav BA, Mackay M, Ward HD (2003) *Cryptosporidium species*: new insights and old challenges. Clin Infect Dis 36:903–908
61. Gentile G, Venditti M, Micozzi A et al (1991) Cryptosporidiosis in patients with hematologic malignancies. Rev Infect Dis 13:842–846
62. Mac Kenzie WR, Hoxie NJ, Proctor ME et al (1994) A massive outbreak in Milwaukee of *cryptosporidium* infection transmitted through the public water supply. N Engl J Med 331:161–167
63. Rossignol JF, Ayoub A, Ayers MS (2001) Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. J Infect Dis 184:103–106

64. Fox LM, Saravolatz LD (2005) Nitazoxanide: a new thiazolide antiparasitic agent. Clin Infect Dis 40:1173–1180
65. Siddiqui AA, Berk SL (2001) Diagnosis of *Strongyloides stercoralis* infection. Clin Infect Dis 33:1040–1047
66. Safdar A, Malathum K, Rodriguez SJ, Husni R, Rolston KV (2004) Strongyloidiasis in patients at a comprehensive cancer center in the United States. Cancer 100:1531–1536
67. Nucci M, Portugal R, Pulcheri W et al (1995) Strongyloidiasis in patients with hematologic malignancies. Clin Infect Dis 21:675–677
68. Lam CS, Tong MK, Chan KM, Siu YP (2006) Disseminated strongyloidiasis: a retrospective study of clinical course and outcome. Eur J Clin Microbiol Infect Dis 25:14–18
69. Machado ER, Teixeira EM, Goncalves-Pires Mdo R, Loureiro ZM, Araujo RA, Costa-Cruz JM (2008) Parasitological and immunological diagnosis of *Strongyloides stercoralis* in patients with gastrointestinal cancer. Scand J Infect Dis. 40:154–158
70. Roxby A, Gottlieb G, Limaye A (2009) Strongyloidiasis in transplant patients. Clin Infect Dis 48:1411–1423
71. Boeckh M, Leisenring W, Riddell SR et al (2003) Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood 101:407–414
72. Reed EC, Wolford JL, Kopecky KJ et al (1990) Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo-controlled trial. Ann Intern Med 112:505–510
73. Nomura K, Kamitsuji Y, Kono E et al (2005) Severe cytomegalovirus enterocolitis after standard chemotherapy for non-Hodgkin's lymphoma. Scand J Gastroenterol 40:604–606
74. Van den Brande J, Schrijvers D, Colpaert C, Vermorken JB (1999) Cytomegalovirus colitis after administration of docetaxel-5-fluorouracil-cisplatin chemotherapy for locally advanced hypopharyngeal cancer. Ann Oncol 10:1369–1372
75. Matthes T, Kaiser L, Weber D, Kurt AM, Dietrich PY (2002) Cytomegalovirus colitis–a severe complication after standard chemotherapy. Acta Oncol 41:704–706
76. Wade JC (2006) Viral infections in patients with hematological malignancies. Hematology Am Soc Hematol Educ Program 368–374
77. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD (1993) Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 118:173–178
78. Aksoy S, Hartuputluoglu H, Kilickap S et al (2007) Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 48(7):1307–1312
79. Martin S, Marty F, Fiumara K (2006) Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. Clin Infect Dis 43:16–24
80. Caliendo AM, George KS, Allega J, Bullotta AC, Gilbane L, Rinaldo CR (2002) Distinguishing cytomegalovirus (CMV) infection and disease with CMV nucleic acid assays. J Clin Microbiol 40:1581–1586
81. Lesprit P, Scieux C, Lemann M, Carbonelle E, Modai J, Molina JM (1998) Use of the cytomegalovirus (CMV) antigenemia assay for the rapid diagnosis of primary CMV infection in hospitalized adults. Clin Infect Dis 26:646–650
82. Yoshida A, Hitomi S, Fukui T et al (2001) Diagnosis and monitoring of human cytomegalovirus diseases in patients with human immunodeficiency virus infection by use of a real-time PCR assay. Clin Infect Dis 33:1756–1761
83. Michel D, Marre E, Hampl W et al (1995) Intestinal cytomegalovirus disease in immunocompromised patients may be ruled out by search for cytomegalovirus DNA in stool samples. J Clin Microbiol 33:3064–3067
84. Torres-Madriz G, Boucher HW (2008) Immunocompromised hosts: perspectives in the treatment and prophylaxis of cytomegalovirus disease in solid-organ transplant recipients. Clin Infect Dis 47:702–711

85. Zaia JA (2002) Prevention of cytomegalovirus disease in hematopoietic stem cell transplantation. Clin Infect Dis 35:999–1004

*Note of added proof*: CDI severity criteria based on WBC count and creatinine level may not be applicable to patients with hematologic malignancies.

# Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients

Michael J. Hoffman and Valentina Stosor

**Abstract**

Central nervous system (CNS) infections in cancer patients present a diagnostic and therapeutic challenge for clinicians. While CNS infections are not frequent complications of cancer, its therapies, or hematopoietic stem cell transplantation, the importance of CNS infections lies in their propensity to result in profound morbidity and substantial mortality in this vulnerable patient population. With an expanding population of patients with malignant disease undergoing more potent and aggressive therapies and with the advent of newer immunomodulatory agents, the incidence of CNS infectious complications is likely to rise. This chapter will summarize the clinical and diagnostic evaluation of potential infections of the CNS in these patients and will discuss particular pathogens of interest with regard to this at-risk patient population.

**Keywords**

Hematopoietic stem cell transplantation · Immunomodulatory agents · Immunodeficiencies · Antimicrobial resistance · Neurologic abnormalities · Neutropenia · Meningitis · Norcardiosis

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## Contents



## 1 Introduction

Central nervous system (CNS) infections in cancer patients present a significant diagnostic and therapeutic challenge for clinicians. While CNS infections are not frequent complications of cancer, its therapies, or hematopoietic stem cell transplantation (HSCT), their importance lies in their propensity to result in profound morbidity and substantial mortality in this vulnerable patient population. Heightened clinical suspicion, early diagnosis, and prompt institution of therapy are essential for optimal outcomes of these infections.

The recognition and diagnosis of CNS infections are limited by a number of factors. First, cancer patients are susceptible to a wide range of both community-acquired and opportunistic pathogens as a consequence of the immunodeficiencies associated with malignancy and its therapies. The spectrum of infection is constantly evolving with the continual introduction of immunomodulatory therapeutic agents, outbreaks of novel pathogens, and emergence of antimicrobial resistance. Furthermore, cancer patients frequently have concomitant infections outside the CNS that complicate or confuse the diagnostic picture [1]. Under-recognition of infection may occur as a result of atypical clinical presentations due to the underlying disease state and the type of therapy received. Finally, non-infectious neurologic abnormalities are common in cancer patients and HSCT recipients, and thus, it is challenging to recognize the early symptoms and signs of CNS infections in these patients. This chapter will discuss the basic clinical presentation of CNS infections, pathogens of particular interest, and the approach to diagnosis and treatment in these patients.

## 2 Special Patient Populations and Epidemiology

Cancer patients are at higher risk of CNS infection than the general population. Investigators from Memorial Sloan–Kettering Cancer Center (MSKCC) reported an increasing incidence of CNS infection admissions from 0.03 to 0.2 % of hospital admissions from 1955 to 1973 [2]. In series from tertiary care and specialized cancer centers, CNS infections occurred in association with these underlying conditions: hematologic malignancies in 25–50 %, CNS malignancy and associated surgical procedures in 16–30 %, head and neck cancers in 38 %, and other solid malignancies in 18–27 % [1, 2]. In a retrospective study of meningitis at MSKCC, nearly 4 of 5 cases occurred following a neurosurgical procedure [3].

Bone marrow and HSCT, especially allogeneic transplantation, represent a special risk of CNS infection. Neurologic complications, both infectious and noninfectious, occur in 11–46 % of HSCT recipients [4]. The reported overall incidence of CNS infection following transplantation varies by patient population, type of transplant, and transplant center, ranging from approximately 2 to 4.2 % [5–7].

Regardless of the underlying disease or etiology, CNS infections in the cancer and transplant population result in significant mortality. In patients with meningitis at MSKCC, the overall 30-day mortality was 13 %. Patients with underlying leukemia had the highest mortality rate at 24 % in contrast to those with primary intracranial and head or neck tumors at 3 % [3]. Many studies report higher mortality rates in transplant patients with neurologic complications, including one study of bone marrow transplant recipients with 26 % of deaths found to be attributable to CNS lesions. As many as 40 % of these neurologic complications were caused by infections [4].

## 3 Types of Immunodeficiencies Encountered

Keeping the patient population subsets in mind, it is important to understand the type and duration of immune deficits that predispose to certain pathogens. Table 1 describes the broad categories of immunodeficiencies encountered in cancer patients and associated typical CNS pathogens. It is important to remember that patients may have more than one significant type of immunodeficiency concomitantly [8].

Immune deficits relate not only to the underlying disease process, but also to the types of treatment being undertaken. Barrier disruption is evident in those with primary CNS tumors who have had surgical therapy, intraventricular device placement, intrathecal chemotherapy, or radiation therapy. Additionally, chemotherapy-related mucositis and central venous catheters represent further infection risk. B-cell deficiency or hypogammaglobulinemia is often seen in association with multiple myeloma, chronic lymphocytic leukemia, or functional or surgical asplenia, and after lymphocyte depleting therapies such as rituximab.

**Table 1** Central nervous system pathogens associated with immunodeficiencies of cancer patients

| Immunodeficiency | Associated conditions or therapies | Typical spectrum of pathogens | | | |
|---|---|---|---|---|---|
| | | Bacteria | Fungi | Viruses | Parasites |
| Barrier disruption | Neurosurgery | *S. aureus* | *Candida* spp. | – | – |
| | Intraventricular devices | CoNS | | | |
| | Mucositis | Enteric bacilli | *Aspergillus* spp. | | |
| | CVC | Streptococci | | | |
| Neutrophil dysfunction and neutropenia | Infiltrative diseases of bone marrow | *S. aureus* | *Candida* spp. | HSV | – |
| | | | *Aspergillus* spp. | | |
| | Chemotherapy | | *Mucorales* | | |
| | Radiation therapy | CoNS | - | HHV-6 | |
| | | Enteric bacilli | | | |
| | | *P. aeruginosa* | | | |
| | | *L. monocytogenes* | | | |
| Humoral immunity | Multiple myeloma | *S. pneumoniae* | – | Enteroviruses | – |
| | CLL | *H. influenzae* | | JC virus | |
| | Asplenia | *K. pneumoniae* | | | |
| | Chronic GVHD | *P. aeruginosa* | | | |
| | Rituximab | | | | |

(continued)

**Table 1** (continued)

| Immunodeficiency | Associated conditions or therapies | Typical spectrum of pathogens | | | |
|---|---|---|---|---|---|
| | | Bacteria | Fungi | Viruses | Parasites |
| Cell-mediated immunity | Lymphoma | *L. monocytogenes* | *C. neoformans* | CMV | *T. gondii* |
| | HSCT | | | VZV | *S. stercoralis* |
| | Corticosteroids | | | HSV | |
| | Fludarabine | *Nocardia* spp. | *Aspergillus* spp. | EBV | |
| | | *M. tuberculosis* | | HHV-6 | |
| | Mycophenolate mofetil | | *Mucorales* | Adenovirus | |
| | Alemtuzumab | | | JC virus | |

*CVC* central venous catheter, *CoNS* coagulase-negative staphylococci, *HSV* herpes simplex virus, *HHV*-6 human herpesvirus-6, *CLL* chronic lymphocytic leukemia, *GVHD* graft-versus-host disease, *HSCT* hematopoietic stem cell transplantation, *CMV* cytomegalovirus, *VZV* varicella zoster virus, *EBV* Epstein–Barr virus

T-cell deficiency occurs in those with HIV and lymphoreticular malignancy or after receipt of chronic corticosteroids and other immunosuppressive therapy, such as that used to prevent and treat graft-versus-host disease (GVHD). Neutropenia is a frequent complication of most chemotherapeutic regimens used for both solid tumors and hematologic malignancies. Neutropenia can also be a complication of radiation therapy or infiltrative processes that affect bone marrow [8, 9].

## 4 Clinical Syndromes

The basic clinical syndromes of CNS infections can be divided into meningitis, encephalitis, or a primary parenchymal process. The symptoms of meningitis are typically those of headache and meningismus, with or without fever, vision changes, photophobia, nausea or vomiting. With encephalitis, the presentation is one of altered mental status (AMS) ranging from confusion to bizarre behaviors to coma, along with seizures and fever. There is a continuum in the spectrum of meningitis (meningeal inflammation) and encephalitis (brain inflammation and edema), hence, the term, meningoencephalitis. Parenchymal processes can be further delineated based on anatomical patterns and will present with focal neurologic deficits. These infections may be further described as focal mass lesions or abscesses, vascular lesions, leukoencephalopathy, or brain stem lesions [8]. Regardless of the underlying etiology, patients with brain abscess classically present with fever and symptoms of a space-occupying lesion such as seizure, focal deficits, and altered sensorium.

Whereas meningitis or encephalitis tends to be the most common clinical presentation of CNS infection in the immunocompetent host, immunocompromised patients more commonly present with vascular lesions or mass lesions. The presentation tends to be more indolent or subacute in onset, and symptoms are frequently more severe and prolonged in course [9]. In a retrospective review of cancer patients with positive cerebrospinal fluid (CSF) bacterial or fungal cultures, only 8 % of patients presented with the classic triad of fever, meningismus, and headache. Very often, AMS may be the only presenting symptom [3].

## 5 Approach to the Diagnosis of CNS Infection

Table 2 summarizes the initial diagnostic evaluation of a cancer patient with suspected CNS infection. A clinician may formulate the differential diagnosis by integrating knowledge of the epidemiology of CNS infections in cancer patients, the type of underlying malignancy, receipt of chemotherapeutic and immunomodulatory agents, and the sum resulting immune deficits. The initial evaluation includes a thorough history and physical examination, understanding that the presentation may be atypical or attenuated. History should include a thorough

**Table 2** Initial diagnostic evaluation of suspected CNS infection in cancer patients

| |
|---|
| *History and physical examination* |
| *Brain imaging* |
| *Chest radiograph* |
| *Blood studies* |
| • CBC with differential |
| • Blood culture |
| • Fungal culture |
| • Serum cryptococcal antigen |
| • Cytomegalovirus viral load (especially in transplant recipients) |
| *Respiratory tract cultures (if pulmonary infiltrate present)* |
| *EEG (if altered mental status or suspected seizures present)* |
| *CSF analysis* |
| • Opening pressure measurement |
| • Cell count with differential |
| • Glucose |
| • Protein |
| • Bacterial gram stain and culture |
| • Fungal stain and culture |
| • AFB smear and culture |
| • Cryptococcal antigen |
| • Herpesviruses PCR studies |
| • VDRL |
| • Cytology |

review of systems, focusing on other symptoms of infection outside of the CNS, as the etiology of neurologic infection may be related to infection elsewhere or to a disseminated process [10]. Initial evaluation should also include a thorough social history including sick contacts, recent and prior travel, and environmental exposures.

Imaging plays an important role in diagnosing CNS infections in cancer patients as it not only evaluates for focal lesions or abscess, but also can rule out non-infectious entities, including metastatic disease, hemorrhage, cerebrovascular accident, thromboembolic disease, and hydrocephalus from mass effect. Additionally, to identify those at risk of brain herniation, it is recommended that those with suspected meningitis who have an immunocompromised state, history of CNS disease, new-onset seizure, papilledema, abnormal level of consciousness, or

focal neurologic deficit undergo computed tomography (CT) scanning prior to lumbar puncture [11, 12].

Magnetic resonance (MR) is the preferred brain imaging method in those with suspected CNS infection, with CT scan reserved for patients with contraindications to MR or cases of limited access to MR. Advantages of MR versus CT scanning include better distinction of gray versus white matter involvement, as well as superior visualization of the posterior fossa and cerebellum, the leptomeninges, and the venous sinuses [1]. In those with suspected encephalitis, MR is the most sensitive imaging technique and certain patterns of findings may assist in determination of the etiologic agent [13]. Several studies have examined whether specialized MR sequencing, such as calculation of apparent diffusion coefficient (ADC) maps or MR spectroscopy, can differentiate infection from malignant processes with conflicting results [14–17]. MR angiography may be helpful in evaluating for arteritis associated with infections such as varicella zoster virus (VZV) [8].

There are inherent limitations of imaging in immunocompromised patients. The imaging modality of choice may not be practical due to renal dysfunction or concomitant use of nephrotoxic agents, thus limiting the administration of contrast dye or gadolinium. Concomitant steroid use may also reduce contrast enhancement, limiting the sensitivity of contrast-enhanced studies. Finally, findings such as leptomeningeal enhancement and mass lesions are often quite difficult to distinguish between recurrence and spread of malignancy versus infection [1].

In the early stages of encephalitis, an electroencephalogram (EEG) may indicate cerebral dysfunction; however, EEG is generally nonspecific with the exception of HSV encephalitis. More than 80 % of patients with HSV encephalitis will have lateralizing epileptiform discharges in sharp and slow wave complexes every 2–3 s from a focus in the temporal lobe. This finding is typically seen on days 2–14 after the onset of symptoms. Other than HSV, EEG is rarely able to help identify the infectious agent involved in patients with encephalitis; however, it is recommended to evaluate for epileptic activity in those with altered sensorium [13].

The recommendations for initial analysis of CSF remain identical to that of the immunocompetent patient. Opening pressure should be recorded, and initial studies should include white blood cell (WBC) count with differential, red blood cell count, glucose, protein, and gram stain. In all cases, CSF should be sent for bacterial and fungal culture. Further CSF analysis should be based upon the individual clinical scenario [10]. The diagnostic test(s) of choice for individual infections will be described throughout the chapter.

## 6 Mimics of CNS Infection in Cancer Patients

There are many non-infectious diseases or syndromes that mimic the signs and symptoms and, thus, complicate the recognition of CNS infection in cancer patients. This list includes drug-induced and chemical meningitis, allergic or

hypersensitivity reactions, and leptomeningeal spread of disease, among others [18]. It is important to remember that treatment regimens themselves, including chemotherapeutic agents and medications used to treat symptoms of pain, nausea, and emesis, can also cause signs or symptoms that can be confused with CNS infections. Calcineurin inhibitors used for GVHD prophylaxis can also be implicated in some cases of encephalopathic symptoms. Bleeding as a result of thrombocytopenia can also mimic CNS infection, as can primary or metastatic lesions in the CNS. Table 3 provides a list of some common imitators of CNS infection [9].

## 6.1 Drug-Induced Meningitis

A multitude of medications are implicated in cases of drug-induced meningitis, but one of the most common observed associations is with non-steroidal anti-inflammatory drugs (NSAIDs). The list of potential medications causing this syndrome also includes antibiotics, most commonly trimethoprim or sulfonamides, but also beta-lactams, fluoroquinolones, and isoniazid [18]. Immunomodulatory agents such intravenous immunoglobulins (IVIG), antithymocyte globulin, and OKT3 can also cause aseptic meningitis [19]. Symptomatically, drug-induced meningitis is indistinguishable from infection as patients present with HA, meningismus, fever, and altered sensorium. Rash, myalgias, arthralgias, facial edema, and abnormal liver chemistries may occur, although these too can be present with infectious meningitis, especially with viral etiologies [19]. Symptoms typically begin within several days to a week after drug exposure but can occur sooner if the patient has been previously sensitized to the offending agent. There are some reported cases that occur as long as 2 years from initial drug exposure [18]. CSF analysis typically reveals a neutrophilic pleocytosis, with CSF WBC ranging from several hundred to several thousand cells per cubic millimeter, elevated protein levels, and normal to slightly low glucose levels. Eosinophils occasionally are found in the CSF. Imaging is nearly always normal [19]. Because it is a diagnosis of exclusion, a negative CSF microbiologic evaluation is necessary. Prompt resolution of symptoms after discontinuation of the offending agent also supports the diagnosis [18].

## 6.2 Chemical Meningitis

Chemical meningitis (arachnoiditis) can occur with intrathecal administration of chemotherapeutic agents such as methotrexate and cytarabine, especially when used concomitantly with high-dose systemic administration of these drugs [18, 20, 21]. Symptoms of neurotoxicity typically begin acutely, 4–24 h after exposure to the offending agent, although cases have been reported to occur as long as 2 weeks after intrathecal infusion. Symptoms include fever, chills, headache, nausea, vomiting,

**Table 3** Conditions that mimic central nervous system infection in cancer patients

| |
|---|
| *Primary or metastatic CNS tumor* |
| • Glioblastoma |
| • Primary central nervous system lymphoma |
| • Melanoma |
| • Breast cancer |
| • Bronchogenic carcinoma |
| • Renal cell carcinoma |
| • Germ cell tumor |
| *Post-transplant lymphoproliferative disorders* |
| *Toxic metabolic encephalopathy* |
| *Drug-induced alterations in sensorium* |
| • Narcotic and opioid analgesics |
| • Antiemetics |
| • Antihistamines |
| *Drug-induced aseptic meningitis* |
| • Nonsteroidal anti-inflammatory agents |
| • Antimicrobial agents |
| Trimethoprim–sulfamethoxazole |
| Beta-lactams |
| Fluoroquinolones |
| Isoniazid |
| • Immunomodulatory agents |
| Intravenous immunoglobulin |
| Anti-thymocyte globulin |
| OKT3 |
| *Chemical meningitis (arachnoiditis)* |
| • Intrathecal methotrexate |
| • Intrathecal cytarabine |
| *Leukoencephalopathy* |
| • Calcineurin inhibitors |
| Cyclosporine A |
| Tacrolimus |
| • Chemotherapeutic agents |

(continued)

**Table 3** (continued)

| |
|---|
| Cisplatin |
| Cytarabine |
| Gemcitabine |
| Bevacizumab |
| *Neoplastic meningitis* |
| • ALL |
| • AML |
| • Lymphoma |
| • Solid tumor |
| *Hematologic dysfunction and coagulopathy* |
| • Leukostasis |
| • Subarachnoid or intracerebral hemorrhage |
| • Graft-versus-host disease |
| *Marantic endocarditis with embolic and thrombotic complications* |
| *Cerebrovascular accident* |

and meningismus. In some cases, confusion and aphasia may predominate, with seizures also being possible [18]. CSF findings include a pleocytosis ranging from a mild increase to several thousand neutrophils per cubic millimeter along with low glucose and elevated protein levels. In acute cases, the opening pressure may be elevated. MRI may reveal diffuse leptomeningeal enhancement in acute cases. As in the case of drug-induced meningitis, clinical symptoms and CSF findings in cases of chemical meningitis significantly overlap findings in acute bacterial meningitis, and thus, this is a diagnosis of exclusion [18].

## 6.3 Posterior Reversible Leukoencephalopathy and Calcineurin Inhibitor Neurotoxicity

Calcineurin inhibitors, used for the prevention and treatment of GVHD in the HSCT population, have neurologic side effects that can be confused with CNS infection. Patients receiving cyclosporine have a 10–40 % incidence of neurotoxicity, with a similar incidence reported with tacrolimus [22, 23]. The spectrum of neurologic side effects is wide and ranges from mild symptoms, most commonly tremor, to more severe symptoms, including altered sensorium, psychosis, hallucinations, blindness, seizures, ataxia, and leukoencephalopathy.

The syndrome of posterior leukoencephalopathy associated with calcineurin inhibitors can mimic meningoencephalitis or progressive multifocal

leukoencephalopathy, as the clinical symptoms are similar, including headache, AMS, and possibly seizure and cortical blindness. Distinguishing this from infectious etiologies, many of the patients with this syndrome are hypertensive and more than half have supra-therapeutic drug levels [23]. The occipital white matter is uniquely susceptible to the potential neurotoxic effects of cyclosporine. While tacrolimus-associated neurotoxicity tends to produce similar pathologic changes as cyclosporine, tacrolimus may cause additional neurotoxic changes, particularly vascular toxicity [22]. Brain imaging typically reveals abnormal multifocal, bilateral white matter findings in the parieto-occipital lobes although lesions may occur in the cerebellum, pons, thalamus, and temporal lobes. With a cerebellar syndrome, dysarthria and ataxia occur along with confusion and seizures. In most patients, the CSF analysis is normal, although elevated protein levels can be present [23].

Similar to the calcineurin inhibitors, some chemotherapeutic agents such as cisplatin, gemcitabine, cytarabine, and bevacizumab are reported to cause a reversible posterior leukoencephalopathy syndrome [24].

## 6.4 Neoplastic Meningitis

Neoplastic meningitis results from the metastatic spread of disease to the leptomeninges and is estimated to occur in 4–7 % of all patients with cancer [25]. It is clinically diagnosed in 4–15 % of patients with solid tumors, 5–15 % of patients with leukemia and lymphoma, and 1–2 % of patients with primary brain tumors [26].

The clinical presentation of neoplastic meningitis varies and the majority of patients present with multifocal symptoms based upon the CNS territories that are involved. The most common symptoms are headache, mental status changes, ataxia, neck or back pain, focal weakness, and seizures [27]. Cranial nerves can also be affected by leptomeningeal disease, and thus, cranial nerve palsy may be one of the presenting clinical signs or symptoms. Symptoms related to spinal cord involvement occur in more than 60 % of patients and include pain with or without radiculopathy, myelopathy, and cauda equina syndrome [28].

The diagnosis is established by neuroimaging and CSF analysis. Suggestive MR findings include parenchymal volume loss, ependymal or subependymal enhancement, and other abnormalities such as sulcal-cisternal enhancement, subarachnoid enhancing nodules, and communicating hydrocephalus [26]. The CSF analysis is almost always abnormal with elevated opening pressure in up to 50 %, pleocytosis, elevated protein levels, and low glucose levels. Abnormal CSF cytology confirms the diagnosis with a specificity of more than 95 %, albeit lower sensitivity [18]. CSF flow cytometry offers enhanced diagnostic sensitivity over traditional cytology [29]. Rarely, meningeal biopsy is necessary to confirm the diagnosis [28].

## 7 Spectrum of Infections with Emphasis on CNS Pathogens of Special Significance for the Cancer Patient

Cancer patients and stem cell recipients are susceptible to a broad range of CNS infections caused by bacterial, fungal, viral, and parasitic pathogens (Table 1). This section will review the predominant infectious etiologies, with a focus on organisms that pose a special problem for these vulnerable patient populations.

### 7.1 Bacteria

The spectrum of bacterial CNS infections is broader than the general population. An analysis of CSF and autopsy cultures obtained from patients at MSKCC from 1955 to 1973 demonstrated that the most prevalent bacterial meningitis pathogens, from more to less frequent, included *Listeria monocytogenes, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae*. Other bacteria found to cause meningitis in this series included the Enterobacteriaceae, other streptococci, and other staphylococci. This was in contrast to the most common causes of meningitis in the general community, *S. pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis*. The spectrum of pathogens causing focal brain abscesses was also found to be different than that in the general population. Gram-negative bacilli including *E. coli, P. aeruginosa*, and *Proteus* spp. were the most common organisms identified, while staphylococci and streptococci were less common [2].

The epidemiology of bacterial infections has evolved over time. Staphylococci have gained importance as a CNS pathogen, presumably related to an increase in the use of intraventricular devices [30]. In a review of CNS infections at MSKCC between 1993 and 2004, there was a marked shift from gram-negative to gram-positive pathogen predominance in recent years: 70 % gram-positive cocci, 10 % gram-positive bacilli, and 14 % gram-negative bacilli. *Listeria* was a much less identified pathogen with only two cases found during this time period [3]. Finally, tuberculosis should also be kept in mind in those with known exposure or those at high risk of prior exposure and can present as basilar meningitis or tuberculoma [31].

#### 7.1.1 *Listeria monocytogenes*

The gram-positive bacterium, *L. monocytogenes*, is a well-known opportunistic pathogen that causes sepsis and meningoencephalitis in cancer patients. The bacterium is acquired primarily via ingestion of contaminated foods, and up to 5 % of healthy adults have evidence of intestinal carriage of this organism [32–35]. Those with depressed cell-mediated immunity, due to underlying disease and therapies, are especially susceptible to disseminated infection with this organism [32, 33]. *Listeria* is a leading cause of community-acquired meningitis, accounting for 4–8 % of all cases in large epidemiologic studies [36, 37].

Established risk factors for non-perinatally acquired listeriosis include age older than 60 years, malignancy, and corticosteroid and other immunosuppressive therapies [32, 35, 38–45]. In cancer centers, listeriosis is a relatively infrequent but serious infection, accounting for 0.04–0.1 % of hospital admissions [46, 47], with a declining overall incidence in US cancer centers in recent years [3, 48]. This infection disproportionately affects patients with lymphoreticular malignancies, although patients with solid tumor malignancies, especially those receiving corticosteroid or other immunosuppressive therapies and those with advanced liver disease are at risk [3, 40, 44–47]. Hematopoietic stem cell transplant recipients are also susceptible to listeriosis, although the reported incidence is low, 0.38–0.58 % [46, 49–51]. In case reports and small series, listeriosis can complicate both autologous and allogeneic stem cell transplantation but is most often described in recipients of unrelated or HLA-mismatched donor transplants, cases complicated by GVHD, and those receiving corticosteroids [47, 49, 51–58].

Twenty-eight to 43 % of patients with non-perinatally acquired listeriosis have CNS involvement that most typically manifests as meningitis or meningoencephalitis [39, 40, 44]. Meningoencephalitis most often presents as an acute illness that is not easily distinguished from other causes of meningitis based on symptomatology alone. Common features include fever (86–100 %), headache (29–88 %), alterations in mental status and/or consciousness (42–100 %), nuchal rigidity (26–73 %), nausea and/or emesis (29–83 %), and focal neurologic deficits (35–37 %) such as cranial neuropathies, disordered speech, paresis, nystagmus, and ataxia [37, 40, 43, 46]. Seizures may occur in 11–29 % [37, 40, 46]. With meningoencephalitis, the CSF analysis demonstrates neutrophilic pleocytosis, elevated protein level, and varying degrees of hypoglycorrhachia [32, 37, 46]. Lymphocytic pleocytosis is occasionally observed. The gram stain will demonstrate gram-positive bacillary forms in only approximately 1/3 of cases [34, 37]. The diagnosis is confirmed by isolation of *Listeria* in culture; the culture yield is >80 % and 46–78 % in CSF and blood, respectively [32, 34, 37, 43, 48]. Serum hyponatremia, attributed to the syndrome of inappropriate antidiuretic hormone secretion, is reported [37].

A less common form of CNS listeriosis is cerebritis characterized by focal brain lesions or abscess often involving the basal ganglia or thalamus; 25 % of such cases have concomitant meningitis [32, 34, 35, 43, 46, 59], see Fig. 1. The CSF analysis in these cases is consistent with a parameningeal focus of infection unless meningitis is also present. *Listeria*-associated rhombencephalitis and spinal cord abscesses are exceptionally rare in the immunocompromised host [32, 34, 35].

Treatment guidelines for CNS listeriosis are based on cumulative clinical experience, in vitro antimicrobial susceptibility testing, and expert opinion [12, 32, 35, 46, 60]. The addition of ampicillin or penicillin for empiric treatment of bacterial meningitis is warranted whenever *Listeria* is a diagnostic consideration. For confirmed cases, parenteral ampicillin or penicillin is recommended for a duration of 3 weeks [12]. In the setting of cerebritis or brain abscess, the antibiotic duration is extended to 4–6 weeks [32, 33]. The addition of an aminoglycoside, for the initial portion or duration of treatment, is considered beneficial due to in vitro synergism.

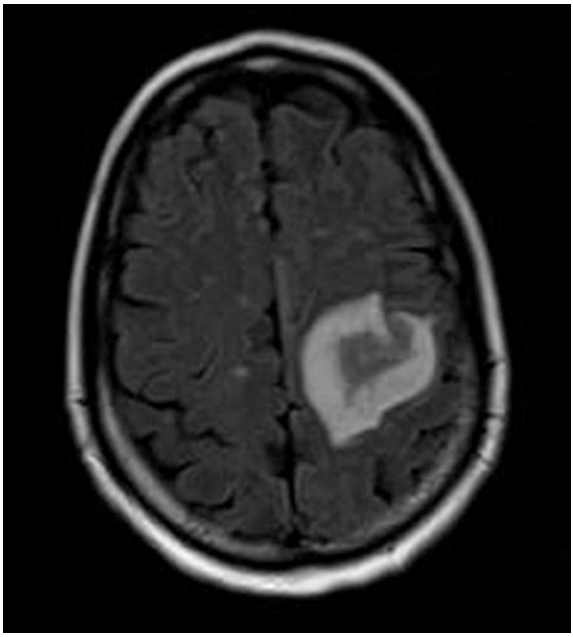

**Fig. 1** A 60-year-old male with Waldenstrom's macroglobulinemia with large cell transformation presented day + 97 status post matched sibling donor non-myeloablative stem cell transplantation with new-onset seizures, right upper extremity weakness, and word-finding difficulties. Brain MR demonstrated a heterogenous mass lesion within the left frontoparietal region associated with a 4.5-cm area of vasogenic edema. Due to suspicion for lymphoma, a brain biopsy was undertaken. *Listeria monocytogenes* was isolated from blood and brain tissue cultures

In the penicillin-allergic patient, the preferred alternative agents are trimethoprim–sulfamethoxazole (TMP-SMX) or meropenem. Although *Listeria* exhibits in vitro susceptibility to vancomycin, cases of listeriosis have developed in patients during vancomycin therapy [61, 62]. Cephalosporin and chloramphenicol treatment failures are reported [49]. There is no clear role for corticosteroids if the diagnosis of *Listeria* meningitis is established. Surgical intervention and intrathecal antimicrobial therapy may be required for refractory cases [35, 43, 63].

The reported mortality for *Listeria* meningitis is 3.1–50 % [37, 39, 40, 46, 48, 64], and the overall mortality of listeriosis is higher in those with malignancy as opposed to other medical conditions [44]. Risk factors for mortality with non-perinatally acquired listeriosis include non-hematologic malignancy, steroid use, and chemotherapy [64–66]. Even with successful treatment for the initial infection, relapsing and recurring infection can occur and permanent neurologic sequelae can result from listeriosis [34, 40, 43, 49]. The prevention of listeriosis focuses largely on avoidance of undercooked meats, raw eggs, and unpasteurized dairy products; thorough washing of raw vegetables prior to ingestion; and cleaning of food preparation utensils and boards after contamination [32, 33, 67]. Additionally, immunocompromised patients should avoid uncooked processed meats such as cold cuts, hot dogs and soft cheeses. While TMP-SMX prophylaxis is effective in reducing *Listeria* infections in AIDS patients and solid organ transplant recipients, breakthrough infections have occurred in stem cell transplant recipients receiving this drug in prophylactic doses [46, 52].

### 7.1.2 *Nocardia* Species

*Nocardia* spp. are aerobic actinomycetes that are widely distributed in nature as a component of soil and decaying matter. At least 16 species are capable of causing human disease, usually as a consequence of inhalation. The more common pathogenic species include *Nocardia asteroides* sensu stricto, *Nocardia brasiliensis*, *Nocardia farcinica*, and *N. nova* [68–70]. Although overall population estimates are difficult to ascertain, previous surveys report that the annual incidence of nocardiosis is 500–1,000 and 150–250 cases in the USA and France, respectively [71, 72]. *Nocardia* spp. are opportunistic pathogens, primarily afflicting patients with underlying conditions, especially those with deficiencies in cell-mediated immunity but also those with neutrophil dysfunction and deficiencies in humoral immunity [68, 73]. Malignancy, corticosteroid therapy, and cytotoxic chemotherapy are well-recognized risk factors for nocardiosis [68, 74–85]. At MD Anderson Cancer Center, nocardiosis accounted for 0.06 % of hospital admissions during 1988 to 2001 [79]. Cases are more frequently described in association with hematologic malignancy, but solid tumor patients are also susceptible [79]. Nocardiosis is also seen as a late complication of bone marrow and HSCT, [78, 79, 86–101] with reported incidences of 0.2 and 1.7 % in recipients of autologous and allogeneic transplants, respectively [89, 94]. Many cases have occurred following the development and steroid treatment of GVHD [79, 89–97, 100–102].

While pulmonary disease is the most common clinical manifestation of nocardiosis, hematogenous dissemination can result in CNS disease [68, 69]. In fact, 7.7–33 % of nocardiosis cases involve the CNS [71, 72, 76, 78, 80, 85, 103]. CNS disease most commonly presents as brain abscess, with a course that is more indolent than with other bacterial causes. The clinical presentation is one of space-occupying brain lesion and elevated intracranial pressure, and because of this, *Nocardia* can be confused for primary or metastatic brain tumors [68, 104]. Common symptoms include headache, nausea, vomiting, confusion, altered consciousness, and seizures [68, 70, 82]. Parkinsonism is also described [68]. Alternatively, but uncommonly, meningoencephalitis occurs, and spinal cord involvement has been reported [68, 82]. Imaging studies will show one or more multiloculated abscesses. Because CNS infection can be silent, it is imperative to perform brain imaging whenever pulmonary nocardiosis is diagnosed.

When the diagnosis of nocardiosis is entertained, respiratory specimens and brain abscess aspirate or tissue are required for routine microbiological studies. *Nocardia* spp. are weakly staining, beaded and branching, gram-positive bacilli. They are also weakly acid fast, a property that is useful in the identification scheme. *Nocardia* can be isolated from routine bacterial cultures within 2–7 days of plating, and recovery can be enhanced by selective and enriched media such as buffered charcoal–yeast extract, colistin–nalidixic acid, modified Thayer-Martin agars and fungal media [68, 69]. If concomitant pulmonary disease is present, it may not be necessary to perform brain biopsy or aspiration. Since there are important species differences in antimicrobial susceptibility patterns, speciation is clinically important, and molecular diagnostic assays, such as 16S rDNA

sequencing, are playing an increasingly important role in the management of nocardial disease. Due to the varying susceptibility patterns of *Nocardia* species, antimicrobial susceptibility testing is generally recommended to guide therapeutic choices [70].

For decades, the primary agents for treatment of nocardiosis have been sulfonamides such as TMP-SMX. With CNS involvement, dual or triple combination therapy with TMP-SMX, imipenem or a third-generation cephalosporin, and amikacin are administered empirically until antimicrobial susceptibility testing results can guide therapy [69, 70]. Other active agents include minocycline and linezolid [70, 105]. Parenteral therapy is continued for a minimum of 3–6 weeks, depending on the severity of infection and response to therapy, and then, oral therapy is continued for at least 12 months to minimize risk of relapse. For refractory cases, surgical intervention may be required [68, 90]. Reduction in immunosuppressive therapies is warranted [68].

While nocardiosis is an infrequent infection, its importance lies in its propensity to cause serious morbidity and mortality. Regardless of whether there is CNS involvement, *Nocardia* is associated with a high mortality rate in cancer patients, ranging from 25 to 100 % [76, 78–80, 84]. Experts advocate for TMP-SMX prophylaxis to reduce the risk of infection in susceptible patients, such as HSCT recipients [94, 97, 106], although breakthrough infections do occur [79, 107].

## 7.2 Fungi

Fungal pathogens are much more frequently isolated from cancer patients with CNS infections compared to the general population and are associated with high mortality. In a series from MSKCC from 1955 to 1973, the etiologic agent of meningitis was fungal in origin in almost one-third of cases [2]. Most cases are caused by *Cryptococcus neoformans*, but other etiologies include *Aspergillus* spp. and *Candida albicans* [2, 3].

The experience at specialized cancer centers varies, but the majority of brain abscesses, particularly post-transplantation, are caused by fungi [108]. The most common fungal etiology of focal brain abscess is *Aspergillus*, followed by Mucorales and *Candida* [2, 6]. Other more rare causes of fungal brain abscess in patients with hematologic malignancy include *Scedosporium* species, *Pseudallescheria boydii*, phaeohyphomycetes such as *Cladophialophora bantiana*, and *Fusarium* species [109].

### 7.2.1 *Aspergillus* Species

The CNS is the most common target organ of disseminated aspergillosis due to hematogenous spread from the lungs. Alternatively, invasive CNS aspergillosis may also occur as a result of direct extension from invasive sinus disease. With an overall reported incidence of only 0.8 % following HSCT, its importance lies in the high rate of mortality [6]. Less than 5 % of cases of CNS aspergillosis are

isolated to the CNS, and the vast majority are associated with invasive disease in other locations, most commonly the lung or sinuses [108, 109].

One of the most important risk factors implicated in the development of invasive aspergillosis includes neutropenia, with a strong relation to both the degree and duration of this deficit. Other host defense deficits that contribute to infection risk include defects in phagocyte function, cell-mediated immunity, and mucosal immunity. These deficits may result from treatment course, underlying malignancy, and/or corticosteroid use [110]. In a retrospective review of 14 cases of CNS aspergillosis in HSCT recipients, 79 % were neutropenic at the time of diagnosis, 93 % had acute GVHD, and 93 % received high-dose methylprednisolone [111].

The clinical presentation can be nonspecific and misdiagnosed as cerebral infarction or hemorrhage. Fever is present in 40–76 % of patients and is more commonly present when concomitant pulmonary aspergillosis is present. AMS is also common and found in 30–65 % of patients. Other signs or symptoms that have been found in one-fourth to one-third of patients include seizure, hemiplegia, and cranial nerve palsies [109]. Neurologic symptoms tend to progress rapidly, and in one study, the time from the initial neurologic symptoms to the diagnosis of cerebral aspergillosis or to death was a median of 7 days with a range of 0–27 days [111]. In HSCT recipients, the median time to diagnosis generally occurs >100 days post-transplant; however, cases have been diagnosed in a range from 49 to 347 days [6, 111].

Diagnostic imaging, typically MRI, will demonstrate findings that are typical for that of fungal brain abscess, including hyperintensity on T2-weighted imaging, hyperintensity on diffusion-weighted imaging (DWI), and hypointensity on ADC mapping. In organized abscesses, contrast enhancement occurs and the lesion will show ring enhancement (Fig. 2a); however, this may not be the case in acute or subacute cases. Because aspergillosis is a vasoinvasive pathogen, evidence of hemorrhagic brain infarction may also be seen on neuroimaging studies [112]. One group of investigators have suggested that "target-like" lesions on DWI may aid in distinguishing *Aspergillus* from other fungal causes of brain abscess and malignancy [113].

Ideally, the diagnosis of CNS aspergillosis requires histopathologic, cytopathologic, or direct microscopic evidence of the pathogen and associated cell damage from brain tissue, with a culture positive for *Aspergillus* spp. (Fig. 2b). In the absence of a positive tissue culture, a positive blood culture would also suffice to make the diagnosis, though this is rarely found with infections due to *Aspergillus* spp. Indirect tests such as detection of galactomannan antigen or 1,3-beta-d-glucan can support the diagnosis [114]. As brain biopsy may not always be feasible, evidence of invasive pulmonary or sinus disease combined with typical CNS imaging findings may lend weight to the diagnosis of cerebral aspergillosis [108].

Generally, CSF examination is of low yield, though it may aid in ruling out other infectious etiologies. CSF findings are typically nonspecific with negative fungal smear and culture. The use of CSF-PCR for diagnosis of cerebral

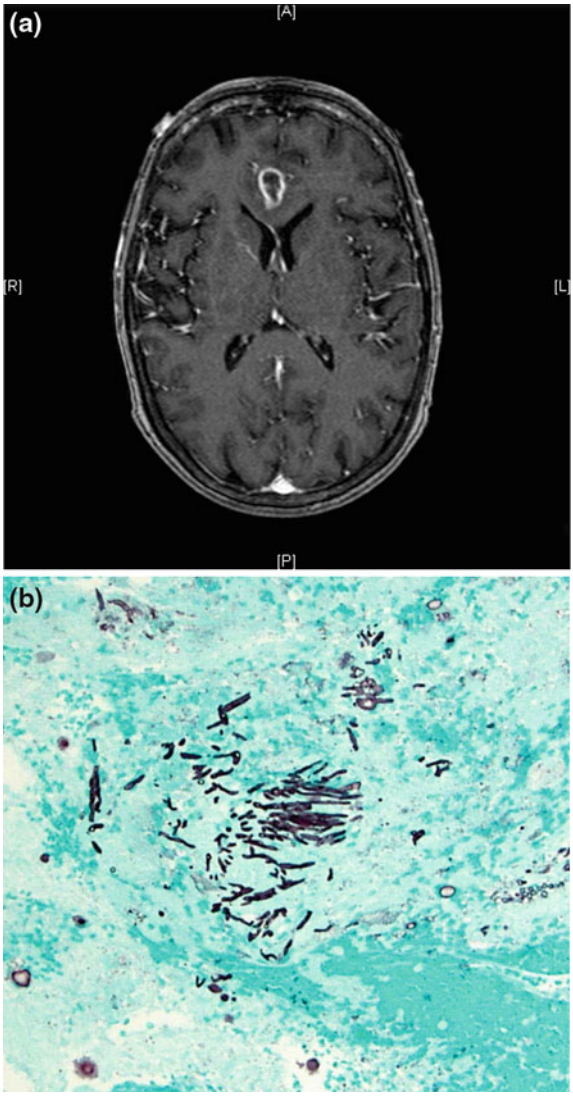


**Fig. 2** A 62-year-old female with diffuse large B-cell lymphoma and invasive pulmonary aspergillosis presented with *right* foot drop; **a** brain MR imaging demonstrated a ring-enhancing lesion within the medial *right* frontal cortex and subcortical white matter; and **b** stereotactic brain biopsy specimen with Gomori's methenamine silver staining revealed fungal hyphae with acute angle branching, consistent with *Aspergillus* spp.

aspergillosis has been reported, but this test is not widely available [115, 116]. Measurements of CSF galactomannan antigen may have some utility [115, 117].

First-line therapy for invasive aspergillosis, including CNS disease, is voriconazole. Voriconazole has wide tissue distribution and achieves levels in the CSF that are approximately 50 % of plasma levels [118]. An open-label, non-comparative multicenter study evaluated the efficacy and safety of voriconazole and demonstrated a therapeutic response in 48 % of cases, including 16 % with cerebral invasive aspergillosis. An additional 26 % of patients with cerebral invasive aspergillosis were found to have had a stable response with voriconazole

therapy [119]. In a randomized trial comparing voriconazole versus amphotericin B (AmB) for primary therapy of invasive aspergillosis, in the subset of patients with extrapulmonary disease, favorable therapeutic responses were achieved in 42.9 % of those receiving voriconazole versus only 12.5 % in those receiving AmB. Additionally, an overall survival benefit was achieved in the voriconazole treatment group [120]. With voriconazole, there is evidence that therapeutic drug monitoring may be of some utility in guiding therapy, as several studies have shown a lack of response to therapy at lower levels as well as an increase in toxicity at higher levels [121].

Agents that can be used for salvage therapy include lipid formulations of AmB, posaconazole, and itraconazole. While there is no definitive evidence that combination therapy is of added benefit, it may be considered [118]. In several studies, adjunctive surgical therapy of CNS disease was associated with improved outcomes [122].

The prognosis of invasive aspergillosis, particularly with cerebral disease, is quite poor. Historically, the mortality rate approaches 100 % in most studies [6]. In all types of invasive aspergillosis, crude mortality rates at 1 year are reported to be anywhere from 70 to 93 % [123].

### 7.2.2 Mucorales

Mucormycosis is the third most common invasive fungal infection after *Aspergillus* and *Candida* spp. infections [124]. These fungi are ubiquitous in nature and are commonly found in soil as well as decomposing plant and animal material. Infection is caused by inhalation or ingestion of airborne sporangiospores [125]. The classic distribution of this opportunistic pathogen is pulmonary or rhinocerebral with destruction and necrosis of the palate allowing extension to nearby structures, including the eyes and brain. Disseminated disease is seen in up to 40 % of patients with hematologic malignancy [124]. The most common cause of invasive mucormycosis is *Rhizopus oryzae*, but other *Rhizopus* spp., *Mucor* spp., *Rhizomucor* spp., *Absidia* spp., and *Cunninghamella* spp. are other agents of mucormycosis [110]. The two most significant risk factors found in a large case series included diabetes and hematologic malignancy in more than 50 % of cases. Some case series also report the use of voriconazole to be a risk factor for the development of mucormycosis [126]. As with aspergillosis, other known risk factors include prolonged neutropenia, receipt of stem cell transplant, and those receiving immunosuppressives that deplete cell-mediated immunity [124].

Patients with rhinocerebral mucormycosis typically present with fever, nasal congestion, sinus tenderness, headache, and periorbital edema with or without proptosis. Mental status changes occur with cerebral involvement [110]. Because direct extension of the infection to the brain from the sinuses occurs via the dura, patients may also present with cranial nerve palsies, thrombosis of the internal carotid artery, hemiplegia, lethargy, and seizures [127].

Imaging studies of the sinuses and brain should be performed if clinical suspicion dictates. CT of the brain with contrast may reveal ring-enhancing lesions in

the frontal or temporal lobes [127]. MRI is typically more sensitive than CT and may reveal minimal enhancement on DWI, with hyperintense lesions in the case of cerebral abscess. In those who present with symptoms of fungal sinusitis, sinus endoscopy may show necrotic or ulcerated tissue due to hyphal invasion into blood vessels, leading to tissue infarction and hemorrhage [110]. Isolated cerebral mucormycosis is more common than that seen with aspergillosis and may occur in up to 20 % of cases. Distinction between cerebral mucormycosis and aspergillosis is difficult to make based on clinical or radiologic findings alone, and histopathology is usually required [109]. Biopsy is thus essential to diagnosis, and in the case of sinus disease, it is usually well tolerated. Cultures are positive in only 40–70 %, but pathology can usually differentiate mucormycosis from other causes of infection [110]. Findings on histopathology that may lead to the diagnosis of mucormycosis include broad, non-septate, hyaline pale, acidophilic hyphae in hematoxylin and eosin stain. Periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) stains can better define the morphology and will reveal irregular branching and angioinvasion. Other pathologic findings that may be demonstrated include vasculitis, thrombosis, and infarction with neutrophilic infiltration and sometimes a granulomatous response [128]. CSF analysis is usually not helpful in the case of fungal abscess, and blood cultures are rarely positive, even in disseminated disease [127]. In addition, no serologic tests are available to aid in diagnosis [109].

Successful treatment for CNS mucormycosis relies on early diagnosis and a multifactorial approach including surgical debridement, antifungal therapy, and resolution of modifiable risk factors. Risk factors that can be modified include correction of hyperglycemia, discontinuation of corticosteroid or immunosuppressive therapy, and aiding in recovery from neutropenia [127].

First-line antifungal therapy for mucormycosis remains the polyene class. Traditionally, AmB, 1–1.5 mg/kg/day, was used and is still the only antifungal agent licensed for the treatment of mucormycosis, but major disadvantages include nephrotoxicity and poor CNS penetration [129]. Lipid formulations of AmB, especially liposomal AmB (L-AmB), have become the preferred therapy for mucormycosis based on several studies. One study of salvage therapy with AmB lipid complex (ABLC) found a 71 % success rate [130]. In another review of zygomycosis in patients with hematologic malignancy, patients who received L-AmB had improved survival versus those who received traditional AmB [131]. With regard to specific lipid formulations, one review of rhino-orbital-cerebral mucormycosis found inferior success rates and higher clinical failure rates with the use of ABLC versus both L-AmB and conventional AmB. It is suggested that poorer outcomes in cases of mucormycosis with CNS extension is worse with ABLC due to decreased CNS penetration compared to L-AmB or AmB, as seen in rabbit models [132].

Fluconazole and voriconazole do not have reliable activity against the pathogens of mucormycosis. Itraconazole has activity limited to *Absidia* species. Posaconazole has in vitro activity against Mucorales; however, variability in levels achieved, especially in patients at risk for malabsorption, such as those with severe

mucositis and GVHD of the gastrointestinal tract, has limited its use. Several murine models of mucormycosis found posaconazole to be inferior in efficacy to AmB and no better than placebo in other studies with *R. oryzae*. Thus, posaconazole is not recommended for primary therapy but can be considered for salvage therapy in those who are refractory to or intolerant of polyenes [129].

Other strategies for the treatment of mucormycosis include combination antifungal therapy. One retrospective study of rhino-orbital-cerebral mucormycosis found a significantly improved outcome in those receiving polyene–caspofungin combination therapy, with the most pronounced improvement in those with cerebral involvement. In this small group of patients, success rate was 100 % versus only 25 % with polyene monotherapy [132]. Animal studies have not shown a benefit to posaconazole–polyene combination therapy, and no clinical studies have yet been performed [129].

Iron chelation therapy has recently been investigated as an adjunctive treatment method for mucormycosis. The basis of this therapy arose from the knowledge that deferoxamine enhances delivery of iron to *Mucorales* and thus predisposes to mucormycosis. Other iron chelators, such as deferasirox, however, cannot be used by *Mucorales* to acquire iron. Deferasirox was also found to be fungicidal for clinical isolates of *Mucorale*s in vitro. Animal studies are promising in showing synergistic efficacy with the use of L-AmB and deferasirox in the treatment for disseminated mucormycosis. A phase II double-blinded, randomized, placebo-controlled trial for the safety and efficacy of adjunctive deferasirox-L-AmB therapy for mucormycosis is currently ongoing [129].

In cases of cerebral mucormycosis, the overall mortality rate is near 80 %. The prognosis is slightly better for those with localized cerebral and rhinocerebral infection, with mortality rates of approximately 60 %. In cases of disseminated disease with CNS involvement, however, mortality approaches 100 % [126].

### 7.2.3 *Cryptococcus* Species

*Cryptococcus* is a ubiquitous basidiomycetous yeast that has approximately 20 known species, of which *C. neoformans* is the main human pathogen. Infection is acquired by inhalation, resulting in focal lung disease and frequent dissemination to the CNS [133]. While 80–90 % of cases now occur in the context of advanced HIV infection, >30 % of non-AIDS-related cryptococcosis cases occur in cancer patients [134]. In fact, there was early recognition of a relationship between hematologic malignancy and cryptococcosis [135].

Trends from major cancer centers suggest a declining frequency of cryptococcosis, perhaps due to improvements in the management of underlying diseases of these patients [3, 30, 136–138]. Most recently, 7 % cases of meningitis cases at MSKCC were attributed to *Cryptococcus* [3].

In cancer patients, identified risk factors for cryptococcosis include hematologic malignancy, corticosteroid therapy, lymphopenia, fludarabine therapy, advanced neoplasia, extensive prior chemotherapy, and leukopenia [136–139]. Cryptococcosis most commonly occurs in those with lymphoma [137–141], chronic

leukemias [142, 143], and other hematologic malignancies such as acute leukemia [144–146] and multiple myeloma [147]. A minority of cases occur in patients with solid tumors, especially those receiving corticosteroids [138, 148]. Cryptococcosis is rarely reported following HSCT [138, 139, 147–154].

Clinically, cancer patients have subacute or chronic onset of meningitis, and compared with AIDS-related cryptococcosis, they have symptoms for longer durations before presentation [140, 155]. The predominating features are altered sensorium and fever [136, 138]. Other presenting signs and symptoms include headache, meningismus, seizures, nausea and vomiting, visual disturbances, and cranial nerve deficits.

The diagnosis of cryptococcal meningitis largely relies on clinical suspicion and obtaining the appropriate clinical specimens for laboratory testing. Brain imaging should be performed to evaluate for mass lesions and elevated intracranial pressure. Lumbar puncture may demonstrate elevated opening pressure, and CSF analysis will reveal widely varying degrees of inflammation with mononuclear pleocytosis, elevated protein, and low glucose [136, 155]. A presumptive diagnosis is based on rapid antigen detection in CSF and serum. This test has supplanted India ink stain for rapid diagnosis of cryptococcal meningitis. The sensitivity and specificity of commercially available latex agglutination assays are 90–100 % and 97–100 %, respectively [156–158]. False-negative results have occurred with early infection (low organism burden) [159], chronic indolent meningitis (high organism burden and prozone effect), and capsule-deficient *C. neoformans* infection [160]. Low-titer false-positive results can occur as a result of cross-reactivity with rheumatoid factor, syneresis fluid (surface condensation from agar) [161, 162], *Trichosporon beigelii* meningitis [163], or *Capnocytophaga canimorsis* (bacterium DF-2) septicemia [164]. False-positive results have also occurred in cancer patients. In a series of twelve such cases, 50 % had a malignant process involving the CNS, and the majority had a positive CSF cryptococcal antigen of 1:8 dilution or lower (range 1:2 to 1:256) but no culture evidence of cryptococcosis [165]. The definitive diagnosis of cryptococcal infection is established by isolation of the pathogen in culture of CSF, blood, lung, and other tissues.

Untreated meningitis in the immunocompromised host is uniformly fatal, and thus, successful management requires early disease recognition, aggressive antifungal therapy, and management of elevated intracranial pressure. The standard induction regimen for cryptococcal meningitis is AmB, 0.7 mg/kg/d plus flucytosine, 100 mg/d. Combination therapy is superior to AmB monotherapy, as demonstrated by better mycological response rates and reduction in early mortality [136, 155, 166–170]. Beyond the induction phase of treatment, a longer course of consolidation therapy is recommended due to high disease relapse rates [171, 172]. An early study demonstrated lower relapse rates by continuing AmB and flucytosine for 6 rather than 4 weeks [173]. Based largely on clinical trials data in the AIDS population, consolidation therapy, alternatively, can be accomplished with oral fluconazole 400 mg/d for a minimum of 10 weeks [167, 169, 171]. The total duration of therapy is determined by clinical resolution of disease. Although limited comparative clinical data exist regarding the use of lipid-based

amphotericin formulations for the treatment of meningitis, these agents offer a more favorable toxicity profile than conventional AmB and are acceptable alternative therapies [172, 174, 175].

In order to prevent adverse neurologic outcomes, patients with elevated ICP are managed with serial lumbar punctures and drainage of CSF [172, 176, 177]. Refractory cases can be managed by lumbar drain placement or with ventriculoperitoneal shunts [178–181]. In general, corticosteroids are not recommended in this setting [172, 176]. Intrathecal or intraventricular instillation of amphotericin can be used when systemic administration of antifungal therapy has failed [182], but this technique is associated with a high rate of toxicity. Lowering doses of immunosuppressive agents, when feasible, are desirable to control infection.

Patients with hematologic malignancies have the highest mortality with cryptococcosis in comparison with other groups [155, 170, 171, 183], perhaps because the underlying immune deficits are not easily reversible. Indicators that predict treatment failure and mortality include corticosteroid therapy, advanced age, organ failure, disseminated infection (with >1 extraneural culture-positive site), abnormal neurologic exam or brain imaging, elevated ICP, high initial serum or CSF cryptococcal antigen titer, persistently low CSF glucose level, and lack of CSF inflammation (CSF WBC <20 cells per cubic millimeter) [140, 155, 171, 183].

## 7.3 Viruses

Herpesviruses are important pathogens in meningoencephalitis in patients with impaired cell-mediated immunity, especially in the post-transplant setting. Herpes simplex encephalitis is the most common cause of viral encephalitis in the general population and also affects the immunocompromised; thus, acyclovir is administered to all patients with encephalitis until a specific etiology is determined. VZV causes meningoencephalitis, either in the setting of disseminated zoster or with primary infection. The characteristic vesicular rash may be absent. Human herpesvirus-6 (HHV-6) may cause meningoencephalitis in the early post-transplant period and is associated with poor outcomes. Primary or reactivation EBV may result in systemic infection, including meningoencephalitis, and EBV-associated post-transplant lymphoproliferative disorder may affect the CNS [184]. Finally, cytomegalovirus (CMV) is an infrequent cause of encephalitis post-transplant, but is occasionally encountered in the setting of disseminated CMV infection [185]. Combination ganciclovir–foscarnet therapy is recommended for the treatment of CMV encephalitis [13]. It is important to note that widespread use of antiviral prophylaxis has successfully reduced the risk of infection due to herpesviruses, including CMV [31]. Additionally, the declining incidence of CMV-associated CNS disease has been attributed to improvements in diagnostics, surveillance strategies, therapeutic advances, and the selective use of CMV-negative blood products [6].

The herpesviruses are important examples of infections that result from endogenous reactivation or donor-derived disease. It is also important to consider the differential diagnosis of viral meningoencephalitis within the context of seasonal and geographic exposures. For example, West Nile virus meningoencephalitis is described in HSCT recipients and is associated with severe disease presentations, long-term neurologic deficits, and fatal outcomes. This flavivirus may be transmitted through marrow transplantation and blood product administration, but it is also naturally acquired via mosquitoes in endemic regions [186–191].

Finally, JC virus and its associated CNS infection, progressive multifocal leukoencephalopathy, can affect cancer patients and has received renewed attention due to increased reports of cases with the introduction of new immunomodulatory agents into clinical practice.

### 7.3.1 Human Herpesvirus-6

HHV-6 is seroprevalent in the adult population with primary infection occurring in early childhood and lifelong viral persistence thereafter [192–194]. There are two distinct viral variants, HHV-6A and HHV-6B. Viral reactivation, most often due to HHV-6 type B, may be triggered by immunosuppression and occurs in 28–81 % of HSCT recipients, with median onset of viremia at 23–40 days post-transplant [192, 195–199]. Identified risk factors for HHV-6 reactivation after HSCT include younger age, leukemia or lymphoma diagnosis, hematologic malignancy with more than one remission, HLA-mismatch donor or unrelated donor transplant, gender mismatch transplant, IVIG use, and steroid use [196, 200–202]. In a subset of HSCT recipients, viral reactivation can lead to clinical disease, including encephalitis. In fact, several studies have shown a correlation between higher levels of HHV-6 viremia and the development of CNS dysfunction [196, 198, 200, 202]. In single-center series and one multicenter survey, the reported incidence of HHV-6 encephalitis following HSCT ranges from 0.41 to 0.96 % [197, 203, 204].

In the setting of malignancy, HHV-6 encephalitis is limited to the allogeneic HSCT population [197, 198, 202–230], with only a few cases reported following autologous HSCT or chemotherapy for hematologic malignancy [231–233]. This clinical entity is most often described in the setting of unrelated or HLA-mismatch donor transplantation [197, 203, 204, 206, 208, 211–214, 221, 222, 224, 225, 227, 228] and cord blood transplantation [203, 204, 215, 220, 223, 229]. A higher incidence (11 %) of encephalitis was recently reported in allogeneic HSCT recipients after alemtuzumab conditioning [226].

Clinically, patients present early in the post-transplant course, with median onset of symptoms occurring 22–60 days post-HSCT [193, 197, 204, 225, 226]. Encephalitic symptoms may be preceded by a viral exanthem and fever; however, neither are consistently reported findings [197, 204]. Virtually all present with alterations in mental status ranging from confusion, disorientation, and agitation to somnolence and coma [197, 203, 204, 212, 218, 226]. Anterograde memory loss,

which can be profound, is reported in 45–100 % of patients [193, 194, 197, 204, 218, 225, 226]. Seizures (10–80 %), insomnia, and emotional and behavioral disturbances are frequent findings [197, 203, 204, 212, 218, 225, 226]. Hyponatremia as a result of the syndrome of inappropriate antidiuretic hormone secretion may be present [194, 225]. Although the CSF analysis may be entirely normal, two-thirds of patients will have an elevated CSF protein level and a mild lymphocytic pleocytosis occurs in approximately 50 % [193, 203, 204, 212, 225, 226, 234]. In 50–100 % of cases, MR imaging abnormalities are reported and classically include hyperintense signal abnormalities in the temporal lobes and limbic system on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [193, 194, 197, 204, 218, 226, 234, 235]. Nonspecific or diffuse EEG abnormalities are common, but occasionally temporal or fronto-temporal seizure foci are found [193, 194, 226, 234].

In the appropriate clinical setting, the diagnosis is confirmed by the detection of HHV-6 DNA in CSF by PCR; the reported sensitivity of this assay is >95 % [13, 234]. In stem cell recipients with encephalitis, the reported median quantitative PCR results are 3,300–10,000 copies/mL [197, 204, 226]. Most will have concomitant HHV-6 viremia. Because HHV-6 may be detected in the CSF of asymptomatic individuals, it is important to exclude other etiologies of CNS infection.

Antiviral agents with in vitro efficacy against HHV-6 include ganciclovir, foscarnet, and cidofovir. While no controlled trials have proven effective antiviral therapy for HHV-6 infections, there are multiple reports of successful treatment for HHV-6 encephalitis with ganciclovir or foscarnet as evidenced by improvement in clinical parameters and measured reductions in HHV-6 serum and CSF viral loads [192, 203, 208, 210, 212]. As such, both agents (or combinations of the two) are recommended for the treatment of HHV-6 encephalitis [13, 234, 236]. Ganciclovir resistance in HHV-6 has occurred via mutations in the protein kinase, U69, and polymerase, U38, genes [230, 237, 238]; however, it is unknown whether this will become a clinically significant problem. Because of its side effect profile, cidofovir alone or in combination with other antivirals is considered a second-line therapeutic agent [234, 239]. Therapy with donor lymphocyte infusions has also been attempted [204, 221].

The overall prognosis for stem cell recipients with HHV-6 encephalitis is poor, and in published series, the attributed mortality is 9–30 % and overall mortality is greater than 50 %. In recipients who survive the acute infection, the incidence of neurologic sequelae is significant, ranging from 18 to 56 %. Consequently, experts emphasize the importance of early recognition and treatment of this entity. While there are small non-randomized studies that report the effective prevention of HHV-6 reactivation with ganciclovir prophylaxis and its pre-emptive use for HHV-6 viremia to prevent encephalitis, there are no current guidelines that routinely recommend such practices to prevent HHV-6-associated disease after stem cell transplantation [240–242].

### 7.3.2 JC Virus

The polyomavirus, JC virus, is the causative agent of PML, a rapidly progressive demyelinating disorder in immunocompromised patients [243–245]. JC virus infection is common, with adult seroprevalence exceeding 50 % [246]. The virus persists in tissues of the urinary tract and bone marrow (including lymphocytes), and impairment of cell-mediated immunity may result in viral reactivation and hematogenous spread to the CNS [245, 247]. In the CNS, JC virus produces a lytic infection of oligodendrocytes leading to demyelination; astrocytes and cerebellar granular cells may also be infected [245, 247].

While PML most often occurs in the setting of HIV infection (50 > 80 % of cases attributed to HIV), the majority of non-HIV-related cases occur in patients with lymphoproliferative disorders, particularly lymphoma and fludarabine-treated CLL [243, 245, 248]. Previous investigations established a 0.07 % incidence of PML in those with hematologic malignancies [249], although the disease frequency may be increasing as a result of the introduction of potent immunomodulatory therapies into clinical practice [245, 250]. There are multiple descriptions of PML complicating the course of leukemia [243, 251–257], lymphoma [243, 254, 258–261], myelodysplastic syndrome [262], mycosis fungoides [263], multiple myeloma [264], polycythemia vera [265], and Waldenstrom's macroglobulinemia [266]; following fludarabine therapy [253, 254]; and affecting those undergoing HSCT [267–277]. There are increasing reports of PML in patients receiving immunomodulatory therapies, especially rituximab [259–261, 275, 278–283], mycophenolate mofetil [284], and alemtuzumab [285].

The clinical presentation of JC virus is dependent upon the areas of brain affected in individual patients. Patients may present with focal neurologic deficits such dysarthria, hemiparesis, visual loss, or ataxia; alterations in cognition; and seizures. The presumptive diagnosis of PML is made by the clinical picture, combined with MR finding of demyelinating brain lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted and FLAIR images, see Fig. 3. Subcortical white matter, cerebellar white matter, and brain stem involvement are most common [245]. Inflammatory variants of PML can be seen with corresponding enhancing MRI lesions [286]. Definitive diagnosis is established by detection of JC virus in CSF by PCR; this assay has reported sensitivity and specificity of 60–80 % and 92–100 %, respectively [287]. In PCR-negative cases, brain biopsy is necessary to confirm the diagnosis; typical histopathologic findings include white matter vacuolization, oligodendrocytes with basophilic nuclei, enlarged bizarre astrocytes, and foamy macrophages. JC virus can be detected in tissue by immunohistochemical staining in situ DNA hybridization [245, 247].

Other than withdrawal of immunosuppressive therapy and, thus, immune restoration [288], there are no established effective therapies for HIV-seronegative patients with PML [243]. Therapies with interleukin-2 [250, 262, 268, 271, 275], intravenous immunoglobulin [250], cidofovir [250, 275, 289, 290], topotecan [291], and nucleoside analogs such as cytarabine [248, 250, 275] have been

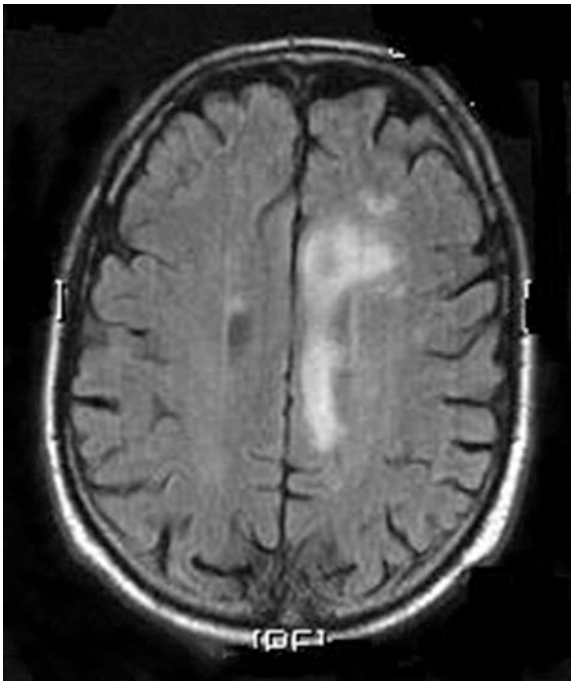

**Fig. 3** A 73-year-old male with chronic lymphocytic leukemia receiving rituximab therapy presented with AMS, expressive aphasia, and ataxia. MR imaging demonstrated FLAIR signal hyperintensity involving the subcortical white matter of the *left* cerebral hemisphere. The diagnosis of progressive multifocal leukoencephalopathy was confirmed by detection of JC virus in CSF by PCR

attempted, but successful treatment is limited to anecdote, and no clear benefit is demonstrated in any clinical trials with these agents. In stem cell transplant recipients, withdrawal of GVHD prophylaxis and donor lymphocyte infusions has been tried as therapy for PML [243]. Recent studies have determined that JC viral entry into oligodendrocytes occurs via the serotonin receptor, $5HT_{2A}$ [292], and so represents a potential for pharmacologic intervention with the use of serotonin receptor antagonists such as mirtazapine [256, 265, 293]. Other proposed therapies in various stages of the development include intrathecal interferon-$\alpha$ and $\beta$ [294, 295], *R*-roscovitine [296], siRNA [297], and mefloquine [298].

In the absence of immune restoration, PML rapidly progresses to death within months of the initial diagnosis [276]. Mortality rate of 90 % is reported, although the prognosis may be better in HSCT recipients [250].

## 7.4 Parasites

Parasites are often overlooked as important CNS pathogens, but in those with impaired cellular immunity, these pathogens can cause serious infection and warrant consideration for patients with endemic exposures and risks. The hyper-infection syndrome caused by *Strongyloides stercoralis* can result in enteric gram-negative meningitis [9]. Toxoplasmosis is the most common parasite infection following stem cell transplantation and is discussed in detail below.

### 7.4.1 Toxoplasmosis gondii

Infection with the protozoal organism, *Toxoplasma gondii*, is extremely common with seroprevalence rates of 16–40 % in the USA and UK, 50–80 % in Europe and Central and South America, and 10–15 % in Japan [299–302]. Despite this, it is an uncommon opportunistic infection following HSCT and lymphocyte depleting therapies. The reported prevalence of toxoplasmosis in transplant centers mirrors the geographic seroprevalence: in the USA 0.2–0.3 % [303, 304], Japan 0.2 % [301], Brazil 1.1 % [305], and Europe 1–5 % [6, 300, 302, 306]. In one European series, toxoplasmosis was the most common CNS infection following bone marrow transplantation [6]. In patients undergoing HSCT, clinical infection most often results from reactivation of latent infection in seropositive allogeneic stem cell recipients [300–302, 304–314]; however, cases of primary infection, presumably as a consequence of donor transmission and leukocyte transfusion or from community exposure or faulty serologic testing have been described [309–312, 315, 316]. Seropositive recipients with unrelated donors [305, 310], haploidentical donors [300], T-cell-depleted allogeneic HSCT [310], acute GVHD [303, 311], and cord blood transplants [302] appear to be at higher risk of reactivation disease. However, toxoplasmosis complicating autologous HSCT or chemotherapy for leukemia and lymphoma is rare and limited to anecdotal reports [300, 317, 318].

*Toxoplasma* encephalitis typically occurs during the first 6 months following HSCT with most cases occurring within the first 3 months post-HSCT with a reported median onset of 45–78.5 days post-HSCT [300, 303, 307, 310, 311]. Later onset cases have occurred, especially in those with courses complicated by GVHD [301, 319–321]. Patients present with fever and neurologic symptoms ranging from headache, seizures, AMS, and focal neurologic deficits [302, 305, 310, 311]. *Toxoplasma* has a predilection for the basal ganglia and the supra- and infratentorial subcortical areas of the brain [321]. MR demonstrates iso- or hypointense multifocal lesions on T1-weighted imaging and iso-, hypo-, or hyperintense lesions on T2-weighted imaging. Ring enhancement, hemorrhage, and edema can be seen with contrast imaging. Alternatively, *Toxoplasma* lesions in HSCT recipients may fail to enhance; a potential explanation for this lack of enhancement is a blunted inflammatory response in the setting of neutropenia or corticosteroid therapy [322–324]. Rarely, imaging will be compatible with meningoencephalitis [304, 305]. There is also an isolated reported of toxoplasmic myelitis following peripheral blood stem cell transplantation [314].

The presumptive diagnosis of toxoplasmosis often is based on the clinical presentation, characteristic radiographic findings, and response to anti-*Toxoplasma* therapy in susceptible (seropositive) patients. CSF findings are nonspecific and may demonstrate elevated protein and some degree of pleocytosis. No diagnostic method is consistently reliable for the definitive diagnosis of toxoplasmic encephalitis, and often a combination of modalities, including serologies, PCR-based detection of *T. gondii* in CSF and brain tissue, and histopathology, is employed [299, 306, 325, 326]. The tachyzoites and cysts of *T. gondii* are visualized in tissue by Giemsa, hematoxylin, and eosin, and immunohistochemical staining.

Toxoplasmic encephalitis is a rapidly fatal illness with a reported mortality of 60–80 % [305, 310, 311]. Too often, toxoplasmosis is a post-mortem diagnosis in HSCT recipients. Because of this, an emphasis should be placed on high clinical suspicion with early treatment; more favorable outcomes have been reported with such a strategy [300]. The standard treatment for toxoplasmic encephalitis is sulfadiazine plus pyrimethamine and leucovorin, although myelosuppression may be problematic following HSCT [299]. Other active agents include: clindamycin, atovaquone, azithromycin, and spiramycin [299, 300, 313].

Efforts to prevent toxoplasmosis after HSCT should focus on identification of recipients at risk of disease by serologic testing of transplant candidates and their donors and education regarding exposure reduction measures, such as avoidance of cat feces and litter boxes, both of which can have a high burden of *Toxoplasma* oocysts, and proper meat handling and preparation [67, 299]. Prophylaxis with TMP-SMX is recommended for susceptible (seropositive) recipients who have GVHD or a history of toxoplasmic chorioretinitis; however, optimal prophylaxis regimens are not well-defined and breakthrough infections do occur in HSCT recipients who receive TMP-SMX for *Pneumocystis* prophylaxis [67, 301–303, 305, 306, 327]. For TMP-SMX-intolerant patients, pyrimethamine and leucovorin plus clindamycin may be considered. Additionally, pyrimethamine–sulfadoxine (Fansidar) was effective in preventing *Toxoplasma* reactivation in allogeneic HSCT recipients, although this agent may result in myelosuppression [328]. Finally, prospective monitoring of the blood of seropositive recipients for *Toxoplasma* reactivation by PCR has been proposed [329], but more data are needed before this approach can be recommended.

## 8 Summary

CNS infections are devastating complications of cancer and its therapies. Due to the multitude of infectious etiologies, a thorough understanding of the epidemiology and clinical presentations of these infections is essential for recognizing and formulating a diagnostic evaluation for suspected CNS infection. Heightened clinical suspicion, expeditious (including empiric) treatment, and modification of immunosuppression may optimize the outcomes of CNS infections in cancer patients and stem cell recipients.

## References

1. Pruitt AA (2003) Nervous system infections in patients with cancer. Neurol Clin 21:193–219
2. Chernik NL, Armstrong D, Posner D (1973) Central nervous system infections in patients with cancer. Medicine 52:563–581
3. Safdieh JE, Mead PA, Sepkowitz KA et al (2008) Bacterial and fungal meningitis in patients with cancer. Neurology 70:943–947

4. Singh N, Husain S (2000) Infections of the central nervous system in transplant recipients. Transpl Infect Dis 2:101–111
5. Denier C, Bourhis JH, Lacroix C et al (2006) Spectrum and prognosis of neurologic complications after hematopoietic transplantation. Neurology 67:1990–1997
6. Maschke M, Dietrich U, Prubaum M et al (1999) Opportunistic CNS infection after bone marrow transplantation. Bone Marrow Transplant 23:1167–1176
7. Coley SC, Jager HR, Szydlo RM et al (1999) CT and MRI manifestations of central nervous system infection following allogeneic bone marrow transplantation. Clin Radiol 54:390–397
8. Pruitt AA (2004) Central nervous system infections in cancer patients. Semin Neurol 24:35–52
9. Cunha BA (2001) Central nervous system infections in the compromised host: a diagnostic approach. Infect Dis Clin N Am 1:567–590
10. Schmidt-Hieber M, Zweigner J, Uharek L et al (2009) Central nervous system infections in immunocompromised patients: update on diagnostics and therapy. Leuk Lymphoma 50:24–36
11. Hasbun R, Abrahams J, Jekel J et al (2001) Computed tomography of the head before lumbar puncture in adults with suspected meningitis. New Engl J Med 345:1727–1733
12. Tunkel AR, Hartman BJ, Kaplan SL et al (2004) Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 39:1267–1284
13. Tunkel AR, Glaser CA, Bloch KC et al (2008) The management of encephalitis: clinical practice guidelines by the infectious diseases society of America. Clin Infect Dis 47:303–327
14. Guzman R, Barth A, Lövblad KO et al (2002) Use of diffusion-weighted magnetic resonance imaging in differentiating purulent brain processes from cystic brain tumors. J Neurosurg 97:1101–1107
15. Dorenbeck U, Butz B, Schlaier J et al (2003) Diffusion-weighted Echo-planar MRI of the brain with calculated ADCs: A useful tool in the differential diagnosis of tumor necrosis from abscess? J Neuroimaging 13:330–338
16. Camacho DL, Smith JK, Castillo M (2003) Differentiation of toxoplasmosis and lymphoma in AIDS patients by using apparent diffusion coefficients. Am J Neurorad 24:633–637
17. Schroeder PC, Post MJ, Oschatz E et al (2006) Analysis of the utility of diffusion-weighted MRI and apparent diffusion coefficient values in distinguishing central nervous system toxoplasmosis from lymphoma. Neuroradiology 48:715–720
18. De Marcaida JA, Reik L Jr (1999) Disorders that mimic central nervous system infections. Neurol Clin 17:901–941
19. Moris G, Garcia-Monco JC (1999) The challenge of drug-induced aseptic meningitis. Arch Intern Med 159:1185–1194
20. Kwong YL, Yeung DY, Chan JC (2009) Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. Ann Hematol 88:193–201
21. Jabbour E, O'Brien S, Kantarjian H et al (2007) Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. Blood 109:3214–3218
22. Bechstein WO (2000) Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int 13:313–326
23. Gijtenbeek JM, van den Bent MJ, Vecht CJ (1999) Cyclosporine neurotoxicity: a review. J Neurol 246:339–346
24. Connolly RM, Doherty CP, Beddy P et al (2007) Chemotherapy induced reversible posterior leukoencephalopathy syndrome. Lung Cancer 56:459–463
25. Chowdhary S, Chamberlain M (2005) Leptomeningeal metastases: current concepts and management guidelines. J Natl Compr Canc Netw 3:693–703
26. Chamberlain MC, Nolan C, Abrey LE (2005) Leukemic and lymphomatous meningitis: incidence, prognosis, and treatment. J Neurooncol 75:71–83

27. Kaplan J, DeSouza T, Farkash A et al (1990) Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas, and leukemias. J Neurooncol 9:225–229
28. Gleissner B, Chamberlain MC (2006) Neoplastic meningitis. Lancet Neurol 5:443–452
29. Chamberlain MC, Glantz M, Groves MD et al (2009) Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. Semin Oncol 36:S35–S45
30. Chernik NL, Armstrong D, Posner JB (1977) Central nervous system infections in patients with cancer. Changing patterns. Cancer 40:268–274
31. Zunt JR (2002) Central nervous system infection during immunosuppression. Neurol Clin 20:1–22
32. Schuchat A, Swaminathan B, Broome CV (1991) Epidemiology of human listeriosis. Clin Microbiol Rev 4:169–183
33. Lorber B (1997) Listeriosis. Clin Infect Dis 24:1–11
34. Bartt R (2000) *Listeria* and atypical presentation of *Listeria* in the central nervous system. Sem Neurol 20:361–373
35. Clauss HE, Lorber B (2008) Central nervous system infection with *Listeria monocytogenes*. Curr Infect Dis Rep 10:300–306
36. Schuchat A, Robinson K, Wenger JD et al (1997) Bacterial meningitis in the United States in 1995. New Engl J Med 337:970–976
37. Brouwer MC, van de Beek D, Heckenberg SGB et al (2006) Community-acquired *Listeria monocytogenes* meningitis in adults. Clin Infect Dis 43:1233–1238
38. Louria DB, Hensle T, Armstrong D et al (1967) Listeriosis complicating malignant disease. Ann Intern Med 67:261–281
39. Cherubin CE, Appleman MD, Heseltine PNR et al (1991) Epidemiological spectrum and current treatment of listeriosis. Rev Infect Dis 13:1108–1114
40. Skogberg K, Syrjänen J, Jahkola M et al (1992) Clinical presentation and outcome of listeriosis in patients with and without immunosuppressive therapy. Clin Infect Dis 14:815–821
41. Paul ML, Dwyer DE, Chow C et al (1994) Listeriosis-a review of eighty-four cases. Med J Aust 160:489–493
42. Goulet V, Marchetti P (1996) Listeriosis in 225 non-pregnant patients in 1992: clinical aspects and outcome in relation to predisposing conditions. Scand J Infect Dis 28:367–374
43. Mylonakis E, Hohmann E, Calderwood SB (1998) Central nervous system infection with *Listeria monocytogenes*: 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine 77:313–336
44. Siegman-Igra Y, Levin R, Weinberger M et al (2002) *Listeria monocytogenes* infection in Israel and review of cases world-wide. Emerg Infect Dis 8:305–310
45. Goulet V, Hedberg C, Le Monnier A, de Valk H (2008) Increasing incidence of listeriosis in France and other European countries. Emerg Infect Dis 14:734–740
46. Rivero GA, Torres HA, Rolston KVI, Kontoyiannis DP (2003) *Listeria monocytogenes* infection in patients with cancer. Diag Microbiol Infect Dis 47:393–398
47. Hantel A, Dick JD, Karp JE (1989) Listeriosis in the setting of malignant disease. Changing issues in an unusual infection. Cancer 64:516–520
48. Safdar A, Armstrong D (2003) Listeriosis in patients at a comprehensive cancer center, 1955–1997. Clin Infect Dis 37:359–364
49. Chang J, Powles R, Mehta J et al (1995) Listeriosis in bone marrow transplant recipients: incidence, clinical features, and treatment. Clin Infect Dis 21:1289–1290
50. Nolla-Salas J, Almela M, Coll P, Gasser I (1997) Listeriosis in bone marrow transplant recipients. Bone Marrow Transplant 19:956–958
51. Safdar A, Papadopoulous EB, Armstrong D (2002) Listeriosis in recipients of allogeneic blood and marrow transplantation: thirteen year review of disease characteristics, treatment

outcomes and a new association with human cytomegalovirus infection. Bone Marrow Transplant 29:913–916
52. Radice C, Munoz V, Castellares C et al (2006) Listeria monocytogenes meningitis in two allogeneic hematopoietic stem cell transplant recipients. Leuk Lymphoma 47:701–703
53. Girmenia C, Lori AP, Bernasconi S et al (2000) Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. Eur J Clin Microbiol Infect Dis 19:711–714
54. Williamson ECM, Millar MR, Steward CG et al (1999) Infections in adults undergoing unrelated donor bone marrow transplantation. Br J Haematol 104:560–568
55. Long SG, Leyland MJ, Milligan DW (1993) *Listeria* meningitis after bone marrow transplantation. Bone Marrow Transplant 12:537–539
56. Weismayr S, Tabarelli W, Stelzmueller I et al (2005) *Listeria* meningitis in transplant recipients. Wien Klin Wochenschr 117:229–233
57. Lopez R, Martino R, Brunet S et al (1994) Infection by *Listeria monocytogenes* in the early period post-bone marrow transplantation. Eur J Haematol 53:251–252
58. Want SV, Lacey SL, Ward L, Buckingham S (1993) An epidemiological study of listeriosis complicating a bone marrow transplant. J Hosp Infect 23:299–304
59. Dee RR, Lorber BL (1986) Brain abscess due to *Listeria monocytogenes*: case report and literature review. Rev Infect Dis 8:968–977
60. Safdar A, Armstrong D (2003) Antimicrobial activities against 84 *Listeria monocytogenes* isolates from patients with systemic listeriosis at a comprehensive cancer center (1955–1997). J Clin Microbiol 41:483–485
61. Arsene O, Linassier C, Quentin R et al (1996) Development of listeriosis during vancomycin therapy in a neutropenic patient. Scand J Infect Dis 28:415–416
62. Peeters AJ, Sedney MI, Telgt D et al (1991) Development of *Listeria* meningitis during vancomycin therapy: a case report. J Infect Dis 164:221–222
63. Richards SJ, Lambert CM, Scott AC (1992) Recurrent *Listeria monocytogenes* meningitis treated with intraventricular vancomycin. J Antimicrob Chemother 29:351–353
64. Guevara RE, Mascola L, Sorvillo F (2009) Risk factors for mortality among patients with nonperinatal listeriosis in Los Angeles County, 1992–2004. Clin Infect Dis 48:1507–1515
65. Gerner-Smidt P, Ethelberg S, Schiellerup P et al (2005) Invasive listeriosis in Denmark 1994–2003: a review of 299 cases with special emphasis on risk factors for mortality. Clin Microbiol Infect 11:618–624
66. Bennion JR, Sorvillo F, Wise ME et al (2008) Decreasing listeriosis mortality in the United States, 1990–2005. Clin Infect Dis 47:867–874
67. (2000) Centers for disease control, infectious diseases society of America, American society of blood and marrow transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 49(RR-10):1–125
68. Lerner PI (1996) Nocardiosis. Clin Infect Dis 22:891–905
69. Saubolle MA, Sussland D (2003) Nocardiosis: review of clinical and laboratory experience. J Clin Microbiol 41:4497–4501
70. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr (2006) Clinical and laboratory features of *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev 19:259–282
71. Beaman BL, Burnside J, Edwards B et al (1976) Nocardial infections in the United States, 1972–1974. J Infect Dis 134:286–289
72. Boiron P, Provost F, Chevrier G et al (1992) Review of nocardial infections in France 1987 to 1990. Eur J Clin Microbiol Infect Dis 11:709–714
73. Frazier AR, Bowsenow EC, Roberts GD (1975) Nocardiosis. A review of 25 cases occurring during 24 months. Mayo Clin Proc 50:657–663
74. Young LS, Armstrong D, Blevins A et al (1971) *Nocardia asteroides* infection complicating neoplastic disease. Am J Med 50:356–367

75. Berkey P, Bodey GP (1989) Nocardial infection in patients with neoplastic disease. Rev Infect Dis 11:407–412
76. Farina C, Boiron P, Goglio A, Provost F (1995) The Northern Italy collaborative group on nocardiosis. Human nocardiosis in Northern Italy from 1982 to 1992. Scand J Infect Dis 27:23–27
77. Menéndez R, Cordero PJ, Santos M et al (1997) Pulmonary infection with *Nocardia* species: a report of 10 cases and review. Eur Respir J 10:1542–1546
78. Farina C, Boiron P, Ferrari I, Provost F, Goglio A (2001) Report of human nocardiosis in Italy between 1993 and 1997. Eur J Epidemiol 17:1019–1022
79. Torres HA, Reddy BT, Raad II et al (2002) Nocardiosis in cancer patients. Medicine 81:388–397
80. Matulionyte R, Rohner P, Uçkay I (2004) Secular trends of *Nocardia* infection over 15 years in a tertiary care hospital. J Clin Pathol 57:807–812
81. Mootsikapun P, Intarapoka B, Liawnoraset W (2005) Nocardiosis in Srinagarind Hospital, Thailand: review of 70 cases from 1996-2001. Int J Infect Dis 9:154–158
82. Martínez Tomás R, Menéndez Villanueva R, Reyes Calzada S et al (2007) Pulmonary nocardiosis: risk factors and outcome. Respirol 12:394–400
83. Castro JG, Espinoza L (2007) *Nocardia* species infections in a large county hospital in Miami: 6 years experience. J Infect 54:358–361
84. Muñoz J, Mirelis B, Aragón LM et al (2007) Clinical and microbiological features of nocardiosis, 1997–2003. J Med Microbiol 56:545–550
85. Minero MV, Marín M, Cercenado E et al (2009) Nocardiosis at the turn of the century. Medicine 88:250–261
86. Petersen DL, Hudson LD, Sullivan K (1978) Disseminated *Nocardia caviae* with positive blood cultures. Arch Intern Med 138:1164–1165
87. Shearer C, Chandresekar PH (1995) The bone marrow transplantation team. Pulmonary nocardiosis in a patient with a bone marrow transplant. Bone Marrow Transplant 15:479–481
88. Freites V, Sumoza A, Bisotti R et al (1995) Subcutaneous *Nocardia asteroides* abscess in a bone marrow transplant recipient. Bone Marrow Transplant 15:135–136
89. Chouciño C, Goodman SA, Greer JP et al (1996) Nocardial infections in bone marrow transplant recipients. Clin Infect Dis 23:1012–1019
90. Machado CM, Macedo MC, Castelli JB et al (1997) Clinical features and successful recovery from disseminated nocardiosis after BMT. Bone Marrow Transplant 19:81–82
91. Elliott MA, Tefferi A, Marshall WF et al (1997) Disseminated nocardiosis after allogeneic bone marrow transplantation. Bone Marrow Transplant 20:425–426
92. van Burick JA, Hackman RC, Nadeem SQ et al (1997) Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis 24:1154–1160
93. Kumar K, Jimenez V (2001) Pulmonary nocardiosis after bone marrow transplantation successfully treated with doxycycline. Int J Infect Dis 5:222–224
94. Daly AS, McGeer A, Lipton JH (2003) Systemic nocardiosis following allogeneic bone marrow transplantation. Transpl Infect Dis 5:16–20
95. Lin JT, Lee MY, Hsiao LT et al (2004) Pulmonary nocardiosis in a patient with CMV relapse undergoing imatinib therapy after bone marrow transplantation. Ann Hematol 83:444–446
96. Kim JE, Landon RE, Connor TB Jr et al (2004) Endogenous ocular nocardiosis. J AAPOS 8:194–195
97. Carradice D, Szer J (2004) Cerebral nocardiosis after allogeneic bone marrow transplantation. Int Med J 34:698–699
98. Chow E, Moore T, Deville J et al (2005) *Nocardia asteroides* brain abscesses and meningitis in an immunocompromized 10-year-old child. Scand J Infect Dis 37:511–513
99. Laurence AD, Peggs KS (2005) Cerebral and pulmonary *Nocardia* in a bone marrow transplant patient. Br J Haematol 129:711

100. Kakihana K, Ohashi K, Iguchi M et al (2007) Frequent exacerbation of pulmonary nocardiosis during maintenance antibiotic therapies in a hematopoietic stem cell transplant recipient. Int J Hematol 86:455–458
101. Lebeaux D, Lanternier F, Degand N et al (2009) *Nocardia pseudobrasiliensis* as an emerging cause of opportunistic infection after allogeneic haematopoietic stem cell transplantation. J Clin Microbiol (Epub ahead of print)
102. Bhave AA, Thirunavukkarasu K, Gottlieb DJ et al (1999) Disseminated nocardiosis in a bone marrow transplant recipient with chronic GVHD. Bone Marrow Transplant 23:519–551
103. Beaman BL, Beaman L (1994) *Nocardia* species: host-parasite relationships. Clin Microbiol Rev 7:213–264
104. Rettenmaier NB, Epstein HD, Oi S et al (2009) Cerebral *Nocardia* masquerading as metastatic disease in an endometrial cancer patient. Eur J Gynaec Oncol 30:90–92
105. Moylett EH, Pacheco SE, Brown-Elliott BA et al (2003) Clinical experience with linezolid for the treatment of *Nocardia* infection. Clin Infect Dis 36:313–318
106. Kennedy GA, Durrant S (2006) *Nocardia* infection following bone marrow transplantation. Int Med J 36:402
107. Ono M, Kobayashi Y, Shibata T et al (2008) *Nocardia exalibda* brain abscess in a patient with follicular lymphoma. Int J Hematol 88:95–100
108. Hagensee ME, Bauwens JE, Kjos B et al (1994) Brain abscess following marrow transplantation: experience at the Fred Hutchinson cancer research center, 1984–1992. Clin Infect Dis 19:402–408
109. Pagano L, Caira M, Falcucci P et al (2005) Fungal CNS infections in patients with hematologic malignancy. Expert Rev Anti Infect Ther 3:775–785
110. Segal BH, Bow EJ, Menichetti F (2002) Fungal infections in nontransplant patients with hematologic malignancies. Infect Dis Clin North Am 16:935–964
111. Jantunen E, Volin L, Salonen O et al (2003) Central nervous system aspergillosis in allogeneic stem cell transplant recipients. Bone Marrow Transplant 31:191–196
112. Zivkovic S (2007) Neuroimaging and neurologic complications after organ transplantation. J Neuroimaging 17:110–123
113. Charlot M, Pialat JB, Obadia N et al (2007) Diffusion-weighted imaging in brain aspergillosis. Eur J Neurol 14:912–916
114. De Pauw B, Walsh TJ, Donnelly JP et al (2008) Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. Clin Infect Dis 46:1813–1821
115. Kami M, Ogawa S, Kanda Y et al (1999) Early diagnosis of central nervous system aspergillosis using polymerase chain reaction, latex agglutination test, and enzyme-linked immunosorbent assay. Br J Haematol 106:536–537
116. Kami M, Shirouzu I, Mitani K et al (1999) Early diagnosis of central nervous system aspergillosis with combination use of cerebral diffusion-weighted echo-planar magnetic resonance imaging and polymerase chain reaction of cerebrospinal fluid. Intern Med 38:45–48
117. Viscoli C, Machetti M, Gazzola P et al (2002) Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 40:1496–1499
118. Walsh TJ, Anaissie EJ, Denning DW et al (2008) Treatment of aspergillosis: clinical practice guidelines of the infectious diseases society of America. Clin Infect Dis 46:327–360
119. Denning DW, Ribaud P, Milpied N et al (2002) Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 34:563–571
120. Herbrecht R, Denning DW, Patterson TF et al (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415

121. Pascual A, Calandra T, Bolay S et al (2008) Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 46:201–211
122. Schwartz S, Ruhnke M, Ribaud P et al (2005) Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 106:2641–2645
123. Upton A, Kirby KA, Carpenter P et al (2007) Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis 44:531–540
124. Pagano L, Offidani M, Fianchi L et al (2004) Mucormycosis in hematologic patients. Haematologica 89:207–214
125. Nosari A, Oreste P, Montillo M et al (2000) Mucormycosis in hematologic malignancies: an emerging fungal infection. Haematologica 85:1068–1071
126. Black KE, Baden LR (2007) Fungal infections of the CNS: treatment strategies for the immunocompromised patient. CNS Drugs 21:293–318
127. Mattiuzzi G, Giles FJ (2005) Management of intracranial fungal infections in patients with haematological malignancies. Br J Haematol 131:287–300
128. Sundaram C, Mahadevan A, Laxmi V et al (2005) Cerebral zygomycosis. Mycoses 48:396–407
129. Spellberg B, Walsh TJ, Kontoyiannis DP et al (2009) Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis 48:1743–1751
130. Walsh TJ, Hiemenz W, Seibel NL et al (1998) Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis 26:1383–1396
131. Gleissner B, Schilling A, Anagnostopolous I et al (2004) Improved outcome of zygomycosis in patients with hematological diseases? Leuk Lymphoma 45:1351–1360
132. Reed C, Bryant R, Ibrahim AS et al (2008) Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis 47:364–371
133. Mitchell TG, Perfect JR (1995) Cryptococcosis in the era of AIDS–100 years after the discovery of Cryptococcus neoformans. Clin Microbiol Rev 8:515–548
134. Vilchez RA, Irish W, Lacombs J et al (2001) The clinical epidemiology of pulmonary cryptococcosis in non-AIDS patients at a tertiary care medical center. Medicine 80:308–312
135. Collins VP, Gellhorn A, Trimble JR (1951) The coincidence of cryptococcosis and disease of the reticulo-endothelial and lymphatic systems. Cancer 4:883–889
136. Kaplan MH, Rosen PP, Armstrong D (1977) Cryptococcosis in a cancer hospital. Clinical and pathological correlates in forty-six patients. Cancer 39:2265–2274
137. Korfel A, Menssen HD, Schwartz S, Thiel E (1998) Cryptococcosis in Hodgkin's disease: description of two cases and review of the literature. Ann Hematol 76:283–286
138. Kontoyiannis DP, Peitsch WK, Reddy BT et al (2001) Cryptococcosis in patients with cancer. Clin Infect Dis 32:e145–e150
139. Pagano L, Fianchi L, Caramatti C et al (2004) Cryptococcosis in patients with hematologic malignancies. A report from GIMEMA-infection program. Haematologicia 89:852–856
140. White M, Cirrincione C, Blevins A et al (1992) Cryptococcal meningitis: outcome in patients with AIDS and with neoplastic disease. J Infect Dis 165:960–963
141. Gupta K, Radotra BD, Gupta V et al (2008) Concurrent presence of cryptococcal meningitis and primary central nervous system (CNS) non-Hodgkin's lymphoma in a non-HIV patient. Neuropathol Appl Neurobiol 34:241–244
142. Melzer M, Colbridge M, Keenan F et al (1998) Cryptococcosis: an unusual infection complicating B cell lymphoproliferative disorders. J Infect 36:220–222
143. Assing K, Birgens H, Arendrup M (2003) *Cryptococcus neoformans* var. *neoformans* resistant to fluconazole in an HIV-negative patient with chronic lymphocytic leukemia. Clin Microbiol Infect 9:441–444
144. Ikpeazu EV, Kaplon MK (1998) Cryptococcal meningitis occurring at 19 months after cladribine therapy for hairy cell leukemia. Eur J Haematol 61:286–287

145. Malhotra P, Chauhan S, Bhatt P et al (2004) Cryptococcal meningitis in acute lymphoblastic leukemia. J Assoc Phys India 52:831–832
146. Dinçol G, Kahraman R (2006) *Cryptococcus neoformans* meningitis in a patient with hairy cell leukemia. Am J Hematol 81:387
147. Mendpara SD, Ustun C, Kallab AM (2002) Cryptococcal meningitis following autologous stem cell transplantation in a patient with multiple myeloma. Bone Marrow Transplant 30:259–260
148. Choi JD, Powers CJ, Vredenburgh JJ et al (2008) Cryptococcal meningitis in patients with glioma: a report of two cases. J Neurooncol 89:51–53
149. Rimek D, Haase G, Lück A et al (2004) First report of a case of meningitis caused by *Cryptococcus adeliensis* in a patient with acute myeloid leukemia. J Clin Microbiol 42:481–483
150. Miniero R, Nesi F, Vai S et al (1997) Cryptococcal meningitis following a thrombotic microangiopathy in an unrelated donor bone marrow transplant recipient. Pediatr Hematol Oncol 14:469–474
151. Ramchandren R, Gladstone D (2004) *Cryptococcus albidus* infection in a patient undergoing autologous progenitor cell transplant. Transplantation 77:956
152. Krcméry V Jr, Kunova A, Mardiak J (1997) Nosocomial *Cryptococcus laurentii* fungemia in a bone marrow transplant patient after prophylaxis with ketoconazole successfully treated with oral fluconazole. Infection 25:130
153. Chou LS, Lewis RE, Ippoliti C et al (2007) Caspofungin as primary antifungal prophylaxis in stem cell transplant recipients. Pharmacotherapy 27:1644–1650
154. Sun HY, Wagener MM, Singh N (2009) Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. Clin Infect Dis 48:1566–1576
155. Dromer F, Mathoulin-Pélissier S, Launay O et al (2007) Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. PLoS Med 4:e21
156. Antinori S, Radice A, Galimberti L et al (2005) The role of cryptococcal antigen assay in diagnosis and monitoring of cryptococcal meningitis. J Clin Microbiol 43:5828–5829
157. Kiska DL, Orkiszewski DR, Howell D et al (1994) Evaluation of new monoclonal antibody-based latex agglutination test for detection of cryptococcal polysaccharide antigen in serum and cerebrospinal fluid. J Clin Microbiol 32:2309–2311
158. Tanner DC, Weinstein MP, Fedorciw B et al (1994) Comparison of commercial kits for detection of cryptococcal antigen. J Clin Microbiol 32:1680–1684
159. Currie BP, Freundlich LF, Soto MA et al (1993) False-negative cerebrospinal fluid cryptococcal latex agglutination tests for patients with culture-positive cryptococcal meningitis. J Clin Microbiol 31:2519–2522
160. Sugiura Y, Homma M, Yamamoto T (2005) Difficulty in diagnosing chronic meningitis caused by capsule-deficient *Cryptococcus neoformans*. J Neurol Neurosurg Psychiatry 76:1460–1461
161. Alexander BD (2005) Cryptococcosis after solid organ transplantation. Transpl Infect Dis 7:1–3
162. Heelan JS, Corpus L, Kessimian N (1991) False-positive reactions in the latex agglutination test for *Cryptococcus neoformans* antigen. J Clin Microbiol 29:1260–1261
163. McManus EJ, Jones JM (1985) Detection of a *Trichosporon beigelii* antigen cross-reactive with *Cryptococcus neoformans* capsular polysaccharide in serum from a patient with disseminated *Trichosporon* infection. J Clin Microbiol 21:681–685
164. Westerink MA, Amsterdam D, Petell RJ et al (1987) Septicemia due to DF-2. Cause of a false-positive cryptococcal latex agglutination result. Am J Med 83:155–158
165. Kontoyiannis DP (2003) What is the significance of an isolated positive cryptococcal antigen in the cerebrospinal fluid of cancer patients? Mycoses 46:161–163

166. Bennett JE, Dismukes WE, Duma RJ et al (1979) A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. New Eng J Med 301:126–131
167. van der Horst CM, Saag MS, Cloud GA et al (1997) Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National institute of allergy and infectious diseases mycoses study group and AIDS clinical trials group. N Engl J Med 337:15–21
168. Brouwer AE, Rajanuwong A, Chierakul W et al (2004) Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet 363:1764–1767
169. Larsen RA, Leal MA, Chan LS (1990) Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial. Ann Intern Med 113:183–187
170. Dromer F, Bernede-Baudin C, Guillemot D et al (2008) Major role for amphotericin B-flucytosine combination in severe cryptococcosis. PLoS One 3:e2870
171. Pappas PG, Perfect JR, Cloud GA et al (2001) Cryptococcosis in human immunodeficiency virus negative patients in the era of effective azole therapy. Clin Infect Dis 33:690–699
172. Saag MS, Graybill RJ, Larsen RA et al (2000) Practice guidelines for the management of cryptococcal disease. Infectious diseases society of America. Clin Infect Dis 30:710–718
173. Dismukes WE, Cloud G, Gallis HA et al (1987) Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. N Engl J Med 317:334–341
174. Leenders AC, Reiss P, Portegies P et al (1997) Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS 11:1463–1471
175. Sharkey PK, Graybill JR, Johnson ES et al (1996) Amphotericin B lipid complex compared with amphotericin B in the treatment of cryptococcal meningitis in patients with AIDS. Clin Infect Dis 22:315–321
176. Graybill JR, Sobel J, Saag M et al (2000) Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID mycoses study group and AIDS cooperative treatment groups. Clin Infect Dis 30:47–54
177. Shoham S, Cover C, Donegan N et al (2005) *Cryptococcus neoformans* meningitis at 2 hospitals in Washington, D.C.: adherence of health care providers to published practice guidelines for the management of cryptococcal disease. Clin Infect Dis 40:477–479
178. Liliang PC, Liang CL, Chang WN et al (2002) Use of ventriculoperitoneal shunts to treat uncontrollable intracranial hypertension in patients who have cryptococcal meningitis without hydrocephalus. Clin Infect Dis 34:E64–E68
179. Liliang PC, Liang CL, Chang WN et al (2003) Shunt surgery for hydrocephalus complicating cryptococcal meningitis in human immunodeficiency virus-negative patients. Clin Infect Dis 37:673–678
180. Macsween KF, Bicanic T, Brouwer AE et al (2005) Lumbar drainage for control of raised cerebrospinal fluid pressure in cryptococcal meningitis: case report and review. J Infect 51:e221–e224
181. Woodworth GF, McGirt MJ, Williams MA et al (2005) The use of ventriculoperitoneal shunts for uncontrollable intracranial hypertension without ventriculomegaly secondary to HIV-associated cryptococcal meningitis. Surg Neurol 63:529–531; discussion 31–32
182. Polsky B, Depman MR, Gold JW et al (1986) Intraventricular therapy of cryptococcal meningitis via a subcutaneous reservoir. Am J Med 81:24–28
183. Diamond RD, Bennett JE (1974) Prognostic factors in cryptococcal meningitis. A study in 111 cases. Ann Intern Med 80:176–181
184. Styczynski J, Einsele H, Gil L et al (2009) Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. Transpl Infect Dis 11:383–392

185. Arribas JR, Storch GA, Clifford DB et al (1996) Cytomegalovirus encephalitis. Ann Intern Med 125:577–587
186. Robertson KB, Barron MA, Nieto Y (2004) West Nile virus infection in bone marrow transplant recipients. Bone Marrow Transplant 34:823–824
187. Reddy D, Davenport R, Ratanatharathorn V et al (2004) West Nile virus encephalitis causing fatal CNS toxicity after hematopoietic stem cell transplantation. Bone Marrow Transplant 33:109–112
188. Martin SE, Grubbs S, Della Valla J et al (2004) Fatal West Nile virus encephalitis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 34:1007–1008
189. Hong DS, Jacobson KL, Raad II et al (2003) West Nile encephalitis in 2 hematopoietic stem cell transplant recipients: case series and review of literature. Clin Infect Dis 37:1044–1049
190. Kleinschmidt-DeMasters BK, Marder BA, Levi ME et al (2004) Naturally acquired West Nile virus encephalomyelitis in transplant recipients. Arch Neurol 61:1210–1220
191. Brenner W, Storch G, Buller R et al (2005) West Nile virus encephalopathy in an allogeneic stem cell transplant recipient: use of quantitative PCR for diagnosis and assessment of viral clearance. Bone Marrow Transplant 36:369–370
192. Clark DA, Griffiths PD (2003) Human herpesvirus 6: relevance of infection in the immunocompromised host. Br J Haematol 120:384–395
193. Zerr DM (2006) Human herpesvirus 6 and central nervous system disease in hematopoietic cell transplantation. J Clin Virol 37(Suppl1):S52–S56
194. Gewurz BE, Mary FM, Baden LR et al (2008) Human herpesvirus 6 encephalitis. Curr Infect Dis Rep 10:292–299
195. Chan PKS, Peiris JSM, Yuen KY et al (1997) Human herpesvirus-6 and human herpesvirus-7 infections in bone marrow transplant recipients. J Med Virol 53:295–305
196. Zerr DM, Corey L, Kim HW et al (2005) Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis 40:932–940
197. Fujimaki K, Mori T, Kida A et al (2006) Human herpesvirus 6 meningoencephalitis in allogeneic hematopoietic stem cell transplant recipients. Int J Hematol 84:432–437
198. Ogata M, Satou T, Kawano R et al (2009) Correlations of HHV-6 viral load and plasma IL-6 concentration with HHV-6 encephalitis in allogeneic stem cell transplant recipients. Bone Marrow Transplant (Epub ahead of print)
199. Rieger CT, Rieger H, Kolb HJ et al (2009) Infectious complications after allogeneic stem cell transplantation: incidence in matched-related and matched-unrelated transplant settings. Transpl Infect Dis 11:220–226
200. Ljungman P, Wang FZ, Clark DA et al (2000) High levels of human herpesvirus 6 DNA in peripheral blood leucocytes are correlated to platelet engraftment and disease in allogeneic stem cell transplant patients. Br J Haematol 111:774–781
201. Yoshikawa T, Asano Y, Ihira M et al (2002) Human herpesvirus 6 viremia in bone marrow transplant recipients: clinical features and risk factors. J Infect Dis 185:847–853
202. Ogata M, Kikuchi H, Satou T et al (2006) Human herpesvirus 6 DNA in plasma after allogeneic stem cell transplantation: incidence and clinical significance. J Infect Dis 193:68–79
203. Zerr DM, Gupta D, Huang ML et al (2002) Effect of antiviral on human herpesvirus 6 replication in hematopoietic stem cell transplant recipients. Clin Infect Dis 34:309–317
204. Muta T, Fukada T, Harada M (2009) Human herpesvirus-6 encephalitis in hematopoietic SCT recipients in Japan: a retrospective multicenter study. Bone Marrow Transplant 43:583–585
205. Drobyski WR, Knox KK, Majewski D et al (1994) Encephalitis due to variant human herpesvirus-6 infection in a bone marrow-transplant recipient. New Eng J Med 330:1356–1360
206. Bosi A, Zazzi M, Amantini A et al (1998) Fatal herpesvirus 6 encephalitis after unrelated bone marrow transplant. Bone Marrow Transplant 22:285–288

207. Cole PD, Stiles J, Boulad F et al (1998) Successful treatment of human herpesvirus 6 encephalitis in a bone marrow transplant recipient. Clin Infect Dis 27:653–654
208. Rieux C, Gautheret-Dejean A, Challine-Lehmann D et al (1998) Human herpesvirus-6 meningoencephalitis in a recipient of an unrelated donor allogeneic bone marrow transplantation. Transplantation 65:1408–1411
209. Tsujimura H, Iseki T, Date Y et al (1998) Human herpesvirus-6 encephalitis after bone marrow transplantation: magnetic resonance imaging could identify the involved sites of encephalitis. Eur J Haematol 61:284–285
210. Bethge W, Beck R, Jahn G et al (1999) Successful treatment of human herpesvirus-6 encephalitis after bone marrow transplantation. Bone Marrow Transplant 24:1245–1248
211. De Almeida Rodrigues G, Nagendra S, Lee CK et al (1999) Human herpes virus 6 fatal encephalitis in a bone marrow recipient. Scand J Infect Dis 31:313–315
212. Wang FZ, Linde A, Hagglund H et al (1999) Human herpesvirus 6 DNA in cerebrospinal fluid specimens from allogeneic bone marrow transplant patients: does it have clinical significance? Clin Infect Dis 28:562–568
213. Kawano Y, Miyazaki T, Watanabe T et al (2000) HLA-mismatched CD34-selected stem cell transplant complicated by HHV-6 reactivation in the central nervous system. Bone Marrow Transplant 25:787–790
214. Tiacci E, Luppi M, Barozzi P et al (2000) Fatal herpesvirus-6 encephalitis in a recipient of a T-cell-depleted peripheral blood stem cell transplant from a 3-loci mismatched related donor. Haematologica 85:94–97
215. Carvajal E, Verdeguer A, Fernández JM et al (2001) Herpesvirus-6 encephalitis complicated by Wernicke-Korsakoff syndrome in a pediatric recipient of unrelated cord blood transplantation. J Pediatr Hematol Oncol 23:926–928
216. Kim YJ, Kim DW, Lee DG et al (2002) Human herpesvirus-6 as a possible cause of encephalitis and hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. Leukemia 16:958–959
217. Maclean HJ, Douen AG (2002) Severe amnesia associated with human herpesvirus 6 encephalitis after bone marrow transplantation. Transplantation 15:1086–1089
218. Wainwright MS, Martin PL, Morse RP et al (2001) Human herpesvirus 6 limbic encephalitis after stem cell transplantation. Ann Neurol 50:612–619
219. Yoshida H, Matsunaga K, Ueda T et al (2002) Human herpesvirus 6 meningoencephalitis successfully treated with ganciclovir in a patient who underwent allogeneic bone marrow transplantation from an HLA-identical sibling. Int J Hematol 75:421–425
220. Chik KW, Chan PKS, Li CK et al (2002) Human herpesvirus-6 encephalitis after unrelated umbilical cord blood transplant in children. Bone Marrow Transplant 29:991–994
221. Yoshihara S, Kato R, Inoue T et al (2004) Successful treatment of life-threatening human herpesvirus-6 encephalitis with donor lymphocyte infusion in a patient who had undergone human leukocyte antigen-haploidentical nonmyeloablative stem cell transplantation. Transplantation 77:835–838
222. de Labarthe A, Gauthert-Dejean A, Bossi P et al (2005) HHV-6 variant A meningoencephalitis after allogeneic hematopoietic stem cell transplantation diagnosed by quantitative real-time polymerase chain reaction. Transplantation 80:539
223. Tanaka M, Taguchi J, Hyo R et al (2005) Human herpesvirus-6 encephalitis after unrelated cord blood transplantation. Leuk Lymphoma 46:561–566
224. Visser AM, van Doornum GJ, Cornelissen JJ et al (2005) Severe amnesia due to HHV-6 encephalitis after allogeneic stem cell transplantation. Eur Neurol 54:233–234
225. Seeley WW, Marty FM, Holmes TM et al (2007) Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology 69:156–165
226. Vu T, Carrum G, Hutton G et al (2007) Human herpesvirus-6 encephalitis following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 39:705–709
227. Holden SR, Vas AL (2007) Severe encephalitis in a haematopoietic stem cell transplant recipient caused by reactivation of human herpesvirus 6 and 7. J Clin Virol 40:245–247

228. Chamberlain MC, Chowdhary S, Seeley WW et al (2008) Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology 70:491–493
229. Matà S, Buidi S, Nozzoli C et al (2008) Human herpesvirus 6-associated limbic encephalitis in adult recipients of unrelated umbilical cord blood transplantation. Bone Marrow Transplant 42:693–695
230. Isegawa Y, Hara J, Amo K et al (2009) Human herpesvirus 6 ganciclovir-resistant strain with amino acid substitutions associated with the death of an allogeneic stem cell transplant recipient. J Clin Virol 44:15–19
231. Mookerjee BP, Vogelsang G (1997) Human herpes virus 6-encephalitis after bone marrow transplantation: successful treatment with ganciclovir. Bone Marrow Transplant 20:905–906
232. Bommer M, Pauls S, Greiner J (2009) Challenging complications of treatment-human herpes virus 6 encephalitis and pneumonitis in a patient undergoing autologous stem cell transplantation for relapsed Hodgkin's disease: a case report. Virol J 6:111
233. Nicolle A, Stark GL, Taylor CE et al (2003) Human herpesvirus 6 encephalitis following FLAG chemotherapy. Br J Haematol 122:166–167
234. Ljungman P, de la Camara R, Cordonnier C et al (2008) Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 42:227–240
235. Provenzale JM, VanLandingham KE, Lewis DV et al (2008) Extrahippocampal involvement in human herpesvirus 6 encephalitis depicted at MR imaging. Radiology 249:955–963
236. Dewhurst S (2004) Human herpesvirus type 6 and human herpesvirus type 7 infections of the central nervous system. Herpes 11(Suppl2):105A–111A
237. De Bolle L, Manichanh C, Agut H et al (2004) Human herpesvirus 6 DNA polymerase: enzymatic parameters, sensitivity to ganciclovir and determination of the role of $A^{961}V$ mutation in HHV-6 ganciclovir resistance. Antiviral Res 64:17–25
238. Manichanh C, Olivier-Aubron C, Lagarde JP et al (2001) Selection of the same mutation in the U69 protein kinase gene of human herpesvirus-6 after prolonged exposure to ganciclovir in vitro and in vivo. J Gen Virol 82:2767–2776
239. Pöhlmann C, Schetelig J, Reuner U et al (2007) Cidofovir and foscarnet for treatment of human herpesvirus 6 encephalitis in a neutropenic stem cell transplant recipient. Clin Infect Dis 44:e118–e120
240. Rapaport D, Engelhard D, Tagger G et al (2002) Antiviral prophylaxis may prevent human herpesvirus-6 reactivation in bone marrow transplant recipients. Transpl Infect Dis 4:10–16
241. Tokimasa S, Hara J, Osugi Y et al (2000) Ganciclovir is effective for prophylaxis and treatment of human herpesvirus-6 in allogeneic stem cell transplantation. Bone Marrow Transplant 29:595–598
242. Ogata M, Satou T, Kawano R et al (2008) Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation: a prospective evaluation. Bone Marrow Transplant 41:279–285
243. Pelosini M, Focosi D, Rita F et al (2008) Progressive multifocal leukoencephalopathy: report of three cases in HIV-negative hematological patients and review of the literature. Ann Hematol 87:405–412
244. Hartman EA, Huang D (2008) Update on PML: lessons from the HIV uninfected and new insights in pathogenesis and treatment. Current HIV/AIDS Reports 5:112–119
245. Cinque P, Koralnik IJ, Gerevini S et al (2009) Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis 9:625–636
246. Egli A, Infanti L, Dumoulin A et al (2009) Prevalence of polyomavirus BK and JC infection and replication in 400 healthy volunteers. J Infect Dis 199:837–846
247. Jiang M, Abend JR, Johnson SF et al (2009) The role of polyomaviruses in human disease. Virology 384:266–273

248. Aksamit AJ (2001) Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. J Neurovirol 7:386–390
249. Power C, Brown Gladden JG, Halliday W et al (2000) AIDS- and non-AIDS-related PML association with distinct p53 polymorphism. Neurology 54:743–746
250. García-Suárez J, de Miguel D, Krsnik I et al (2005) Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. Am J Hematol 80:271–281
251. Farge D, Hervé R, Mikol J et al (1994) Simultaneous progressive multifocal leukoencephalopathy, Epstein-Barr virus (EBV) latent infection and cerebral parenchymal infiltration during chronic lymphocytic leukemia. Leukemia 8:318–321
252. Cid J, Revila M, Cervera A et al (2000) Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. Ann Hematol 79:392–395
253. Saumoy M, Castell G, Escoda L et al (2002) Progressive multifocal leukoencephalopathy in chronic lymphocytic leukemia after treatment with fludarabine. Leuk Lymphoma 43:433–436
254. Vidarsson B, Mosher DF, Salamat MS et al (2002) Progressive multifocal leukoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease. Am J Hematol 70:51–54
255. Kiewe P, Seyfert S, Körper S et al (2003) Progressive multifocal leukoencephalopathy with detection of JC virus in a patient with chronic lymphocytic leukemia parallel to onset of fludarabine therapy. Leuk Lymphoma 44:1815–1818
256. Kesari S, Akar S, Saad A et al (2008) Progressive multifocal leukoencephalopathy in a patient with relapsed acute myelogenous leukemia. J Clin Oncol 26:3804–3807
257. Visco C, Marcioni E, Pomponi F et al (2009) Progressive multifocal leucoencephalopathy and autoimmune haemolytic anemia in chronic lymphocytic leukaemia: more than a fortuitous combination? Ann Hematol 88:189–191
258. Saad ED, Thomas DA, Brian S et al (2000) Progressive multifocal leukoencephalopathy with concurrent Richter's syndrome. Leuk Lymphoma 38:183–190
259. Baehring JM, Vives K, Bannykh S (2007) Progressive multifocal leukoencephalopathy in a patient with marginal zone B-cell lymphoma. J Neurooncol 85:289–290
260. Rey J, Belmecheri N, Bouayed N et al (2007) JC papovavirus leukoencephalopathy after first line treatment with CHOP and rituximab. Haematologia 92:e101
261. Kranick SM, Mowry EM, Rosenfeld MR (2007) Progressive multifocal leukoencephalopathy after rituximab in a case of non-Hodgkin lymphoma. Neurology 69:704–706
262. Kunschner L, Scott TF (2005) Sustained recovery of progressive leukoencephalopathy after treatment with IL-2. Neurology 65:1510
263. Lee J, Richardson SK, Melhem ER et al (2007) Progressive multifocal leukoencephalopathy from JC virus in a patient with advanced mycosis fungoides. J Am Acad Dermatol 57:893–895
264. Lebrun C, Chanalet S, Frenay M et al (1999) Leukoencephalopathy in multiple myeloma: two case reports. Ann Oncol 10:1515–1517
265. Verma S, Cikurel K, Koralnik IJ et al (2007) Mirtazapine in progressive multifocal leukoencephalopathy associated with polycythemia vera. J Infect Dis 196:709–711
266. Ng C, Slavin MA, Seymour JF (2003) Progressive multifocal leukoencephalopathy complicating Waldentström's macroglobulinaemia. Leuk Lymphoma 44:1819–1821
267. Mesquita R, Parravicini C, Björkholm M et al (1992) Macrophage association of polyomavirus in progressive multifocal leukoencephalopathy: an immunohistochemical and ultrastructural study. Case report. APMIS 100:993–1000
268. Przepiorka D, Jaeckle KA, Birdwell RR et al (1997) Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. Bone Marrow Transplant 20:983–987

269. Re D, Bamborschke S, Feiden W et al (1999) Progressive multifocal leukoencephalopathy after autologous bone marrow transplantation and alpha-interferon immunotherapy. Bone Marrow Transplant 23:295–298
270. Coppo P, Laporte JPh, Aoudijhane M et al (1999) Progressive multifocal leucoencephalopathy with peripheral demyelinating neuropathy after autologous bone marrow transplantation for acute myeloblastic leukemia (FAB5). Bone Marrow Transplant 23:401–403
271. Buckanovich RJ, Liu G, Stricker C et al (2002) Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. Ann Hematol 81:410–413
272. Goldberg SL, Pecora AL, Alter RS et al (2002) Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 99:1486–1488
273. Osorio S, de la Cámara R, Golbano N et al (2002) Progressive multifocal leukoencephalopathy after stem cell transplantation unsuccessfully treated with cidofovir. Bone Marrow Transplant 30:963–966
274. Matteucci P, Magni M, Di Nicola M et al (2002) Leukoencephalopathy and papovavirus infection after treatment with chemotherapy and anti-CD20 monoclonal antibody. Blood 100:1104–1105
275. Steurer M, Gotwald T, Gunsilius E et al (2003) Progressive multifocal leukoencephalopathy after allogeneic stem cell transplantation and posttransplantation rituximab. Transplantation 76:435–448
276. Kharfan-Darbaja MA, Ayala E, Greene J et al (2007) Two cases of progressive multifocal leukoencephalopathy after allogeneic hematopoietic cell transplantation and a review of the literature. Bone Marrow Transplant 39:101–107
277. Focosi D, Fazzi R, Montanaro D et al (2007) Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: a clinical, neuroradiological, and virological response after treatment with risperidone. Antiviral Res 74:156–158
278. U.S. Food and Drug Administration. Public Health Advisory. Life-threatening brain infection in patients with systemic lupus erythematosus after Rituxan (rituximab) treatment. http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124345.htm Accessed 30 Oct 2009
279. Freim Wahl SG, Folvik MR, Torp SH (2007) Progressive multifocal leukoencephalopathy in a lymphoma patient with complete remission after treatment with cytostatics and rituximab: case report and review of the literature. Clin Neuropathol 26:68–73
280. Yokoyama H, Watanabe T, Maruyama D et al (2008) Progressive multifocal leukoencephalopathy in a patient with B-cell lymphoma during rituximab-containing chemotherapy: case report and review of the literature. Int J Hematol 88:443–447
281. Hopfinger G, Plessl A, Grisold W et al (2008) Progressive multifocal leukoencephalopathy after rituximab in a patient with relapsed follicular lymphoma and low IgG levels and a low CD4 + lymphocyte count. Leuk Lymphoma 4(9):2367–2369
282. Carson KR, Focosi D, Major EO et al (2009) Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a review from the research on adverse drug events and reports (RADAR) project. Lancet Oncol 10:816–824
283. Tuccori M, Focosi D, Maggi F, et al. Progressive multifocal leukoencephalopathy: a report of three cases in HIV-negative patients with non-Hodgkin's lymphoma treated with rituximab. Ann Hematol 2009 Aug 29. [Epub ahead of print]
284. U.S. Food and Drug Administration. Communication about an ongoing safety review of CellCept (mycophenolate mofetil) and Myfortic (mycophenolic acid). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm072438.htm Accessed 30 Oct 2009

285. Martin SL, Marty FM, Fiumara K et al (2006) Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. Clin Infect Dis 43:16–24
286. Huang D, Cossoy M, Li M et al (2007) Inflammatory progressive multifocal leukoencephalopathy in human immunodeficiency virus-negative patients. Ann Neurol 62:34–39
287. Bassolasco S, Calori G, Moretti F et al (2005) Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. Clin Infect Dis 40:738–744
288. Crowder CD, Gyure KA, Drachenberg CB et al (2005) Successful outcome of progressive multifocal leukoencephalopathy in a renal transplant recipient. Am J Transplant 5:1151–1158
289. Marra CM, Rajicic N, Barker D et al (2002) A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. AIDS 16:1791–1797
290. De Luca A, Ammassari A, Pezzotti P et al (2008) Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. AIDS 22:1759–1767
291. Royal W 3rd, Dupont B, McGuire D et al (2003) Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. J Neurovirol 9:411–419
292. Elphick GF, Querbes W, Jordan JA et al (2004) The human polyomavirus, JCV, uses serotonin receptors to infect cells. Science 306:1380–1383
293. Focosi D, Kast RE, Maggi F (2008) 5-$HT_{2a}$ inhibitors for progressive multifocal leukoencephalopathy: old drugs for an old disease. J Infect Dis 197
294. Co JKG, Verma S, Gurav U et al (2007) Interferon-$\alpha$ and $\beta$– restrict polyomavirus JC replication in primary human fetal glial cells: implications for progressive multifocal leukoencephalopathy therapy. J Infect Dis 196:712–718
295. Tashiro K, Doi S, Moriwaka F et al (1987) Progressive multifocal leukoencephalopathy with magnetic resonance imaging verification and therapeutic trials with interferon. J Neurol 234:427–429
296. Orba Y, Sunden Y, Suzuki T et al (2008) Pharmacological cdk inhibitor *R*-Roscovitine suppresses JC virus replication. Virology 370:173–183
297. Radhakrishnan S, Gordon J, Del Valle L et al (2004) Intracellular approach for blocking JC virus gene expression by using RNA interference during viral infection. J Virol 78:7264–7269
298. Brickelmaier M, Lugovskoy A, Kartikeyan R et al (2009) Identification and characterization of mefloquine efficacy against JC virus in vitro. Antimicrob Agents Chemother 5(3):1840–1849
299. Hill D, Dubey JP (2002) *Toxoplasma gondii*: transmission, diagnosis, and prevention. Clin Microbiol Infect 8:634–640
300. Aoun M, Georgala A, Mboumi K et al (2006) Changing spectrum of toxoplasmosis in bone marrow transplant recipients. Int J Antimicrob Agents 27:570–575
301. Matsuo Y, Takeishi S, Miyamoto T et al (2007) Toxoplasmosis encephalitis following severe graft-vs.-host disease after allogeneic hematopoietic stem cell transplantation: 17 yr experience in Fukuoka BMT group. Eur J Haematol 79:317–321
302. Derouin F, Pelloux H (2008) Prevention of toxoplasmosis in transplant recipients. Clin Microbiol Infect 14:1089–1101
303. Slavin MA, Meyers JD, Remington JS et al (1994) *Toxoplasma gondii* infection in marrow transplant recipients: a 20 year experience. Bone Marrow Transplant 13:549–557
304. Seong DC, Przepiorka D, Bruner JM et al (1993) Leptomeningeal toxoplasmosis after allogeneic marrow transplantation. Am J Clin Onc 16:105–108
305. de Medeiros BC, de Medeiros CR, Werner B et al (2001) Disseminated toxoplasmosis after bone marrow transplantation: report of 9 cases. Transplant Infect Dis 3:24–28

306. Martino R, Bretagne S, Rovira M et al (2000) Toxoplasmosis after hematopoietic stem cell transplantation. Report of a 5-year survey from the infectious diseases working party of the European group for blood and marrow transplantation. Bone Marrow Transplant 25:1111–1114
307. Derouin F, Devergie A, Auber P et al (1992) Toxoplasmosis in bone marrow-transplant recipients: report of seven cases and review. Clin Infect Dis 15:267–270
308. Derouin F, Gluckman E, Beauvais B et al (1986) Toxoplasma infection after human allogeneic bone marrow transplantation: clinical and serological study of 80 patients. Bone Marrow Transplant 1:67–73
309. González MI, Caballero D, López C et al (2000) Cerebral toxoplasmosis and Guillain-Barré syndrome after allogeneic peripheral stem cell transplantation. Transplant Infect Dis 2:145–149
310. Small TN, Leung L, Stiles J et al (2000) Disseminated toxoplasmosis following T cell-depleted related and unrelated bone marrow transplantation. Bone Marrow Transplant 25:969–973
311. Mele A, Paterson PJ, Prentice HG et al (2002) Toxoplasmosis in bone marrow transplantation: a report of two cases and systematic review of the literature. Bone Marrow Transplant 29:691–698
312. Chandrasekar PH, Momin F (1997) Disseminated toxoplasmosis in marrow recipients: a report of three cases and a review of the literature. Bone Marrow Transplant 19:685–689
313. Power M, Vandenberghe E, Conneally E et al (2005) Retinal and cerebral toxoplasmosis following nonmyeloablative stem cell transplant for chronic lymphocytic leukemia. Bone Marrow Transplant 36:1019–1020
314. Strathoff CSM, Korbeek LM, Roerdik H et al (2001) A solitary spinal cord *Toxoplasma* lesion after peripheral stem-cell transplantation. J Neurol 248:814–815
315. Jorges E, Young Y, Eltumi M (1992) Transmission of toxoplasmosis by bone marrow transplant associated with Campath-1G. Bone Marrow Transplant 9:65
316. Siegel SE, Lunde MN, Gelderman AH et al (1971) Transmission of toxoplasmosis by leukocyte transfusion. Blood 37:388–394
317. Geissmann F, Deroin F, Marolleau JP et al (1994) Disseminated toxoplasmosis following autologous bone marrow transplantation. Clin Infect Dis 19:800–801
318. Re D, Reiser M, Bamborschke S et al (1999) Two cases of toxoplasmic encephalitis in patients with acute T-cell leukaemia and lymphoma. J Infect 38:26–29
319. Bretagne S, Costa JM, Kuentz M et al (1995) Late toxoplasmosis evidenced by PCR in a marrow transplant recipient. Bone Marrow Transplant 15:809–811
320. Brinkman K, Debast S, Sauerwein R et al (1998) *Toxoplasma* retinitis/encephalitis 9 months after allogeneic bone marrow transplantation. Bone Marrow Transplant 21:635–636
321. Tefferi A, O'Neill BP, Inwards DJ (1998) Late-onset cerebral toxoplasmosis after allogeneic bone marrow transplantation. Bone Marrow Transplant 21:1285–1288
322. Dietrich U, Maschke M, Dörfler A et al (2000) MRI of intracranial toxoplasmosis after bone marrow transplantation. Neuroradiology 42:14–18
323. Ionita C, Wasay M, Balos L et al (2004) MR imaging in toxoplasmosis encephalitis after bone marrow transplantation: paucity of enhancement despite fulminant disease. AJNR Am J Neuroradiol 25:270–273
324. Mueller-Mang C, Mang TG, Kalhs P et al (2006) Imaging characteristics of toxoplasmosis encephalitis after bone marrow transplantation: report of two cases and review of the literature. Neuroradiology 48:84–89
325. Held TK, Krüger D, Switala AR et al (2000) Diagnosis of toxoplasmosis in bone marrow transplant recipients: comparison of PCR-based results and immunohistochemistry. Bone Marrow Transplant 25:1257–1262
326. Khoury H, Adkins D, Brown R et al (1999) Successful treatment of cerebral toxoplasmosis in a marrow transplant recipient: contribution of a PCR test in diagnosis and early detection. Bone Marrow Transplant 23:409–441

327. Cibickova L, Horacek J, Prasil P et al (2007) Cerebral toxoplasmosis in an allogeneic peripheral stem cell transplant recipient: case report and review of literature. Transplant Infect Dis 9:332–335
328. Foot ABM, Garin YJF, Ribaud P et al (1994) Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. Bone Marrow Transplant 14:241–245
329. Edvinnson B, Lundquist J, Ljungman P et al (2008) A prospective study of *Toxoplasma gondii* infection after bone marrow transplantation. APMIS 116:345–351

# Dermatologic Infections in Cancer Patients

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**Abstract**

Dermatologic infections are among the most commonly experienced complications of cancer and anti-cancer therapy. Alterations in host immune function secondary to the underlying malignant process and/or its treatment have been linked to an increase in the risk of infections. The skin and its appendages (i.e., hair and nails) represent the first line of defense against infectious microorganism; its dysfunction as a physical barrier and an immunologic organ in cancer patients leads to an increased susceptibility to infectious organisms. Moreover, a cancer patients' vulnerable state facilitates dissemination of infections to other sites, secondarily involving the skin. This chapter delineates dermatologic infections that are unique to cancer patients as a result of their underlying malignancies and associated comorbidities as well as those resulting from antineoplastic therapies.

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Dermatoxicity · Cutaneous infection · Anti-cancer therapy · Therapy-related infection · Bacterial dermatologic infection · Viral dermatologic infection · Fungal dermatologic infection · Secondary infection

## Contents



## 1 Introduction

Dermatologic infections are among the most commonly experienced complications of cancer and anti-cancer therapy. Alterations in host immune function secondary to the underlying malignant process and/or its treatment have been linked to an increase in the risk of infections [1]. The skin and its appendages (i.e., hair and nails) represent the first line of defense against infectious microorganism; its dysfunction as a physical barrier and an immunologic organ in cancer patients leads to an increased susceptibility to infectious organisms. Moreover, a cancer patient's vulnerable state facilitates dissemination of infections to other sites, secondarily involving the skin. This chapter delineates dermatologic infections that are unique to cancer patients as a result of their underlying malignancies and associated comorbidities as well as those resulting from antineoplastic therapies (Table 1, Fig. 1).

**Table 1** Dermatologic infections by cancer type

| Cancer type | Clinical presentation or diagnosis | Pathogen(s) |
|---|---|---|
| Adult hematologic malignancies | Paronychia, subcutaneous nodules, abscesses, folliculitis, ulcers, and eschars | *Aspergillus, Mucor, Rhizopus, Fusarium,* and Phaeohyphomycosis |
| | Vesicles in a dermatomal distribution | Varicella zoster virus |
| | Clusters of vesicles | Herpes simplex types 1 and 2 |
| | Erythematous, tender plaques, papules, or subcutaneous nodule (skin and soft tissue infections) | *Staphylococcus aureus* |
| | | *Cryptococcus neoformans* |
| | | *Toxoplasma gondii* |
| | | *Acanthamoeba* |
| | | Cytomegalovirus |
| | Intertrigo, rash, vaginitis, balanitis, and paronychia | *Candida albicans, Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis, and Candida lusitaniae* |
| Cutaneous T-cell lymphoma/Sezary syndrome | Erythematous, tender plaques, papules, or subcutaneous nodule (skin and soft tissue infections) | *Staphylococcus aureus* |
| Pediatric hematologic malignancies | Erythematous, tender plaques, papules, or subcutaneous nodule (skin and soft tissue infections) | *Corynebacterium bovis and Corynebacterium jeikeium* |
| | Metastatic cellulitis and mucocutaneous ulcers | *Stenotrophomonas maltophilia* |
| Pediatric solid tumors | Skin and soft tissue infection | *Mycobacterium* spp. *and Corynebacterium* spp. |
| Pediatric brain tumors | Skin and soft tissue infection | *Corynebacterium aquaticum* |
| Adult solid tumor | Erythematous, tender plaques, papules, or subcutaneous nodule (skin and soft tissue infections) | *Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa* |
| | Erythematous, tender plaques, papules, or subcutaneous nodule (skin and soft tissue infections) | *Staphylococcus aureus* |
| | Neutrophilic eccrine hidradenitis | *Serratia marcescens, Staphylococcus aureus, and Enterobacter cloacae* |
| | Intertrigo, rash, vaginitis, balanitis, and paronychia | *Candida albicans, Candida tropicalis,Candida glabrata, Candida krusei, Candida parapsilosis, and Candida lusitaniae* |

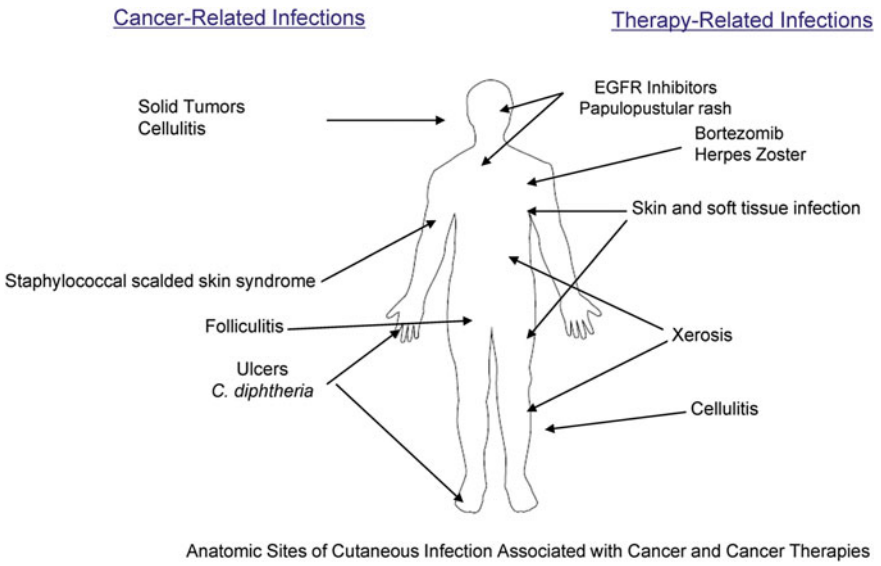


**Fig. 1** Anatomical classification of cutaneous infection associated with cancer and cancer therapies

## 2 Bacterial Dermatologic Infections

### 2.1 Gram-Positive Infections

#### 2.1.1 *Staphylococcus aureus* Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTI) comprise 85–95 % of all infections caused by *Staphylococcus aureus* in the community [2, 3]. Notably, presence of an underlying malignancy is an independent risk factor for skin and soft tissue staphylococcal infection [2]. It has been demonstrated that 23 % of all bacteremic episodes seen in cancer patients are caused by *S. aureus*, and SSTI are the source in 60 % of cases, with only 6 % associated with granuloctyopenia [2, 4]. Conversely, staphylococcal scalded skin syndrome (SSSS), which is characterized by an acute, generalized exfoliation of the skin following erythematous plaques, has rarely been reported in the oncology setting, with only one case of a patient with T-lymphoblastic non-Hodgkin's lymphoma. The two epidermolytic exotoxins, exfoliatins A and B, which are synthesized by *S. aureus*, are proteases that cleave desmoglein 1, resulting in epidermal detachment between the stratum granulosum and the stratum spinosum. Whereas SSSS is rare in adults with cancer, it can occur in immunocompromised patients and those with renal disease [5].

Of 709 adult and pediatric patients having undergone allogenic stem cell transplantation (SCT), the incidence of late (occurring greater than 50 days post-

transplant) *S. aureus* bacteremia was found to be 6/100,000 patient-days [6]. Of the patients who developed bacteremia, 84 % were community acquired and 40 % were secondary to a focal infection. Risk factors for late *S. aureus* bacteremia included acute or chronic skin graft vs. host disease, corticosteroid use, liver dysfunction, and prolonged hospital stay. Based on this analysis, prophylactic anti-staphylococcal antibiotics can be advocated in the high-risk allogeneic stem cell transplant patients set forth previously [6].

*S. aureus* is a known colonizer of the nares, axilla, and intertriginous, inguinal, and perineal areas. In healthy adults, carrier rates are approximately 11–32 % [7]. Of 106 patients with mycosis fungoides (MF) and Sezary syndrome (SS), 42 % had cultures positive for *S. aureus* with 5 % of the cultures being positive for methicillin-resistant *S. aureus* (MRSA). The *S. aureus* skin colonization rate in MF/SS patients (42 %) was found to be higher than the 28 % reported in the general population and lower than that found in patients with psoriasis (48 %) [7]. Antibiotic therapy and sodium hyperchlorite baths [8] results in partial clearance of *S. aureus* colonization, both of which are noteworthy observations, as bacteremia and bacterial pneumonia are the most common causes of death in patients with MF and SS [7, 9]. In addition, *S. aureus* colonization in patients with cutaneous T-cell lymphoma (CTCL) was found to be directly related to a small increase in body surface area of CTCL involvement ($P = 0.05$) [8]. Increased rates of infection in these patients are hypothesized to occur as a result of an impaired skin barrier as well as a decrease in the function of normal circulating T cells, resulting in immunosuppression [8]. Infrequently, other organisms found in the skin and nares of such patients can include group B B-hemolytic *Streptococcus, Propionibacterium acnes, Bordetella, Haemophilus, Enterococcus, Escherichia coli, Pseudomonas, Serratia marcescens,* and *Pantoea agglomerans* [7].

### 2.1.2 Corynebacteria Infections: Non-healing Ulcers

*Corynebacterium* species are normal skin flora, but in the immunocompromised host, these gram-positive bacteria can be pathogenic due to higher colonization rates and increased antibiotic resistance [10]. *Corynebacterium diphtheriae* can cause painful, non-healing skin ulcers. Initially, lesions are vesicular, but with time, they become punched out and may become covered by an eschar [10].

In a case series of 16 pediatric oncology patients, five had skin and soft tissue infections caused by *C. diphtheriae*, three were central venous catheter associated, and two involved post-surgical wound sites. Of those with infections, three of the children had solid tumors and the remaining two had a hematologic malignancy, and all presented with soft tissue inflammation and fever. After initiation of antibiotic therapy, symptoms resolved within a median time of 48 h [11]. Notably, infection with *Corynebacterium* occurs late in the course of anti-cancer therapy and patients may develop symptoms as outpatients.

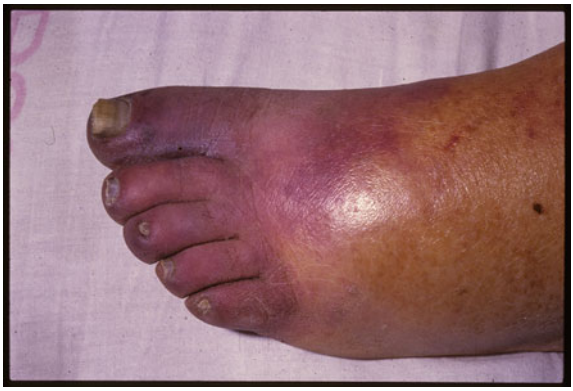

**Fig. 2** Gram-negative cellulitis infection

## 2.2 Gram-Negative Skin and Soft Tissue Infections

### 2.2.1 Cellulitis and Wound Infections

In 772 hospitalized patients with both leukemic and solid tumors, 185 gram-negative bacterial isolates were found at sites of skin infection. Over half (64.5 %) of the gram-negative nosocomial infections in solid tumor patients affected their skin and included pathogens including *Klebsiella pneumonia* (25.4 %), *E. coli* (22.2 %), *and Pseudomonas aeruginosa* (18.9 %) (Fig. 2) [12]. In contrast, no gram-negative isolates were found in leukemic patients. Treatment of nosocomial gram-negative skin and soft tissue infections are based on cultures and antimicrobial sensitivities [12].

### 2.2.2 Neutrophilic Eccrine Hidradenitis

Neutrophilic eccrine hidradenitis (NEH), or inflammation of the excretory ducts of eccrine (sweat) glands, may occur as a result of therapy with cytosine arabosinide and granulocyte colony-stimulating factor [13] or secondary to bacterial infection (e.g., *S. aureus, Enterobacter cloacae, S. marcescens).* Clinically, NEH presents as crops of small, indolent, erythematous papules located on legs, thighs, and abdomen. Skin histology reveals focal necrosis of eccrine secretory coils extending to the excretory ducts with a neutrophilic infiltrate [13]. In cases where infection is the culprit, pathogenic microorganisms are also identified through gram stain and/or culture. When an infectious origin is identified, treatment with antibiotics is indicated, and topical corticosteroids are indicated when caused by cytotoxic chemotherapy.

### 2.2.3 *Stenotrophomonas maltophilia* Skin Infection

*Stenotrophomonas maltophilia* is an aerobic, gram-negative bacterium which is ubiquitous in aqueous environments, including water, urine, or respiratory secretions. It has been implicated in the cause of multiple SSTI in cancer patients including primary cellulitis, nodular skin lesions, gangrenous cellulitis, soft tissue necrosis, ecthyma gangrenosum, and mucocutaneous ulcers [14]. *S. maltophilia*

frequently colonizes breathing devices such as endotracheal or tracheostomy tubes, the respiratory tract, and indwelling urinary or intravenous catheters. Metastatic cellulitis is a form of cellulitis with tender, nodular, erythematous, and warm subcutaneous infiltrates surrounded by areas of skin inflammation usually located on limbs and chest [14]. Primary cellulitis is characterized by widespread tender erythema without distinct borders. Mucocutaneous infections with *S. maltophilia* have been reported in association with neutropenia, immunosuppression, prolonged hospital stay, intravenous catheter use, broad-spectrum antibiotics, and hematologic malignancies [14]. Clinical findings include ulceration of gingiva, lips, and buccal mucosa. Recommended treatment is trimethoprim–sulfamethoxazole, ticarcillin–clavulanate, or fluoroquinolones based on the results of antimicrobial susceptibility testing, but prognosis can be poor due to severe underlying immunosuppresion [14, 15].

## 3 Fungal Dermatologic Infections

There are two types of cutaneous fungal infections: primary, which develop *de novo* at a cutaneous site, and secondary which are caused by hematogenous spread of a fungal pathogen [16–18]. Neutropenic patients, especially those with leukemia and lymphoma who have undergone a SCT, are at highest risk to develop cutaneous fungal infections [16].

### 3.1 Cutaneous Candidiasis

In the majority of cancer patients, cutaneous candidiasis does not differ in presentation between the immunocompromised and immunocompetent host. Common manifestations include intertrigo, rash, vaginitis, balanitis, and paronychia [16]. For identification by light microscopy, a scraping or swab of the affected area is placed on a slide with 10 % potassium hydroxide (KOH) solution and specimens will show a deep dermal and subcutaneous necrosis accompanied by acute neutrophilic inflammation. Infectious organisms can be seen on routine hematoxylin–eosin (H and E); but cultures are recommended to confirm presence of pathogen.

Cutaneous candidiasis is caused by 13 different candidal species, including *Candida albicans, Candida tropicalis, Candida glabrata, Candida krusei, Candida parapsilosis,* and *Candida lusitaniae*, with *C. albicans* accounting for over half of the isolates recovered from infected patients. However, recent epidemiological data reveal a shift from *C. albicans* to the non-*albicans Candida* species, specifically *C. glabrata* and *C. krusei* [19]. Clinically, superficial pustules and vesicles are evidenced, and histology shows pseudohyphae and hyphae in the stratum corneum [19]. Patients with solid tumors, acute leukemia, and hematological cancer patients on antifungal prophylaxis are at significant risk for non-*albicans* candidemia and subsequent cutaneous infection [19].

## 3.2 Cutaneous Cryptococcal Infection

There are two forms of cutaneous cryptococcal infection: primary cutaneous cryptococcosis and cutaneous manifestation due to hematogenous dissemination, also known as secondary cutaneous cryptococcosis [20]. Clinically, a tender patch or plaque with ulceration, typically on an extremity, is observed, with regional lymphadenopathy. Risk factors include hematologic malignancies, especially when corticosteroids and polychemotherapy is being administered; however, granulocytopenia is the greatest risk factor for fungal infection [20]. Secondary cutaneous cryptococcosis is seen in 10–20 % of cases of systemic disease, which is most often caused by hematogenous spread of *Cryptococcus neoformans* after pulmonary inoculation. The skin is involved in 10–20 % of cases [20]. Diagnosis is achieved after identifying *C. neoformans* on biopsy, culture, or histological examination showing the spherical budding yeast within edema and a polymorphous inflammatory infiltrate [21]. Treatment consists of a course lipid-based amphotericin therapy or oral fluconazole, but in severe cases, life-long maintenance therapy is required. Risk factors are multiple and include the following: coexisting HIV infection, corticosteroid therapy, malignancy, autoimmune disease, and immune system disorder with CD4+ lymphopenia [21].

## 3.3 Opportunistic Cutaneous Fungal Infections

*Aspergillus, Mucor, Rhizopus,* and *Fusarium* are opportunistic fungi that are responsible for primary cutaneous infections in hospitalized neutropenic patients. Intravenous catheters, prolonged use of corticosteroids, and occlusive dressings contribute to these uncommon infections (Fig. 3) [16]. The opportunistic fungal pathogens can cause a variety of cutaneous lesions, including paronychia, subcutaneous nodules, abscesses, and folliculitis. Fungal paronychia presents with inflammation surrounding the nail plate accompanied by pain. *Fusarium* and *Aspergillus* can cause digital eschars after minor trauma to the digit [16, 22]. Eschars and ulcers can also occur on lower extremities and sites of venous stasis. Diagnosis is confirmed with skin biopsy; positive culture alone does not confirm the presence of an infection. Primary skin infection leading to hematogenous dissemination is rare but is associated with mortality. In a case series of 35 adult cancer patients who developed *Fusarium* skin lesions, the following hazards and physical findings were identified: hematologic malignancy, severe neutropenia, digital paronychia, presence of digital eschar, and disseminated skin lesions [23, 24]. Treatment for cutaneous lesions is with prolonged, systemic antifungal therapy. For the majority, disseminated mold infections are fatal unless neutropenia improves. In these instances, granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor, white blood cell transfusions, and interferon-$\gamma$ may provide some benefit [16].

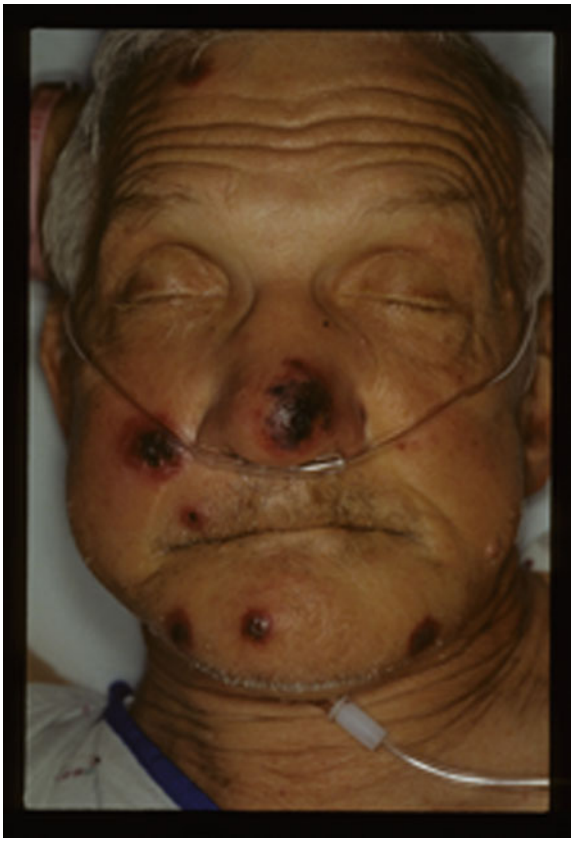

**Fig. 3** Cutaneous *Mucor* infection

Phaeohyphomycosis is a rare opportunistic infection that is responsible for affecting various organs including skin, as well as causing invasive disease. From January 1989 through March 2008 at MD Anderson Cancer Center, 348 isolates of dematiaceous fungi were recovered in a retrospective analysis, and in 39 isolates (11 %) identified in 39 patients, an association with proven or probable invasive fungal disease (33 proven and six probable) was determined, and interestingly, the burden of disease increased from 1.0 to 3.0 cases per 100,000 patient-days during this 10-year period. Fifteen cases (38 %) were localized to the skin. Notably, many of these fungal isolates were not susceptible to either voriconazole or caspofungin [25]. Major risk factors for infection included the following: hematologic malignancy, anti-cancer treatment with induction chemotherapy, and subsequent neutropenia and lymphopenia [25]. Clinically, subcutaneous nodules, eschar, ulcers, and cellulitic lesions are present and gomori metheamine silver stain can aid in identification of fungal pathogen on skin histology [25]. Recommended management is with amphotericin B-based therapy combined with a triazole [25].

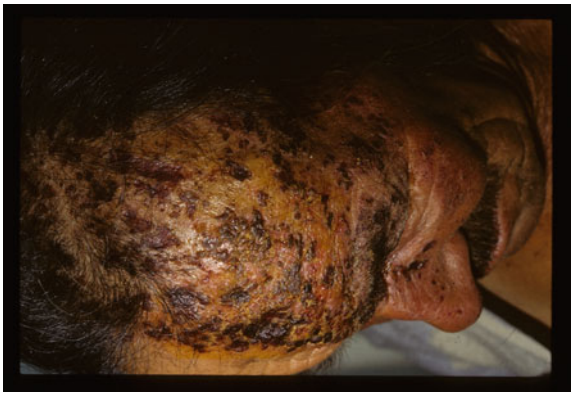

**Fig. 4** Disseminated herpes zoster infection

## 4 Viral Dermatologic Infections

### 4.1 Varicella Zoster Virus

Varicella zoster virus infection in skin (VZV) occurs in approximately 30 % of allogeneic hematopoietic SCT [26] between 2 and 6 months after transplant (Fig. 4) [27]. Clinical significance of VZV infection lies in significant pain, post-herpetic neuralgia, scarring, and secondary infection [26]. Without appropriate treatment, disseminated VZV infection results in mortality in 10 % of patients with leukemia and/or allogenic SCT recipients [27].

In a retrospective analysis of 760 adult cancer patients with 766 episodes of a VZV, the highest risk for zoster was seen in patients with leukemia and lymphoma [28]. The presence of active tumor during the period of infection was associated with increased risk of VZV dissemination [28]. The median time to infection after therapy was 7 months post-radiation and less than 1 month post-chemotherapy [28]. In a cohort of 1,186 patients undergoing bone marrow transplantation (BMT), the following risk factors were identified: age >10 years, radiation pre-BMT, and VZV seropositivity. These variables were associated with a 44 % incidence by 3 years [29].

The use of prophylactic acyclovir, 800 mg twice daily given for 1 year post-transplantation has been found to be safe and highly effective in preventing VZV infection. Of the 38 subjects on acyclovir, only 2 (5 %) developed VZV disease compared to ten out of 39 in the placebo group (26 %). Graft versus host disease (GVHD) was also present in 82 % of those who developed VZV. However, GVHD is not an independent risk factor for development of VZV infection, as it can also occur in allogenic hematopoietic SCT recipients without GVHD as well as in autologous transplant recipients [26].

Regarding treatment, varicella-zoster immunoglobulin (VZIG) should be considered post-exposure in seronegative patients, at a dose of 12.5 units/kg or up to 625 units one time. If VZIG is unavailable within 96 h of exposure, then 400 mg/kg of standard intravenous immunoglobulin (IVIG) should be administered [27]. For treatment of acute zoster pain and post-herpetic neuralgia, tricyclic and anticonvulsant medications are recommended. The role of opiates in this setting has shown variable efficacy and is associated with more side effects [30].

## 4.2 Herpes Simplex Virus 1 and 2

Reactivation of herpes simplex virus (HSV-1 and HSV-2) after hematopoietic SCT occurs frequently and is most often associated with the underlying malignancy, mucosal damage, neutropenia, and lymphopenia. Reactivation occurs within the first few weeks after transplant with lesions most often presenting on mucocutaneous sites. In patients undergoing chemotherapy for leukemia, rates of reactivation are between 3 and 33 % [27]. Treatment with purine analogs or alemtuzumab and CD4 cell count less than 50 cells/mL increases the risk for infection [27].

Prophylaxis with anti-viral medication (i.e., acyclovir, valacyclovir) is strongly recommended for all seropositive SCT recipients from conditioning to 4 weeks post-transplant [27]. In high-risk leukemic patients receiving purine analogs or alemtuzumab and those with prolonged neutropenia prophylaxis is also recommended.

## 4.3 Cutaneous Cytomegalovirus Infection

Cutaneous cytomegalovirus (CMV) infection is rare even in the immunocompromised host. Typical CMV infection affects the eyes, central nervous system, gastrointestinal tract, and lung [31]. Cutaneous CMV can present non-specifically and must be considered in the immunocompromised cancer patient. A rare case reported in the literature describes an immunocompromised female with multiple red-brown papules located on upper and lower extremities and trunk accompanied by perianal ulceration, fevers, and weakness. Initial differential diagnosis included folliculitis, bacillary angiomatosis, and eosinophilic folliculitis. Biopsy with immunohistochemistry stains showing intranuclear inclusions confirmed cutaneous CMV; serologic studies showed high anti-CMV IgG titers with normal IgM [31].

Clinical appearance of lesions can be extremely variable including generalized macules and papules, vesicles, plaques, and/or nodules. It is hypothesized that cutaneous CMV may be a form of CMV microvasculitis. Recommended treatment is intravenous ganciclovir 5 mg/kg twice daily, valganciclovir 900 mg twice daily, or foscarnet 90 mg/kg every 12 h.

## 5 Cutaneous Parasitic Infection

### 5.1 Cutaneous Toxoplasmosis

Toxoplasmosis is a rare but fatal infection that can occur after SCT [32]. Skin histology reveals dermal edema, extravasated erythrocytes, necrotic collagen, and small cysts containing parasites within the epidermis, skin appendages, and endothelial cells in the dermis [32]; *Toxoplasma gondii* presence in skin can be confirmed by PCR.

Cutaneous toxoplasmosis has been reported in two cases following SCT. This presentation is rare, but there is an increased risk with development of GVHD and use of corticosteroids. If small parasite-containing cysts are seen in histology, then special staining and PCR should be performed to confirm diagnosis.

### 5.2 Cutaneous Acanthamoeba Infection

*Acanthamoeba* are free-living ameba that lives in the water and soil. In immunocompromised hosts, the most common manifestation of disease is subacute meningoencephalitis [33]. Skin lesions have rarely been reported, as in a patient with acute lymphocytic leukemia who developed extensive GVHD and became septic, with papular, ulcerative lesions on his face and extremities; histology of these sites confirmed presence of *Acanthamoeba*, despite being on prophylactic therapy with voriconazole. The patient was started on liposomal amphotericin B (5 mg/kg) daily in combination with trimethoprim–sulfamethoxazole (5 mg/kg of the trimethoprim component) every 8 h, but patient expired 5 weeks after diagnosis. Risk factors for development of this infection include: solid organ transplantation, connective tissue disease, diabetes, cirrhosis, renal failure, malignancy, and tuberculosis [33].

## 6 Dermatologic Infections from Anti-cancer Therapies

The effect of anti-cancer therapies on the systemic and cutaneous immune system, as well as on the structural and functional integrity of skin and nails, results in increased susceptibility of infections.

## 7 Cyototoxic or Targeted Therapy-Related Infections

Nowhere is the structural integrity of skin consistently in greater disarray and then with the use of epidermal growth factor receptor inhibitors (EGFRI), agents used to treat solid organ malignancies including those of the breast, lung, head and neck, and colon and rectum. The use of these drugs leads to a papulopustular rash,

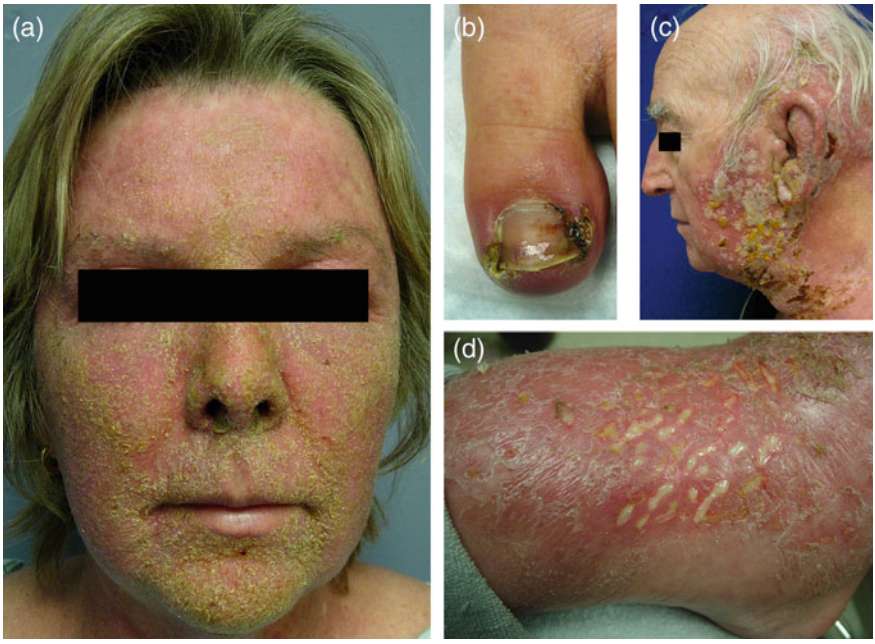


**Fig. 5** **a** Papulopustular rash with secondary infection. **b** Paronychia. **c** Herpes zoster. **d** Xerosis with secondary infection

xerosis, paronychia, and hair abnormalities (Fig. 5). Cutaneous toxicities can be severe and lead to dose modification by 72–76 % of oncologists [34].

In a case series of 221 patients being treated with EGFRI, 29 % were secondarily infected at sites of dermatoxicity. Sixty-four patients had bacterial infections, and of those, 50 patients (78 %) were positive for *S. aureus,* four patients (6.3 %) cultured positive for *MRSA*, and 14 (21.9 %) cultured positive for other bacteria including *P. aeruginosa, S. marcescens, Enterococcus faecalis, and Klebsiella pneumoniae*. Of the 84 patients with dermatologic infection during EGFRI therapy, twenty-three had fungal infections [35]. The incidence of secondary herpetic infection was found to be 13 %. Seven of these patients developed herpes simplex infections, and four had herpes zoster while on EGFRI treatment. The data suggest that those with neutropenia and preexisting dermatoxicity are at a higher risk for developing secondary infection [35].

In multiple clinical trials [36], bortezomib has been shown to be associated with an increased risk of VZV infection in myeloma patients [37]. Rituximab, a monoclonal antibody used to treat B-cell non-Hodgkin's lymphoma, and temozolomide, an alkylating agent for solid tumors, have also been linked to VZV [38, 39]. The etiology for zoster development may be due to B-cell suppression and lymphopenia, but, notably, 400 mg acyclovir daily prophylactically has been shown to decrease incidence of disease [37].

Arsenic trioxide, used for the treatment of acute promyelocytic leukemia, lymphoma, myeloma, and other myeloproliferative disorders, has been linked to many dermatologic conditions including the following: pigmentation, keratosis, squamous cell carcinoma, and reactivation of herpes zoster [40]. In a study of 44 patients taking arsenic for hematologic malignancy, 11 developed VZV reactivation. At 1 year, actuarial risk was 26 % [40].

## 8 Radiation Therapy

Radiation therapy (RT) has been shown to decrease systemic host defense and compromise skin barrier function, leading to local invasion by colonizing pathogens [41–43]. In the oral cavity, RT results in proliferation of basal epithelial cells, causing atrophy and tissue edema largely contributing to development of systemic infection which can complicate therapy [41]. In skin, most of the post-radiation wounds are colonized with bacteria, including staphylococci and streptococci, which produce exogenous erythrotoxins or plasmid containing superantigens that cause severe skin inflammation leading to toxicity [44–46]. Superinfected radiation dermatitis presents with increased erythema and often times micropustules (Fig. 6) [46]. Current management includes culturing the pustule and initiation of appropriate oral antibiotic and topical mupirocin to lesions and nares [46].

It is interesting to note a case of Kaposi's varicelliform eruption in a patient being treated with electron beam radiation for MF. After receiving 500 cGy, the patient developed numerous 2–3-mm vesicles, pustules, yellow-crusted erosions, and hemorrhagic erosions on preexisting MF plaques. The patient was treated successfully with intravenous acyclovir, and RT was stopped indefinitely [47].

Radiation therapy also has been associated with the development of scabies infection in an 86-year-old patient with history of SS. It is hypothesized that RT significantly diminishes the number of Langerhans cells in the chest skin, allowing for increased susceptibility to scabies infection [48].

## 9 Lymphedema

Lymphedema is among the most frequent and clinically significant complications of breast cancer therapy; the reported incidence varies between 4 and 56 % [49]. Repeated episodes of lymphedema-associated infection require treatment with antibiotics and in severe cases necessitate hospitalization for parenteral antibiotic therapy.

A major contributing factor to lymphedema-associated infections is the alteration of lymphatic circulation (i.e., lymphatic stasis) secondary to radiotherapy and/or lymphadenectomy. Erysipelas is a soft tissue infection due to streptococci that affects the dermis and dermal lymphatic system [50, 51]. On clinical examination,

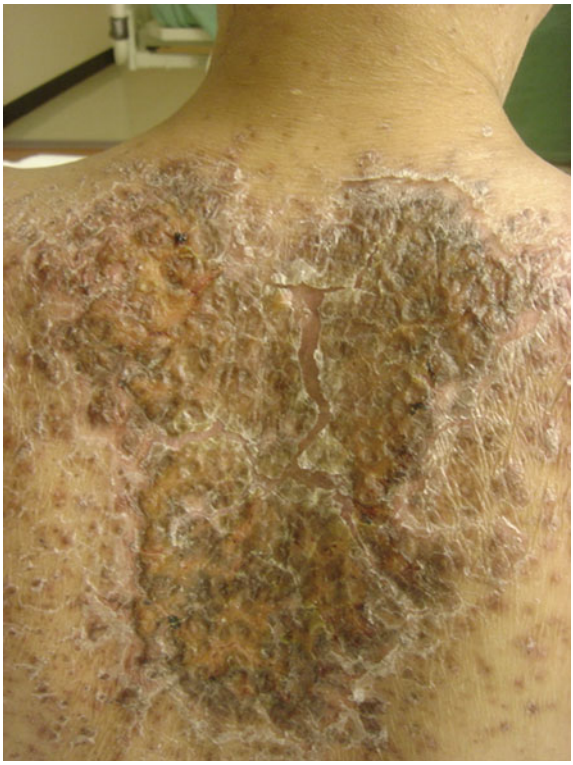

**Fig. 6** Radiation dermatitis with secondary superinfection

warm indurated plaques with painful erythema are observed, which can mimic cutaneous metastasis [50], especially in immunosuppressed patients [51]. Portals of infection in 26 patients with lymphedema-associated erysipelas included post-traumatic wounds (16 patients), post-radiotherapy burns (3 patients), interdigital tinea (2 patients), infected eczema (1 patient), paronychia (1 patient), and herpetic whitlow (1 patient). Prophylactic intramuscular penicillin has been shown to decrease the rate of recurrent lymphedema-associated erysipelas in 48 patients, 66 % of whom did not experience recurrence during the first 2 years of prophylactic therapy [50]. Currently, there are no set guidelines for when prophylactic therapy should be initiated. However, if there is a known high risk of erysipelas, then therapy should be initiated prior to the first or second reoccurrence [50].

## 10 Subcutaneous Ports

Subcutaneous ports are frequently applied in oncology patients for the administration of chemotherapy and acquisition of blood samples. As foreign bodies and in the setting of a relative immunosuppresion, they can become a culprit for infections. Cutaneous flora can colonize the external catheter insertion site and

travel along the exterior of the catheter (extraluminal) or directly along inside of the lumen (endoluminal), reaching the blood stream [52, 53]. Extraluminal catheter-related bloodstream infection (CRBI) occurs primarily during this first week of insertion, whereas endoluminal CRBI tends to occur later and is attributable to catheter manipulation and use [52].

In a case series of 41 subjects with totally implanted venous access device, the incidence of positive skin and blood cultures was examined and related to development of CRBI [52]. Blood and cutaneous ($n = 163$) cultures were obtained. Four (2.5 %) positive blood cultures which yielded *Staphylococcus simulans, Staphylococcus capitis, and S. aureus* were obtained ($n = 3$ subjects) [52]. In contrast, those with negative blood cultures did not develop CRBI. In 11 subjects, there was bacterial colonization surrounding the device's surgical wound without sign of cutaneous infection. The greatest risk of infection is during the period shortly after insertion, but there is no correlation between risk of infection and perioperative use of antibiotics or frequency of port use [54, 55]. The most common infective pathogens include *S. aureus, Staphylococcus epidermidis, Klebsiella, E. coli, C. albicans,* and *Aspergillus* [54]. In regard to management, it is recommended to treat with appropriate antibiotics per culture and sensitivities [54].

## 11 Summary

Dermatologic infections generally occur more frequently in the setting of neutropenia, but can occur at any time point in oncology patients. Bacterial, fungal, viral, and parasitic skin infections are highly prevalent and necessitate early recognition and management, as they can lead to severe and sometimes fatal complications. Best clinical practice dictates culture and sensitivity when infection is suspected and prior to initiation of antimicrobial therapy. Anti-cancer therapy should also be recognized as a potential hazard for increasing the risk of skin infection.

## References

1. Polsky B, Armstrong D (1985) Infectious complications of neoplastic disease. Am J Infect Control 13(5):199–209
2. Trilla A, Miro JM (1995) Identifying high risk patients for *Staphylococcus aureus infections*: Skin and soft tissue infections. J Chemother 7(3):37–43
3. Miller LG, Kaplan SL (2009) *Staphylococcus aureus*: a community pathogen. Infect Dis Clin North Am 23(1):35–52
4. Carney DN, Fossieck BE Jr, Parker RH, Minna JD (1982) Bacteremia due to *Staphylococcus aureus* in patients with cancer: report on 45 cases in adults and review of the literature. Rev Infect Dis 4(1):1–12
5. Scheinpflug K, Schalk E, Mohren M (2008) Staphylococcal scalded skin syndrome in an adult patient with T-lymphoblastic non-Hodgkin's lymphoma. Onkologie 31(11):616–619 Epub 2008 Oct 27

6. Mihu CN, Schaub J, Kesh S, Jakubowski A et al (2008) Risk factors for late Staphylococcus aureus bacteremia after allogeneic hematopoietic stem cell transplantation: a single-institution, nested case-controlled study. Biol Blood Marrow Transplant 14(12):1429–1433
7. Talpur R, Bassett R, Duvic M (2008) Prevalence and treatment of Staphylococcus aureus colonization in patients with mycosis fungoides and Sezary syndrome. Br J Dermatol 159(1):105–112 Epub 2008 Jul 1
8. Nguyen V, Huggins R, Lertsburapa T, Bauer K et al (2008) Cutaneous T-cell lymphoma and Staphylococcus aureus colonization. J Am Acad Dermatol 59(6):949–952 Epub 2008 Oct 2
9. Tsambiras PE, Patel S, Greene J et al (2001) Infectious complications of cutaneous T-cell lymphoma. Cancer Control 8:185–188
10. Frassetto LA (2009) Corynebacterium Infections. http://emedicine.medscape.com/article/215100-overview. 22 April 2009
11. Adderson EE, Boudreaux JW, Hayden RT (2008) Infections caused by coryneform bacteria in pediatric oncology patients. Pediatr Infect Dis J 27(2):136–141
12. Ashour HM, El-Sharif A (2009) Species distribution and antimicrobial susceptibility of gram-negative aerobic bacteria in hospitalized cancer patients. J Transl Med 19(7):14
13. Combemale P, Faisant M, Azoulay-Petit C, Dupin M et al (2000) Neutrophilic eccrine hidradenitis secondary to infection with *Serratia marcescens*. Br J Dermatol 142(4):784–788
14. Teo WY, Chan MY, Lam CM, Chong CY (2006) Skin manifestation of Stenotrophomonas maltophilia infection–a case report and review article. Ann Acad Med Singapore 35(12):897–900
15. Moser C, Jonsson V, Thomsen K, Albrectsen J et al (1997) Subcutaneous lesions and bacteremia due to *Stenotrophomonas maltophilia* in three leukemic patients with neutropenia. Br J Dermatol 136:949–952
16. Mays SR, Bogle MA, Bodey GP (2006) Cutaneous fungal infections in the oncology patient: recognition and management. Am J Clin Dermatol 7(1):31–43
17. Quatresooz P, Piérard-Franchimont C, Arrese JE et al (2008) Clinicopathologic presentations of dermatomycoses in cancer patients. J Eur Acad Dermatol Venereol 22(8):907–917 Epub 2008 May 23
18. Nucci M, Pulcheri W, Spector N et al (1992) Cutaneous involvement of systemic fungal infections in neutropenic patients. Haematologica 77(6):522–523
19. Gugic D, Cleary T, Vincek V (2008) Candida glabrata infection in gastric carcinoma patient mimicking cutaneous histoplasmosis. Dermatol Online J 14(2):15
20. Devirgiliis V, Panasiti V, Borroni RG, Rossi M et al (2008) Cutaneous cryptococcosis in a patient affected by chronic lymphocytic leukaemia: a case report. Int J Immunopathol Pharmacol 21(2):463–466
21. Courville P, Favennec L, Viacroze C, Barrel A et al (2002) Co-existent cutaneous cryptococcosis of the forearm and cutaneous alternariosis of the leg in patient with metastatic thymoma. J Cutan Pathol 29(1):55–58
22. D'Antonio D, Pagano L, Girmenia C et al (2000) Cutaneous aspergillosis in patients with haematological malignancies. Eur J Clin Microbiol Infect Dis 19(5):362–365
23. Bodey GP, Boktour M, Mays S et al (2002) Skin lesions associated with Fusarium infection. J Am Acad Dermatol 47(5):659–666
24. Musa MO, Al Eisa A, Halim M et al (2000) The spectrum of Fusarium infection in immunocompromised patients with haematological malignancies and in non-immuno compromised patients: a single institution experience over 10 years. Br J Haematol 108(3):544–548
25. Ben-Ami R, Lewis RE, Raad II, Kontoyiannis DP (2009) Phaeohyphomycosis in a tertiary care cancer center. Clin Infect Dis 48(8):1033–1041
26. Boeckh M, Kim HM, Flowers MED, Meyers JD et al (2006) Long-term acyclovir for prevention of varicella zoster virus disease after allogenic hematopoietic cell transplantation-a radndomized double-blind placebo-controlled study Blood. 107(5):1800–1805

27. Angarone M, Ison MG (2008) Prevention and early treatment of opportunistic viral infections in patients with leukemia and allogeneic stem cell transplantation recipients. J Natl Compr Canc Netw 6(2):191–201
28. Rusthoven JJ, Ahlgren P, Elhakim T et al (1988) Varicella-zoster infection in adult cancer patients. A Popul Study Arch Intern Med 148(7):1561–1566
29. Han CS, Miller W, Haake R et al (1994) Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. Bone Marrow Transplant 13(3):277–283
30. Niscola P, Perrotti AP, del Poeta G et al (2007) Case reports: zoster pain in haematological malignancies: effective pain relief with oxycodone in patients unresponsive to other analgesic measures. Herpes 14(2):45–47
31. Abdull Gaffar B, Raman LG, Al Muala A (2008) Cutaneous cytomegalovirus infection in a patient with acquired immunodeficiency syndrome. Int J Dermatol 47(9):944–946
32. Amir G, Salant H, Resnick IB, Karplus R (2008) Cutaneous toxoplasmosis after bone marrow transplantation with molecular confirmation. J Am Acad Dermatol 59(5):781–784 Epub 2008 Aug 23
33. Kaul DR, Lowe L, Visvesvara GS, Farmen S et al (2008) Acanthamoeba infection in a patient with chronic graft-versus-host disease occurring during treatment with voriconazole. Transpl Infect Dis 10(6):437–441 Epub 2008 Aug 13
34. Boone SL, Rademaker A, Liu D et al (2007) Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. Oncology. 72(3–4):152–159 Epub 2007 Dec 21
35. Eilers RE, West DP, Ortiz S, Witherspoon JN, Lacouture ME (2009) Dermatologic infections complicate epidermal growth factor receptor inhibitor (EGFRI) therapy in cancer patients. *J Am Acad Dermatol,* 60(3)(Suppl 1):AB3
36. Chanan-Khan A, Sonneveld P, Schuster MW et al (2008) Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 26(29):4784–4790 Epub 2008 Aug 18
37. Vickrey E, Allen S, Mehta J et al (2009) Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. Cancer 115(1):229–232
38. Aksoy S, Harputluoglu H, Kilickap S et al (2007) Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 48(7):1307–1312
39. Schwarzberg AB, Stover EH, Sengupta T et al (2007) Selective lymphopenia and opportunistic infections in neuroendocrine tumor patients receiving temozolomide. Cancer Invest 25(4):249–255
40. Au WY, Kwong YL (2005) Frequent varicella zoster reactivation associated with therapeutic use of arsenic trioxide: portents of an old scourge. J Am Acad Dermatol 53(5):890–892
41. Khan SA, Wingard JR (2001) Infection and mucosal injury in cancer treatment. J Natl Cancer Inst Monogr 29:31–36
42. Brook I (1988) Use of antibiotics in the management of postirradiation wound infection and sepsis. Radiat Res 115(1):1–25
43. Hughes LL, Styblo TM, Thoms WW et al (1997) Cellulitis of the breast as a complication of breast-conserving surgery and irradiation. Am J Clin Oncol 20(4):338–341
44. Mak SS, Yuen ML, Li C et al (2006) Exploratory analysis of the bacteriological status of post-irradiation wounds and its relationship to healing. Clin Oncol R Coll Radiol 18(7):519–524
45. Johnson LB, Jorgensen LN, Adawi D et al (2005) The effect of preoperative radiotherapy on systemic collagen deposition and postoperative infective complications in rectal cancer patients. Dis Colon Rectum 48(8):1573–1580
46. Hill A, Hanson M, Bogle MA et al (2004) Severe radiation dermatitis is related to Staphylococcus aureus. Am J Clin Oncol 27(4):361–363

47. Smith BD, Son CB, Wilson LD (2003) Disseminated herpes simplex after total skin electron beam radiotherapy for mycosis fungoides. J R Soc Med 96(10):500–501
48. McGregor DH, Yang Q, Fan F et al (2001) Scabies associated with radiation therapy for cutaneous T-cell lymphoma. Ann Clin Lab Sci 31(1):103–107
49. Shih YC, Xu Y, Cormier JN, Giordano S et al (2009) Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. J Clin Oncol 27(12):2007–2014 Epub 2009 Mar 16
50. Vignes S, Dupay A (2006) Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study. J Eur Acad Dermatol Venereol 20(7):818–822
51. Masmoudi A, Maaloul I, Turki H, Elloumi Y et al (2005) Erysipelas after breast cancer treatment 26 cases. Dermatol Online J 11(3):12
52. Laurenzi L, Natoli S, Benedetti C et al (2004) Cutaneous bacterial colonization, modalities of chemotherapeutic infusion, and catheter-related bloodstream infection in totally implanted venous access devices. Support Care Cancer 12(11):805–809
53. Schwarz RE, Groeger JS, Coit DG (1997) Subcutaneously implanted central venous access devices in cancer patients: a prospective analysis. Cancer 79(8):1635–1640
54. Ballarini C, Intra M, Pisani Ceretti A et al (1999) Complications of subcutaneous infusion port in the general oncology population. Oncology. 56(2):97–102
55. Brothers TE, Von Moll LK, Niederhuber JE et al (1988) Experience with subcutaneous infusion ports in three hundred patients. Surg Gynecol Obstet 166:295–301

# Infections in Patients with Leukemia and Lymphoma

Vicki A. Morrison

**Abstract**

Infectious complications remain a significant issue in the care of patients with hematologic malignancies. Inherent immune defects related to the primary disease process are present in patients with disorders such as chronic lymphocytic leukemia, multiple myeloma, hairy cell leukemia, and Hodgkin lymphoma. Therapy-related immunosuppression is also commonplace in these patients. This includes not only treatment-related neutropenia, but also defects in cell-mediated immunity, such as those that occur with purine analog therapy. In this chapter, we will review the pathogenesis of infection in these disorders, as well as the spectrum of infectious complications seen and suggested strategies for the prevention of infection.

**Keywords**

Immunosuppression · Neutropenia · Purine analog therapy · Pathogenesis of infection · Chronic lymphocytic leukemia · Multiple myeloma · Hairy cell leukemia · Hodgkin lymphoma

## Contents



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## 1 Introduction

Infections remain a common cause of morbidity and mortality in patients with hematologic malignancies. In many cases, the risk for infection is therapy related, with resultant neutropenia predisposing to these complications. However, with the advent of newer therapeutic agents for these disorders over the past several decades, some of which cause cell-mediated immunocompromise, the spectrum of infectious complications has evolved to include various fungal and viral opportunistic pathogens, as well as common bacterial organisms. In addition, some of these malignancies have inherent immune defects that are present in untreated patients, adding to the milieu of infectious complications. In this chapter, we will discuss the pathogenesis of infection, spectrum of infections seen, and approaches to the prevention of infection in specific hematologic disorders that have inherent as well as therapy-related immunosuppression, specifically chronic lymphocytic leukemia, multiple myeloma, hairy cell leukemia, large granular lymphocytic leukemia, Hodgkin lymphoma, and myelodysplastic syndrome. The infectious complications of therapy-related neutropenia, as that seen with the treatment for acute leukemia and high-grade lymphoproliferative disorders, will be reviewed in chapter Neutropenic Fever and Sepsis: Evaluation and Management on this specific topic.

## 2 Pathogenesis of Infection in Specific Disease Processes

### 2.1 Chronic Lymphocytic Leukemia

Infections remain a major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL). Up to 80 % of patients will sustain an infectious complication at some time in their disease course. It has been estimated that infection accounts for up to 60 % of deaths in patients with CLL. These

**Table 1** Pathogenesis of infection in patients with chronic lymphocytic leukemia and multiple myeloma

| |
|---|
| *Disease-related inherent immune defects* |
| Hypogammaglobulinemia |
| Complement defects |
| Cell-mediated immune defects (T-cells, delayed hypersensitivity) |
| Defects in neutrophil phagocytic/bactericidal activity |
| Defects in monocyte function/deficiencies in monocyte enzyme levels |
| Potential mucosal immune defects |
| *Therapy-related immune defects* |
| Neutropenia |
| Steroid-induced cell-mediated immune defects |
| Alemtuzumab- and purine-analog-related T-cell defects |

patients are predisposed to infection not only from therapy-related immunosuppression, but also from inherent immune defects related to the primary disease process, which are seen even in previously untreated patients with CLL (Table 1) [1, 2]. These disease-related immune defects involve multiple arms of immune defense and include hypogammaglobulinemia, as well as abnormalities in cell-mediated immunity, complement activity, and neutrophil function.

Hypogammaglobulinemia, related to abnormalities in the functions of both T- and non-clonal CD5-negative B-cells, down-regulation of B-cell immunoglobulin synthesis by large granular lymphocytes, and interaction of malignant B-cells with plasma cells, occurs in virtually all CLL patients. The hypogammaglobulinemia is more pronounced in advanced-stage disease and longer duration of disease and has been found to correlate with the frequency of infections and survival. However, response to therapy is not associated with an improvement in the defect. No clear-cut association between a specific immunoglobulin (Ig) class deficiency and infection risk has been determined.

Several studies have assessed the impact of immunoglobulin $V_H$ mutation status on humoral immunity and infectious complications [3, 4]. In one study, no significant differences were demonstrated in immunoglobulin levels, mannan-binding lectin, immune responses to *Haemophilus influenza* B vaccination, and infection rates among patients with unmutated or mutated immunoglobulin $V_H$ genes [3]. In another retrospective analysis of 231 CLL patients carrying differences in the mutation status of the Ig $V_H$ gene, patients with unmutated immunoglobulin $V_H$ gene status ($n = 52$) had a significantly shorter time to first infection (31 vs. 62 months, $P < 0.001$) and higher infection-related mortality ($P < 0.001$) compared to those with mutated immunoglobulin $V_H$ genes [4]. In addition, patients with cytogenetic abnormalities and CD38 positivity had a shorter time to first infection (both $P < 0.001$).

Despite the known impact of hypogammaglobulinemia in patients with CLL, the integrity of the mucosal immunity, the relationship between systemic immune dysfunction and mucosal immune dysfunction, and the relationship, if any, of the mucosal B-cells with the malignant B-cell clone are not well understood. In a preliminary report evaluating serum and salivary immunoglobulin levels, the latter as a marker of mucosal immune function, salivary IgM levels were substantially decreased in CLL patients with hypogammaglobulinemia, but no differences in salivary IgG or IgA levels were found between CLL patients and controls [5]. There was no correlation between salivary immunoglobulin levels and infection occurrence.

Although defects in cell-mediated immunity and complement activity in CLL patients are also recognized, the relationship of these defects with infection risk has not been delineated.

Defects in cell-mediated immunity include reversal of the CD4/CD8 ratio, an increase in T-cell suppressor activity, functional defects in helper T-cells and LAK cells, and an increase in NK cell activity. As with the B-cell defects, T-cell defects also become more prominent with advanced-stage disease. Decreased complement levels have been observed in most advanced-stage CLL patients with at least one component of the complement system, usually properdin, being abnormal [1]. Defects in complement activation and binding have also been demonstrated. Lastly, quantitative and qualitative defects of neutrophils and monocytes have been reported in CLL patients, including intracellular enzyme deficiencies and defects in chemotaxis.

## 2.2 Multiple Myeloma

Infections are also a major cause of morbidity/mortality in patients with multiple myeloma. Up to 60 % of patients will have infection at some time in their disease course, and about 20–50 % of myeloma patients will die of an infectious cause [6, 7]. Patterns of infection are similar in Waldenstrom's macroglobulinemia and the less common heavy chain diseases [8]. However, the risk for infection in patients with these disorders appears to be about a third of that seen in myeloma patients.

As in patients with CLL, patients with myeloma also have inherent immune defects related to the primary disease process, as well as immunosuppression related to administered therapies (Table 1). Hypogammaglobulinemia is the predominant immune defect in myeloma patients [7]. However, this is on the basis of decreased synthesis, as well as increased catabolism of normal immunoglobulins, in contrast to CLL patients [9, 10]. The degree of hypogammaglobulinemia is proportional to both disease burden and duration of disease. The hypogammaglobulinemia may normalize in response to the underlying myeloma to therapy. In addition to the lower immunoglobulin levels in these patients, there is also an underproduction of antibodies against specific bacterial and viral antigens, and lipid A, which is a component of the bacterial cell wall of gram-negative organisms [11–15]. There is also suppression of B-cells and plasma cells by suppressor macrophages, such that

the polyclonal B-cell population is markedly reduced [16–23]. It has been estimated that 5–10 % of the circulating cells have the same immunoglobulin gene rearrangement as is present in the malignant plasma cell clone.

Other facets of the innate immune response are also abnormal in myeloma patients. Cellular immune impairment is present, with suppression in delayed hypersensitivity, with an abnormal recall response to delayed-type hypersensitivity antigens [7, 24, 25]. The T-cell response to mitogens may also be abnormal. However, this T-cell hypo-responsiveness may be due to the altered frequency of T-cell subsets, rather than active suppression by a suppressor cell. These patients also have a defective response to immunization [8, 25–30]. The primary response, which occurs after exposure to "new" antigens, appears to be more suppressed than the secondary response to previously encountered antigens, the latter of which is generally intact in most patients. Response to immunization is not related to immunoglobulin levels. However, the degree of impairment does appear to correlate with the frequency of infection [8]. In addition, a deficiency in functional complement activity is present, although there is no consistent pattern of deficiency in a specific subtype (C1q, C2, C3, C4) [7, 31–33]. In one study, defects in C3 binding correlated with *Streptococcus pneumoniae* infections [33]. Defects in neutrophil function are also present, including impairment in the production of oxygen-dependent bactericidal substances, defective migration, low levels of intracellular lysozyme, a decrease in granulocyte receptors for immunoglobulin G and the 3b component of complement, and the presence of a heat-labile factor in plasma, but not serum, that inhibits granulocyte adherence [7, 34–39]. These functional neutrophil abnormalities appear to correlate with the disease progression, but not with the incidence of infection [34, 37]. Monocyte chemotaxis may be normal or decreased, but phagocytosis is normal [40, 41].

Various mechanisms of immunosuppression have been hypothesized to result in these inherent immune defects [7]. These immune defects are not thought to be induced directly by the monoclonal paraprotein, nor to be primarily T-cell mediated [42–48]. Potential mechanisms postulated from studies in the murine model are as follows. First, suppressor monocytes and macrophages may have a role, in that they secrete plasmacytoma-induced macrophage substance (PIMS), which inhibits antibody production by antigen-stimulated B-cells [7, 49–55]. The affected B-cells cannot respond to antigens or mitogens and are "frozen" in the G1 phase, thus preventing clonal expansion and subsequent antibody formation. Thus, there is an exaggerated form of innate feedback inhibition. Suppressor T-cells may also have a role, in that there are an increased number of T-cells with Fc receptor specific for the paraprotein isotype, which may negatively control immunoglobulin production by the non-malignant B-cells [7, 56–60]. Expansion of this population is caused directly by the monoclonal protein. There are correlates of these murine model findings in humans with myeloma, as some T helper cell subsets are depleted and there is a significant decrease in the T helper/suppressor (T4/T8) ratio in untreated patients, which may be due to a decrease in T4 cells or an increase in T8 cell numbers. These cells are functionally intact. In some studies, a correlation

of these findings with disease stage has been found. A third potential mechanism is related to leu-1 + B-cells, which suppress immunoglobulin production [7, 21–23, 61–65]. These cells are present but seemingly inactive in normal adults and those with monoclonal gammopathy of undetermined significance, but are active in myeloma patients, although no correlation with disease stage is apparent. A fourth controversial mechanism is the negative autoimmune immunoregulatory network initiated by the monoclonal protein, which results in arrested B-cell differentiation [7, 16–23]. Lastly, production of the malignant light chain isotype is suppressed in the non-malignant B-cells (in the peripheral blood, intestine), although the relationship of this finding with infectious complications is unknown [7, 16, 66, 67].

## 2.3 Hairy Cell Leukemia

Infectious complications of patients with hairy cell leukemia may influence the natural history of this disorder. In the era before effective chemotherapy options were available, about 70 % of patients sustained infectious complications, with infection-related mortality rates up to 60 % and multiple infections being commonplace [68–73]. However, with more effective therapies as the purine analogs, infections have become significantly less frequent [74, 75]. These complications are related to the presence of cytopenia, in particular neutropenia, which is related not only to the splenomegaly, but also to the hairy cell infiltration of the bone marrow with cytokine-mediated suppression of hematopoiesis [68]. While leukopenia is seen in at least 60 % of patients, neutropenia with an absolute neutrophil count of less than 500 cells/μl occurs in over a third of patients [68]. Microbicidal function may also be impaired in the neutrophils [76]. Marked monocytopenia may also be seen in these patients. The mechanism of this finding is not clear, but may also be related to cytokine-induced suppression. In addition to this quantitative defect, qualitative abnormalities in monocyte function may be present, with defects in migration and chemotaxis [77, 78]. Natural killer cell and dendritic cell defects are also seen in these patients, resulting in the depressed T-cell immune function [79–81]. Response to chemotherapy generally results in an improvement in these findings [68]. Lastly, immune defects related to therapeutic splenectomy may complicate the immune milieu of these patients.

Risk factors for infection in these patients have been examined, with the finding of lymphopenia at diagnosis, defined as an absolute lymphocyte count of less than $1.0 \times 10^9/\mu l$, found to be predictive for later infection in one series [82]. The findings of neutropenia or monocytopenia were not predictive for infection among these patients. However, in another series, a low absolute neutrophil count at baseline was predictive of subsequent infections [83]. Four-year survival was shorter in patients with infections, as compared to those sustaining no infections, in one large series (49 vs. 92 %, respectively) [70]. In this series, baseline neutropenia or monocytopenia was not found to be predictive of later infection.

## 2.4 Large Granular Lymphocytic Leukemia

Infections are common in patients with large granular lymphocytic leukemia. It has been estimated that half of these patients are diagnosed in the workup of recurrent infections [84]. The enhanced risk for infection is related to neutropenia, which occurs in approximately 85 % of patients with this disorder, and may be cyclic in nature [84, 85]. The pathogenesis of the neutropenia has not been clearly elucidated, but is not thought to be related to marrow replacement by the lymphocytes [86]. An absolute lymphocytosis is generally present, although the majority of the lymphocytes are of the large granular subtype. These lymphocytes display poor responsiveness to T-cell mitogens and have decreased NK cell activity [84].

## 2.5 Hodgkin Lymphoma

Infections were a significant complication of patients with Hodgkin lymphoma in series from four decades ago. In one series, although 25 % of patients had no infections during their clinical course, the remaining 75 % averaged 1.3 infections per patient [87]. Infection accounted for over 50 % of deaths in Hodgkin lymphoma in this era [88]. However, with more current chemotherapy regimens, the impact of infectious complications has lessened. Humoral immunity is generally normal in untreated patients, with normal immunoglobulin levels and primary antibody production generally being unaffected [89]. However, the enhanced risk for infection is related to inherent abnormalities in cell-mediated immunity that are present even in untreated patients [90, 91]. It has even been suggested in limited series that survival may be shorter in those patients with significant immune defects [92].

Qualitative and quantitative lymphocyte abnormalities are present in these patients. Lymphocytopenia is present in approximately 30 % of untreated patients, especially in those patients with advanced-stage disease [89, 92–94]. However, this alone does not account for the degree of immunologic impairment found in these patients. T lymphocyte counts are lower than normal in 50 % of patients [94, 95]. Alterations in circulating T lymphocytes are present, with enhanced T-suppressor lymphocyte activity and impairments in lymphocyte function in untreated patients [89, 96–98]. A state of cell-mediated suppression, implying an inhibitory interaction between suppressor cells (lymphocytes, monocytes) and effector lymphocytes, has been described [99, 100]. It has been postulated that sequestration of functional T lymphocytes may explain the immune defects [89]. Although peripheral blood monocyte counts are generally normal, monocyte function may be altered, with reduced chemotaxis response and decreased phagocytic activity [89].

Delayed hypersensitivity responses to recall or new antigens are impaired in these untreated patients [88, 94, 101–106]. Proliferative responses of peripheral blood lymphocytes to various mitogens, as well as lymphokine/interleukin production after antigen or mitogen stimulation, are impaired in these patients [88, 92,

98, 107–109]. Anergy to skin tests may be present in untreated patients and may be more common in patients with advanced-stage, in contrast to limited-stage, disease, as well as those with B symptoms [110–114]. Skin test reactivity may also correlate with the histologic subtype of Hodgkin lymphoma, in that patients with nodular sclerosing or lymphocyte-predominant histologies may be more likely to have reactivity than those with mixed cellularity or lymphocyte-depleted variants [112]. In addition, high levels of circulating immune complexes have been described in these patients [88, 115–117].

These inherent immune defects may not all improve after therapeutic response, although this evaluation is complicated by therapy-related immune abnormalities [118]. Several series evaluating immune function, with some conflicting results, in long-term responding patients have been reported [119–123]. The mean T lymphocyte count was lower, severe impairment in T lymphocyte function remained, although response to some, but not all, mitogens was normal in some series [119, 120]. Similar findings of persistent abnormalities in mitogen-induced lymphocyte proliferation, even in long-term survivors, have been described in other series [122]. Return of normal cell-mediated immunity in patients achieving complete remission for more than 10 years was described in a 62-patient series [120]. In contrast, Skovmann et al. [123] reported that immune abnormalities remain many years after completion of therapy in long-term responders.

## 2.6 Myelodysplastic Syndrome

Even though infection remains a significant cause of morbidity and mortality in patients with myelodysplastic disorders (MDS), these complications are not as clearly characterized as in patients with other related disorders such as acute myeloid leukemia. In one large series, the infection rate was one per patient-year, which is slightly less than the estimated infection rate in patients with either multiple myeloma or hairy cell leukemia [124]. The rate of infections was also related to the French–American–British (FAB) classification of the MDS in this series. Infection rates were the highest in those patients with refractory anemia with excess blasts in transformation (RAEB-T), followed by those with RAEB, and the lowest in those patients with refractory anemia, with or without ringed sideroblasts (RA ± RS). In addition, infection rates were higher in those patients with an absolute neutrophil count less than or equal to $1.0 \times 10^9$/μl as compared to patients with an absolute neutrophil count greater than $1.0 \times 10^9$/μl. In addition to quantitative neutrophil defects, qualitative neutrophil defects such as decreased myeloperoxidase activity, as well as defective adhesion, chemotaxis, phagocytosis, and microbicidal activity, have been found [125–129]. The use of therapy with corticosteroids or cytotoxic agents increases the risk for infections [124]. In more recent treatment series utilizing pyrimidine nucleoside analogs as azacytidine, there was a 20 % incidence of infection related to treatment [130]. The rate of infection per patient-year was 0.64 with azacytidine and 0.95 with best supportive care [131]. Infection was the cause of death in 2 % of patients treated with

azacytidine. In another trial in which azacytidine was compared to other conventional care regimens, it was found that the incidence of infection was comparable in the azacytidine-treated patients and those receiving best supportive care [132]. In addition to this trial, the infection rate was lower in those receiving azacytidine, as compared to low-dose cytarabine or intensive acute leukemia induction chemotherapy.

## 3 Spectrum of Infections with Specific Therapeutic Agents

### 3.1 Chronic Lymphocytic Leukemia

The spectrum of infectious complications in patients with CLL has evolved over the decades with advances in the therapy of this disease process. Recurrent infections are frequent, as are infections at mucosal sites, especially the respiratory tract.

#### 3.1.1 Alkylator-Based Therapy

For decades, the standard CLL treatment regimen was chlorambucil, given alone or with concurrent corticosteroids. With this therapy, the majority of infections are bacterial in etiology, caused by organisms as *Staphylococcus aureus*, *S. pneumoniae*, *H. influenzae, Klebsiella pneumoniae,* and *Escherichia coli* (Table 2). Infections caused by mycobacteria, *Nocardia,* and *Listeria* are uncommon. When seen, fungal or viral infections tend to occur in more heavily pretreated patients with advanced-stage disease. It has been estimated that the lifetime incidence of herpes zoster is up to 15–20 % [133].

#### 3.1.2 Fludarabine

Over the past two decades, the preferred regimen for initial therapy of CLL patients has included the purine analogs, specifically fludarabine, which has altered the spectrum of infections [134, 135]. The pathogenesis of infection with these agents is related to their impact on cell-mediated immunity. Both quantitative and qualitative T-cell abnormalities are induced by these agents. The decline in peripheral blood T-cell counts occurs early in treatment and is related to the inhibition of cytokine-induced signal transducers and activators of transcription (STAT)-1 activity and resultant decrease in STAT-1-dependent gene transcription. The reduction in the number of CD4+ cells is more pronounced compared to CD8+ or natural killer (NK) cells and may persist for up to 1–2 years after discontinuation of therapy. Monocytopenia and a decline in the B-cell count may also be seen. The impact of these agents on the immunoglobulin levels is variable. A similar spectrum of infection is seen among all purine analogs. In addition to bacterial infections common to CLL patients, a variety of opportunistic infections caused by pathogens as *Listeria*, *Mycobacterium* species, *Pneumocystis*, and herpesviruses, specifically herpes simple and varicella zoster, occur [2]. The risk of these infections is increased with concomitant corticosteroid administration, and thus, their use should be avoided.

**Table 2** Etiologic agents of infection in CLL patients

| |
|---|
| *Conventional alkylator therapy* |
| Bacteria (most common) |
| *Staphylococcus aureus* |
| *Streptococcus pneumoniae* |
| *Haemophilus influenzae* |
| *Escherichia coli* |
| *Klebsiella pneumoniae* |
| *Pseudomonas aeruginosa* |
| Fungi (uncommon, except in heavily pretreated patients) |
| *Candida* |
| *Aspergillus* |
| *Purine analog/alemtuzumab therapy* |
| Bacteria |
| *Listeria* |
| *Nocardia* |
| *Mycobacterium tuberculosis* |
| Atypical mycobacteria |
| *Legionella* |
| Fungi |
| *Candida* |
| *Aspergillus* |
| *Pneumocystis* |
| *Cryptococcus* |
| Viral |
| Cytomegalovirus (especially with alemtuzumab) |
| Varicella zoster virus |
| Herpes simplex virus |

### 3.1.3 Risk Factors for Infection with Fludarabine Therapy

Risk factors for infection in fludarabine-treated patients have been identified (Table 3). Most commonly, infections occur in the first several cycles of therapy and are infrequent in responding patients after discontinuation of therapy. In one large retrospective analysis of CLL patients treated with fludarabine plus prednisone, the risk factors included advanced-stage disease, prior therapy, lack of response to fludarabine therapy, and an elevated serum creatinine [136]. In another retrospective series, multivariate analysis identified the number of prior regimens (risk ratio [RR] 1.8) and hemoglobin <12 g/dl (RR 0.6) as risk factors for

**Table 3** Risk factors for infection in patients receiving fludarabine-based therapy

| |
|---|
| Prior therapy for CLL, number of prior regimens |
| Response to therapy |
| Older age |
| Advanced Rai-stage disease |
| Elevated serum creatinine |
| Anemia (hemoglobin <12 g/dl) |
| Hypogammaglobulinemia (low IgG level) |

incidence of major infections [137]. No impact of age and renal function on infection rate was noted in this study.

The relative risk and spectrum of infections in patients treated with fludarabine versus conventional alkylator-based regimens have been assessed in several series. In a meta-analysis of single-agent fludarabine or alkylator-based therapy trials, the incidence of grade 3/4 infections was greater with fludarabine [138]. The incidence and spectrum of infections were also assessed in a large intergroup trial of previously untreated CLL patients who were randomized to therapy with single-agent fludarabine, chlorambucil, or both agents (FC) [135]. Patients receiving the FC combination had more infections than those receiving either single agent. Comparing patients treated with the two single agents, an increased number of infections per month of follow-up, major infections, and herpesvirus infections were observed in fludarabine-treated patients. *Pneumocystis* infections occurred rarely, and no *Aspergillus* infections were observed. A low baseline serum IgG level was identified as a significant risk factor for the number of infections occurring in all patients ($p = 0.02$), while advanced age ($p = 0.004$) and a decreased creatinine clearance ($p = 0.03$) were risk factors for infection among patients who received FC. In contrast to prior studies of fludarabine-treated patients, no association between infection risk and either response to therapy or advanced disease stage was noted in this study. Lastly, in a large French trial randomizing treatment-naïve, advanced-stage CLL patients to fludarabine, or one of two anthracycline-based regimens, no opportunistic infections occurred among the fludarabine-treated patients [139].

### 3.1.4 Fludarabine-Based Combination Therapy

In subsequent trials, other active agents were added to the fludarabine backbone. In a German trial comparing initial therapy with fludarabine as a single agent or combined with cyclophosphamide (FC), the occurrence of severe and opportunistic infections was comparable between the treatment groups (33 vs. 40 %, respectively) [140]. However, because of more myelosuppression in the FC arm and subsequent dose reductions, the infection rate with FC may have been influenced. No increase in the risk of opportunistic infections has been noted with addition of

oblimersen, a bcl-2 antisense compound, to the FC regimen [141]. In the relapsed setting, 57 % of patients receiving FC had infections (including ones caused by herpesviruses [26 %] and fungal pathogens [7 %]) or fever of unknown origin [142]. Of these complications, 74 % occurred in the first three cycles of therapy.

Rituximab may be used in the treatment regimen of CLL patients, either as monotherapy, or more commonly in combination with other agents [143, 144]. This agent causes a transient reduction in the B-cell counts. When used as a single agent, grade 3, as well as opportunistic infections, is uncommon with single-agent rituximab therapy [133]. In a randomized phase II Cancer and Leukemia Group B (CALGB) study, fludarabine plus rituximab (FR) (concurrent or sequential) were administered to 104 previously untreated CLL patients [144]. Grade 3/4 infections were observed in 9 and 41 % of the patients, respectively. Opportunistic infections, mainly localized herpesvirus infections, occurred in eight (16 %) patients receiving concurrent therapy and 14 (26 %) on sequential treatment. Only two cases of *Pneumocystis* pneumonia were seen. Rituximab combined with FC (FCR) has been studied in both treatment-naive and pretreated CLL patients, with most patients receiving antiviral as well as *Pneumocystis* prophylaxis [145, 146]. When given as initial therapy, although 52 % of the 224 patients had grade 3/4 neutropenia, a third had at least one infection and 10 % had fever of unknown origin; however, major infections were observed in only 3 % of patients [145]. Five percent of patients had reactivation of herpes simplex or herpes zoster, with no cases diagnosed in patients on antiviral prophylaxis. In relapsed/refractory CLL, FCR therapy was discontinued in 6 % of patients due to infectious complications [146]. Major infections (including one case of cytomegalovirus [CMV] pneumonitis) occurred in 16 % of patients and minor infections in 18 %. The frequency of infections was comparable in fludarabine-sensitive and fludarabine-refractory patients.

### 3.1.5 Cladribine

Cladribine results in quantitative abnormalities in the T-cell subsets similar to that seen with fludarabine. Significant reduction in the CD4 counts may persist for 1–2 years after discontinuation of therapy. Receipt of prior therapy was a risk factor for infection in a series of patients <55 years receiving cladribine [147]. In a phase II CALGB trial of cladribine in fludarabine-refractory CLL patients, grades 3–5 infections were reported in 43 % of patients [148]. Although most infections were bacterial, cases of viral (herpes simplex and herpes zoster), fungal (candidal esophagitis), and parasitic (cerebral toxoplasmosis) infections were also reported. In a trial of 378 CLL patients treated with cladribine, alone or with prednisone, the incidence of infections/fever of unknown origin was significantly less among treatment-naïve patients than those who had received prior therapy (38 vs. 49 %, $p = 0.03$) [149]. In another series of treatment-naïve CLL patients randomized to therapy with cladribine or chlorambucil plus concurrent prednisone, granulocytopenia (23 vs. 11 %, $p = 0.02$), infections/fever of unknown origin (56 vs. 40 %, $p = 0.02$), and herpesvirus infections (21 vs. 11 %) were more frequent with cladribine therapy [150].

### 3.1.6 Pentostatin

Pentostatin-induced cellular immune defects also persist for several months after discontinuation of therapy. In a CALGB phase II trial of pentostatin therapy for previously treated and untreated CLL patients, infections occurred in 52 % of patients, with opportunistic infections in 26 % [151]. Furthermore, the infections occurred early in treatment and were especially common in relapsed/refractory, advanced-stage patients. In an Eastern Cooperative Oncology Group (ECOG) study of pentostatin, chlorambucil, and prednisone as first-line CLL therapy, grade 3/4 infections were observed in 31 % of patients, including bacterial/fungal pneumonia, *Pneumocystis* pneumonia, urosepsis, and herpes zoster (the latter in 11 of 55 [20 %] patients) [152]. Pentostatin has been combined with cyclophosphamide and rituximab (PCR) in previously treated and untreated CLL patients in two trials [153, 154]. Grade 3/4 infections were noted in 28 % of previously treated and in approximately 10 % of treatment-naïve patients.

### 3.1.7 Alemtuzumab

Alemtuzumab, a CD52 antibody, has been investigated in patients with CLL in the past decade. In addition to neutropenia, this agent is associated with profound defects in cell-mediated immunity. Significant reductions in B, T, and NK cells and monocytes develop early in therapy and persist for 4–9 months after treatment discontinuation, with recovery of these parameters occurring earlier than after fludarabine therapy. There is no apparent correlation of severity or length of immunosuppression with the alemtuzumab cumulative dose or route of administration, although non-responding patients are at a greater risk of infection. CMV reactivation occurs in approximately 10–25 % of patients. *Pneumocystis*, antifungal, and antiviral prophylaxes is generally given with this agent. In the pivotal trial of alemtuzumab therapy in 93 relapsed/refractory CLL patients who had failed fludarabine therapy, 27 % developed grade 3/4 infectious complications, including cases of aspergillosis, zygomycosis, candidiasis, *Listeria* meningitis, *Pneumocystis* pneumonia, and CMV reactivation [155]. The infection rate was significantly lower in responding patients than non-responders (10 vs. 36 %, $p < 0.01$). In the first-line treatment setting, alemtuzumab resulted in improvements in response rate (83 vs. 55 %, $p < 0.0001$) and progression-free survival (hazard ratio [HR] 0.54; $p = 0.0001$) as compared to chlorambucil [156]. However, more CMV events were noted with alemtuzumab. The results of single-agent alemtuzumab therapy for lymphoproliferative disorders, predominantly CLL, have been reported [157]. Seven of ten deaths were related to infection. Opportunistic infections occurred in 56 % of patients, including CMV viremia in 44 %. The majority of these infections did not occur in the setting of neutropenia. Non-opportunistic infections occurred in 82 % of patients, including three deaths from enterococcal bacteremia. In the authors' subsequent literature review of 410 patients, opportunistic infections occurred in 64 % of patients, with herpes simplex virus infections and CMV reactivation being most common. Sepsis and pneumonia were the most frequent non-opportunistic infections.

Alemtuzumab has also been studied as a component of combination therapy. The use of fludarabine plus alemtuzumab in the relapsed/refractory CLL disease setting was examined in a phase II trial [158]. Both agents were given for three consecutive days every 4 weeks, with *Pneumocystis* and antiviral prophylaxis, which was continued for 2 months after completion of therapy. Among the 36 patients, two cases of grade 3 CMV reactivation and two cases of *Aspergillus* pneumonia were seen. In a single-center trial in which therapy with alemtuzumab plus rituximab was given to patients with relapsed/refractory B-cell disorders, over half of the patients had infectious complications, despite *Pneumocystis* prophylaxis and antiviral prophylaxis [159]. CMV reactivation occurred in 27 % of patients, over half of whom required therapeutic intervention.

Alemtuzumab has also been used as consolidation therapy in a variety of CLL clinical trials, with CMV reactivation being a significant issue. In a single-center trial, patients attaining a response with initial chemotherapy received alemtuzumab consolidation at a median period of 5 months after completion of induction therapy [160]. Fifteen of 41 patients (37 %) developed infections, including nine cases of CMV reactivation. Additionally, three cases of Epstein–Barr-virus-positive large cell lymphoma were diagnosed. In a smaller Italian series of fludarabine therapy followed by alemtuzumab consolidation 5 months later, one-third of patients had CMV reactivation [161]. In a German trial, patients received initial therapy with either fludarabine or FC, followed by randomization to alemtuzumab consolidation versus observation 2 months later [162]. This study was terminated early as 7 of 11 patients in the alemtuzumab arm sustained grade 3/4 infections, including four cases of CMV viremia.

Infectious complications observed in several CALGB CLL trials have also been reported. In CALGB 19901, previously untreated CLL patients received four cycles of fludarabine therapy, followed 2 months later by alemtuzumab consolidation in patients with responsive or stable disease [163, 164]. In the first 57 patients, grade 3/4 infections were common, including eight cases of CMV reactivation, one of which was fatal. Weekly qualitative polymerase chain reaction (PCR) CMV testing was subsequently implemented, with three of the following 18 patients having CMV reactivation with no disease. Data on infectious complications from three serial CALGB CLL trials have also been reported, including therapy with single-agent fludarabine (CALGB 9011; $n = 188$), FR (CALGB 9712; $n = 104$), and fludarabine induction ($n = 85$), followed by alemtuzumab consolidation ($n = 59$) (FA) (CALGB 19901) [165]. Patients receiving FA had significantly more infections during protocol therapy compared to patients receiving either single-agent fludarabine (38 vs. 23 %, $p = 0.01$) or FR (38 vs. 20 %, $p = 0.0007$). Three *Pneumocystis* and no CMV infections occurred among fludarabine-treated patients, compared to three *Pneumocystis* and one CMV infection(s) among those receiving FR. In patients receiving FA, one *Pneumocystis* and no CMV infections occurred during fludarabine induction, but 12 of 59 patients developed CMV infection during alemtuzumab consolidation. Preliminary data on infectious complications from CALGB 10101, in which patients received induction therapy with FR followed by alemtuzumab consolidation 4 months later,

have also been reported [166]. There were seven grade 5 infectious toxicities reported in responding patients, caused by agents such as Epstein–Barr virus, *Listeria, Legionella*, CMV, and *Pneumocystis*, as well as viral meningitis, sepsis, and transfusion-associated graft-versus-host disease. The impact of alemtuzumab consolidation on infectious complications, and the influence on the immune milieu of the cumulative dose of fludarabine or alemtuzumab, prior rituximab therapy, the timing between completion of induction therapy and response status, is not clearly delineated.

## 3.2 Multiple Myeloma

Infection may be the presenting manifestation of myeloma [167]. The risk for infection is the greatest in the first 2 months after diagnosis and in first 2 months of chemotherapy for the disorder [168, 169]. Infectious complications are less common in patients who achieve a therapeutic response. A biphasic pattern of infection has also been described, with one peak incidence early in the disease course (within 8 months of diagnosis) in responding patients, caused by organisms as *S. pneumoniae* and *H. influenzae*, and a second peak in those patients with refractory or advanced disease, caused by gram-negative organisms [170]. Longer disease duration and the presence of neutropenia are not predictive of infection [170–174]. The infection rate ranges from 0.68 to 2.22 infections/patient/year, which is a 7–15-fold increase compared to hospitalized patients without malignancy. However, most of these observations were made before the advent of imidazole or bortezomib therapy for this disorder.

A change in the spectrum of infections in myeloma patients historically has also been described. Prior to 1964, the incidence of infection in these patients, especially of the lower respiratory tract, was high, with 20–70 % of patients having at least one episode of pneumonia [8, 24, 26]. *S. pneumoniae* was the primary pathogen, with gram-negative infections being uncommon. Over half of the patients had recurrent infections, often with same organism. The second most common site of infection was the urinary tract, caused by organisms as *E. coli* and other gram-negatives isolates. However, in the next decade, a change in the spectrum of infections was seen, with more gram-negative infections, fewer cases of pneumonia, and more patients being heavily pretreated, with advanced-stage disease and neutropenia [170–174]. Despite this, the incidence of gram-positive infections did not decline.

Because patients with myeloma have a reduction in specific opsonizing antibodies, they are at risk for infection with encapsulated organisms such as *S. pneumoniae, H. influenzae,* and *Neisseria meningitidis.* In historical series, gram-negative infections were more common in those patients with refractory, advanced disease, especially in the setting of azotemia, prior antimicrobial therapy, instrumentation (including urinary catheters), immobilization, and

colonization with nosocomial pathogens [170]. Infections associated with cellular immune dysfunction, as those of a fungal, viral, or mycobacterial etiology, were uncommon in these series, and if seen, occurring in those patients with advanced, refractory disease. A series of 31 non-allografted patients with invasive aspergillosis diagnosed between 1984 and 1996, with 75 % of cases occurring between 1992 and 1996, has been described [175]. The median time from myeloma diagnosis to *Aspergillus* infection was 8 months, with a range of 1–75 months. The vast majority of these patients had advanced-stage disease. Slightly more than half of the patients were neutropenic, for a median of 19 (range, 10–37) days. Recent treatment included corticosteroid therapy in 45 % and high-dose melphalan in 36 %. A pulmonary site of infection was present in 28 of the 31 patients. Other sites of infection included the central nervous system ($n = 4$), sinuses ($n = 3$), and pericardium, kidney, and myocardium in one case each. The mortality rate was 45 %. In a more recent series, infection was found at autopsy in 60 % of cases [6]. This included bacterial infections in 50 % (70 % pneumonia) and fungal infections in 10 %, including *Candida* esophagitis, invasive aspergillosis, and pulmonary cryptococcosis.

The use of newer therapeutic agents, specifically bortezomib, has resulted in a change in the usual spectrum of infections, with the emergence of herpesvirus infections, especially herpes zoster [176–178]. In a phase III trial in which patients with relapsed or refractory myeloma were randomized to therapy with bortezomib or high-dose dexamethasone, herpes zoster infections were more common in those receiving bortezomib (13 vs. 5 %, $p < 0.001$) [176, 177].

## 3.3 Hairy Cell Leukemia

The most common sites of infection in patients with hairy cell leukemia include the respiratory and urinary tracts and bloodstream. Less common sites include the skin and soft tissue, central nervous system, and liver [68, 70]. A wide variety of pathogens may cause infections in hairy cell leukemia patients. Approximately half of the infections are caused by bacterial pathogens common in neutropenic patients, such as *S. aureus*, *S. pneumoniae*, *E. coli*, and *Pseudomonas aeruginosa*, with gram-positive and gram-negative infections being comparable in number [68, 70, 72, 73, 83]. Interestingly, the incidence of atypical mycobacterial infections, especially in patients with active disease, is also increased in these patients, being as high as 9–18 % in older series [71, 83, 179–183]. The finding of disseminated infection caused by organisms, such as *Mycobacterium kansasii*, *M. avium-intracellularae*, and *M. chelonii*, has been reported [70, 72, 73, 83, 179]. Other less common pathogens, including *Listeria*, *Legionella*, *Pneumocystis*, *Aspergillus*, *Histoplasma*, *Cryptococcus*, zygomycetes, and cytomegalovirus, are likely related to the inherent T-cell defects [73, 83, 184–188]. Herpes zoster may also be seen in patients receiving antimetabolite therapy [74].

### 3.4 Large Granular Lymphocytic Leukemia

Both cytotoxic drugs and immunosuppressive agents have been utilized to treat patients with large granular lymphocytic leukemia, which may impact the spectrum of infectious complications seen [85, 86, 189–191]. Myeloid growth factors have also been employed with variable success [85, 192]. Recurrent bacterial infections are a hallmark of this disorder. However, some patients may not sustain any infectious complications over extended periods, despite the presence of neutropenia. These infections are typically caused by common gram-positive and gram-negative organisms and frequently involve the lungs, skin/soft tissue, and bloodstream. Prognosis of this disorder is related to the severity of the neutropenia [191]. Although the clinical course of this disease is usually indolent, sepsis related to neutropenia remains a leading cause of death in these patients [86, 193, 194].

### 3.5 Hodgkin Lymphoma

In older series, up to 70 % of infections in patients with Hodgkin lymphoma were caused by common gram-positive and gram-negative bacteria, with the remaining 30 % of infections due to a viral, fungal, or mycobacterial etiology [89, 195–202]. In one of these reports, a higher incidence of tuberculosis at autopsy was found in Hodgkin lymphoma patients than in the general population [202]. These opportunistic infections may be in part related to the cellular immune defects found in these patients. A variety of disseminated fungal infections, in particular cryptococcosis, have been described (see Chapter Fungal Infections in Cancer Patients) [89, 203]. Herpesvirus infections, including cytomegalovirus, herpes zoster, and herpes simplex, have also been noted [87, 89, 195, 198–201]. A 15–25 % incidence of herpes zoster in these patients was based on large studies published three or four decades ago [87, 89, 204–215]. The incidence of zoster infection during the first year of treatment ranged from 8 to 50 % [213, 214]. An increased risk for zoster is present in both treatment-naïve patients and those receiving cytotoxic therapy [215]. More complicated herpetic infections, as ulcerative herpetic esophagitis, have also been described [87, 89]. Deficiencies in in vitro lymphocyte responses may correlate with increased susceptibility to varicella zoster virus infection [212]. Additional opportunists affecting these patients include tuberculosis (typical and atypical), toxoplasmosis, and *Pneumocystis* [87, 89, 198–201].

### 3.6 Myelodysplastic Syndrome

The most common types of infections in patients with MDS are bacterial pneumonias and skin abscesses, accounting for approximately 40 % of infections in one large series [124]. Urinary tract infections and bacteremia were also somewhat common in this series. In more recent treatment series, the most common sites of infection remained the lungs, urinary tract, and bloodstream [131]. The majority of

infections are caused by common bacterial pathogens, similar to those causing infection in neutropenic patients. Fungal and viral infections are considerably less common in these patients.

## 4 Strategies for the Prevention and Prophylaxis of Infection

### 4.1 Chronic Lymphocytic Leukemia

#### 4.1.1 Immunoglobulin Replacement

The benefit of prophylactic intravenous immunoglobulin (IVIG) in CLL patients with either hypogammaglobulinemia or prior infections was evaluated in a randomized, placebo-controlled, multicenter study [216]. Minor or moderate bacterial infections were significantly lower in patients receiving IVIG ($p = 0.01$); however, there was no difference in the incidence of major infections or mortality. In addition, it was found that routine IVIG therapy was not cost-effective. Prophylactic low-dose IVIG has also been studied. Although a reduction in infection has been noted in some studies, no correlation with improvement in Ig levels has been demonstrated. Furthermore, cost-effectiveness remains an issue, especially in comparison with prophylactic oral antimicrobial agents. The optimal dose, schedule, and subset of patients that would benefit from such an approach are not clear. Finally, an important aspect of IVIG infusions is that it replaces neither IgM nor A.

#### 4.1.2 Prophylactic Antimicrobial Agents

The role of prophylactic antimicrobial agents has not been analyzed in prospective randomized trials in CLL patients; however, some guidelines have been proposed based on results from a variety of trials and anecdotal reports. The use of concomitant corticosteroids with fludarabine appears to increase the risk of opportunistic infections. In the intergroup trial comparing the occurrence of infections on fludarabine-treated versus chlorambucil-treated patients retrospectively, incidence of varicella zoster and herpes simplex infections was more frequent among patients who had received fludarabine [135]. Despite this evidence, the use of routine antiviral prophylaxis in fludarabine-treated patients should be mandated only after the results are confirmed prospectively. The addition of rituximab to fludarabine therapy increases infections caused by localized herpesvirus only slightly and does not appear to increase the risk of either bacterial or *Pneumocystis* infection [217]. No routine prophylactic antimicrobial therapy is recommended for patients receiving this regimen. However, routine antiviral prophylaxis and *Pneumocystis* prophylaxis are recommended for therapy with both FC and FCR, as with alemtuzumab therapy; antifungal prophylaxis is utilized in some, but not in all trials. It is also recommended that prophylaxis is continued for up to 6 months after completion of therapy as the immune defects rendered by both purine analog and alemtuzumab therapies may persist for up to 2 years after discontinuation of therapy.

Guidelines for preemptive therapy of CMV infections were devised in 2004 and updated in 2006 [218]. Weekly PCR testing was recommended. Although

cytomegalovirus antigen assays, such as the pp65 assay, or quantitative PCR testing may be used to screen for these infections, PCR tests are thought to be more sensitive and reliable and also offer the advantage of discrete cutoffs for the institution of antiviral therapy [219].

The incidence of symptomatic CMV infection with alemtuzumab therapy has been estimated to range from 4 to 29 %, with a peak onset 4–6 weeks after initiation of therapy [218]. These infections appear to be uncommon after completion of therapy and are more common in previously treated patients than in treatment-naïve patients. In the setting of symptomatic CMV infection, therapy with either IV or oral ganciclovir, or alternatively valganciclovir, is recommended, for a 14–21-day course, until resolution of symptoms and one negative PCR test, or two consecutive negative PCR tests is achieved. In the updated recommendations, it is advised that alemtuzumab therapy may be continued, unless patients are persistently symptomatic. In the setting of asymptomatic CMV infection, therapy with either IV or oral ganciclovir can be instituted for 7–14 days, with continuation of alemtuzumab therapy. This sort of surveillance and preemptive therapy has been found to significantly decrease the rate of symptomatic CMV reactivation.

Alternatively, CMV prophylaxis may be utilized in patients receiving alemtuzumab therapy. In a small series, valganciclovir has been found to be the most effective prophylactic agent [220]. It is recommended that prophylaxis be continued for 2 months after completion of therapy. Patients should have PCR screening every 2 weeks during prophylaxis.

### 4.1.3 Immunization

Although a variety of immunizations have been examined in CLL patients, these have shown only suboptimal responses due to impaired antibody production and defects in antigen presentation. Most of the analyses have been conducted in small studies; therefore, formal recommendations for vaccine use in this patient population have not been devised. However, it certainly is reasonable to provide pneumococcal and influenzal vaccine coverage for all CLL patients, as per standard adult vaccination guidelines. Superior responses may be obtained with protein and conjugated vaccines rather than with polysaccharide vaccines. Herpes zoster virus vaccines, which are live virus products, have not been studied in immunocompromised patients, and the efficacy as well as side-effect profile is not known in this patient population. Thus, these vaccines should not be utilized in patients with CLL, whether they are receiving therapy or are treatment-naïve.

## 4.2 Multiple Myeloma

### 4.2.1 Antimicrobial Prophylaxis

The role of routine antimicrobial prophylaxis in myeloma patients is controversial. Although daily oral penicillin prophylaxis is utilized by some providers, there are no data supporting this usage. In a prospective randomized prophylaxis study, 54 myeloma patients receiving initial chemotherapy were randomized to

trimethoprim–sulfamethoxazole versus placebo for the first 2 months of chemotherapy, when the rate of infection is twice that as the rest of the disease course, and were followed for 3 months [221]. Infections occurred in 42 % ($n = 11$) of the placebo recipients, compared to 7 % ($n = 2$) of patients on trimethoprim–sulfamethoxazole ($p = 0.004$). Among the control patients, 15 of 16 infections were bacterial in etiology (one *Candida* pharyngitis). In contrast, two of five infections in those on trimethoprim–sulfamethoxazole were bacterial, with herpes zoster, fungal skin rash, and viral syndrome accounting for the remainder. Severe infections, including pneumonia ($n = 5$; three with sepsis), urinary tract infection ($n = 2$), 1 diverticulosis ($n = 1$), and staphylococcal scalded skin syndrome ($n = 1$), were diagnosed in eight control patients and only one patient receiving trimethoprim–sulfamethoxazole. The rate of bacterial infection per patient-year was 2.43 in controls and 0.29 in patients on trimethoprim–sulfamethoxazole. However, this prophylaxis was discontinued in 25 % due to rash and nausea.

### 4.2.2 Immunization

With pneumococcal vaccination, normal-fold rises in antibody titers are seen in patients with myeloma. However, as markedly reduced preimmunization titers are present in these patients, resultant post-immunization titers are low, generally being below protective levels [28, 30]. The antibody titers fall rapidly after an initial response, being at levels at less than baseline for 50 % of antigens 18 months later, which may be due to increased catabolism. The present American College of Physicians recommendations are that pneumococcal vaccination should be offered to myeloma patients, but that they should be counseled regarding the potential for a poor response and lack of protection [222]. However, with the low cost, minimal toxicity, and possible benefit, this vaccination should be encouraged. There are limited data with regard to revaccination in myeloma patients. One may consider revaccination after titers fall below a defined cutoff, although the increase in titer may well be less than the initial response.

There are minimal data on other polysaccharide and protein vaccines for myeloma patients. In theory, meningococcal and *H. influenzae* vaccines should be of benefit. Viral vaccines, such as influenza, are not well studied. In general, vaccination with live attenuated viral vaccines is not recommended.

### 4.2.3 Immunoglobulin Replacement

Intramuscular gamma globulin appears to have no impact on incidence of infections [223, 224]. In one trial, the use of intravenous immunoglobulin (IVIG) (0.6–1.0 g/kg initial dose, 0.2 g/kg every 3 weeks) resulted in a decreased incidence and frequency of infection, thought to be due to an improvement in granulocyte function. In another 93-patient randomized trial, patients received 10 g IVIG every 3–4 weeks versus no therapy. After 6 months, patients were crossed over, with a four-month follow-up. Significantly fewer infections were seen with IVIG administration. However, this study had no placebo control and was not double-blinded. In conclusion, although there is a possible role for IVIG prophylaxis, only use in the setting of recurrent or life-threatening infections is now recommended.

## References


1. Wadhwa PD, Morrison VA (2006) Infectious complications of chronic lymphocytic leukemia. Semin Oncol 33:240–249
2. Morrison VA (2007) Management of infectious complications in patients with chronic lymphocytic leukemia. Hematology 332–338
3. Sinisalo M, Aittoniemi J, Koski T et al (2004) Similar humoral immunity parameters in chronic lymphocytic leukemia patients independent of VH gene mutation status. Leuk Lymphoma 45:2451–2454
4. Francis S, Karanth M, Pratt G, Starczynski J, Hooper L, Fegan C, Pepper C, Valcarcel D, Milligan DW, Delgado J (2006) The status on immunoglobulin $V_H$ gene mutation status and other prognostic factors on the incidence of major infections in patients with chronic lymphocytic leukemia. Cancer 107:1023–1033
5. Morrison VA, Hibbs JR, Janoff EN (1996) Systemic and mucosal immunoglobulin levels and risk of infection in patients with chronic lymphocytic leukemia and multiple myeloma. Blood 88:240a
6. Oshima K, Kanda Y, Nannya Y et al (2001) Clinical and pathologic findings in 52 consecutively autopsied cases with multiple myeloma. Am J Hematol 67:1–5
7. Jacobson DR, Zolla-Pazner S (1986) Immunosuppression and infection in multiple myeloma. Semin Oncol 282–290
8. Fahey JL, Scoggins R, Utz JP et al (1963) Infection, antibody response and gamma globulin concentrations in multiple myeloma and macroglobulinemia. Am J Med 35:698–707
9. Broder S, Humphrey R, Durm M et al (1975) Impaired synthesis of polyclonal (non-paraprotein) immunoglobulins by circulating lymphocytes from patients with multiple myeloma. N Engl J Med 293:887–892
10. Morell A, Terry WD, Waldmann TA (1970) Metabolic properties of IgG subclasses in man. J Clin Invest 49:673–680
11. Marks J (1953) Antibody formation in myelomatosis. J Clin Pathol 6:62–63
12. Lawson HA, Stuart CA, Paull AM et al (1955) Observations on the antibody content of the blood in patients with multiple myeloma. N Engl J Med 252:13–18
13. Heath RB, Hamilton F, Malpas JS (1964) Production of antibodies against viruses in leukaemia and related diseases. Br J Haematol 10:365–370
14. Fink PC, Galanos C (1985) Serum anti-lipid A antibodies in multiple myeloma and Waldenstrom's macroglobulinaemia. Immunobiology 169:1–10
15. Stoll C, Schedel I, Peest D et al (1985) Serum antibodies against common antigens of bacterial lipopolysaccharides in healthy adults and patients with multiple myeloma. Infection 13:115–119
16. Van Camp B, Reynaert PH, Broodtaerts L (1981) Studies on the origin of the precursor cells in multiple myeloma, Waldenstrom's macroglobulinemia and benign monoclonal gammopathy. I. Cytoplasmic isotype and idiotype distribution in peripheral blood and bone marrow. Clin Exp Imunol 44:82–89
17. Dillman RO, Royston I, Meserve BL et al (1981) Alterations of peripheral blood B-lymphocyte populations in plasma cell disorders. Cancer 48:2211–2217
18. King MA, Wells JV (1981) Cell-bound immunoglobulin on peripheral blood mononuclear cells of patients with myeloma. Clin Exp Immunol 45:522–556
19. Bast EJEG, Van Camp B, Reynaert P et al (1982) Idiotypic peripheral blood lymphocytes in monoclonal gammopathy. Clin Exp Immunol 47:677–682
20. Pilarski LM, Mant MJ, Ruether BA et al (1984) Severe deficiency of B lymphocytes in peripheral blood from multiple myeloma patients. J Clin Invest 74:1301–1306
21. Lindstrom FD, Hardy WR, Eberle BJ et al (1973) Multiple myeloma and benign monoclonal gammopathy: differentiation by immunofluorescence of lymphocytes. Ann Intern Med 78:837–844

22. Abdou NI, Abdou NL (1975) The monoclonal nature of lymphocytes in multiple myeloma. An Intern Med 83:42–45
23. Chen Y, Bhoopalam N, Yakulis BS et al (1975) Changes in lymphocyte surface immunoglobulins in myeloma and the effect of an RNA-containing plasma factor. Ann Intern Med 83:625–631
24. Glenchur H, Zinnerman HH, Hall WH (1959) A review of fifty-one cases of multiple myeloma. Arch Intern Med 103:173–183
25. Cone L, Uhr JW (1964) Immunological deficiency disorders associated with chronic lymphocytic leukemia and multiple myeloma. J Clin Invest 43:2241–2248
26. Zinneman HH, Hall WH (1954) Recurrent pneumonia in multiple myeloma and some observations on immunologic response. Ann Intern Med 41:1152–1163
27. Larson DL, Tomlinson LJ (1952) Quantitative antibody studies in man. II. The relation of the level of serum proteins to antibody production. J Lab Clin Med 39:129–134
28. Lazarus HM, Lederman M, Lubin A et al (1980) Pneumococcal vaccination: the response of patients with multiple myeloma. Am J Med 69:419–423
29. Schidt RA, Rubin RR, Schiffman G et al (1981) polyvalent pneumococcal immunization of patients with plasma cell dyscrasias. Cancer 48:1377–1380
30. Birgens HS, Espersen F, Hertz JB et al (1983) Antibody response to pneumococcal vaccination in patients with myelomatosis. Scand J Haematol 30:324–330
31. Cheson BD, Plas PR, Rothstein G (1980) Defective opsonization in multiple myeloma. Blood 55:602–606
32. Kraut EH, Sagone AL (1981) Alternate pathway of complement in multiple myeloma. Am J Hematol 11:335–345
33. Cheson BD, Walker HS, Heath ME et al (1984) Defective binding of the third component of complement (C3) to *Streptococcus pneumoniae* in multiple myeloma. Blood 63:949–957
34. MacGregor RR, Negendank WG, Schreiber AD (1978) Impaired granulocyte adherence in multiple myeloma: relationship to complement system, granulocyte delivery, and infection. Blood 51:591–599
35. Spitler LE, Spath P, Petz L et al (1975) Phagocytes and C4 in paraproteinaemia. Br J Haematol 29:279–292
36. Penny R, Galton DAG (1966) Studies on neutrophil function II. Pathological aspects. Br J Haematol 12:633–645
37. Hopen G, Glette J, Halstensen A et al (1983) Granulocyte function in malignant monoclonal gammopathy. Scand J Haematol 31:133–143
38. Ziegler JB, Hansen PJ, Penny R (1975) Leucocyte function in paraproteinemia. Aust NZ J Med 5:39–43
39. Naess A, Hopen G, Solberg CO (1984) Decrease of Fc$\gamma$ and C3b receptor-bearing granulocytes and of T lymphocytes in myelomatosis. Scand J Haematol 33:83–90
40. Dammacco F, Miglietta A, Ventura MT et al (1982) Defective monocyte chemotactic responsiveness in patients with multiple myeloma and benign monoclonal gammopathy. Clin Exp Immunol 47:481–486
41. Blom J, Nielsen H, Larsen SO et al (1984) A study of certain functional parameters of monocytes from patients with multiple myeloma: comparison with monocytes from healthy individuals. Scand J Haematol 33:425–431
42. Fahey JL, Humphrey JH (1962) Effect of transplantable plasma-cell tumors on antibody response in mice. Immunology 5:110–115
43. Havas HF, Schiffman G (1978) The effect of an IgM plasmacytoma (TEPC-183) on the primary immune response of BALB/c mice. Immunology 34:1–8
44. Smith F, Grenan ZMM, Owens J (1960) Effect of a transplanted plasma-cell tumor on antibody formation. J Natl Cancer Inst 25:803–812
45. Zolla S (1972) The effect of plasmacytomas on the immune response of mice. J Immunol 108:1039–1048

46. Hirano S, Imamura Y, Takaku F et al (1968) Immune response in mice with plasma-cell tumor (X5563) assayed by agar plaque technique. Blood 31:252–257
47. Zolla S, Naor D, Tanapatchaiyapong P (1974) Cellular basis of immunodepression in mice with plasmacytomas. J Immunol 112:2068–2076
48. Ullrich S, Zolla-Pazner S (1982) Immunoregulatory circuits in myeloma. Clin Haematol 11:87–111
49. Tanapatchaiyapong P, Zolla S (1974) Humoral immunosuppressive substance in mice bearing plasmacytomas. Science 186:748–750
50. Kolb J-P, Arrian S, Zolla-Pazner S (1977) Suppression of the humoral immune response by plasmacytomas: mediation by adherent mononuclear cells. J Immunol 118:702–709
51. Kennard J, Zolla-Pazner S (1980) Origin and function of suppressor macrophages in myeloma. J Immunol 124:268–273
52. Krakauer RS, Strober W, Waldmann TA (1977) Hypogammaglobulinemia in experimental myeloma: the role of suppressor factors from mononuclear phagocytes. J Immunol 118:1385–1390
53. Katzmann JA (1978) Myeloma-induced immunosuppression: a multistep mechanism. J Immunol 121:1405–1409
54. Hamburger AW (1980) Inhibition of B-lymphocyte clonal proliferation by spleen cells from plasmacytoma-bearing mice. J Natl Cancer Inst 65:1337–1343
55. Berman JE, Zolla-Pazner S (1985) Control of B cell proliferation: inhibition of responses to B cell mitogens induced by plasma cell tumors. J Immunol 134:2872–2878
56. Hoover RG, Dieckgraefe BK, Lake J et al (1982) Lymphocyte surface membrane immunoglobulin in myeloma. III. IgA plasmacytomas induce large numbers of circulating, adult thymectomy-sensitive, $\theta$+, Lyt-1 − 2+ lymphocytes with IgA-Fc receptors. J Immunol 129:2329–2331
57. Hoover RG, Lynch RG (1983) Isotype-specific suppression of IgA: suppression of IgA responses in BALB/c mice by T$\alpha$ cells. J Immunol 130:521–523
58. Hoover RG, Dieckgraefe BK, Lynch RG (1981) T cells with Fc receptors for IgA: induction of T cells in vivo and in vitro by purified IgA. J Immunol 127:1560–1563
59. Mather A, Lynch RG (1986) Increased T$\gamma$ and T$\mu$ cells in BALB/c mice with Ig G and IgM plasmacytomas and hybridomas. J Immunol 136:521–525
60. Muller S, Hoover RG (1985) T cells with Fc receptors in myeloma: suppression of growth and secretion of MOPC-315 by T$\alpha$ cells. J Immunol 134:644–647
61. Jones SV, McFarlane H (1975) T and B cells in myelomatosis. Br J Haematol 31:545–552
62. Sato I, Abo T, Onodera S et al (1978) Detection of monoclonal B lymphocytes in multiple myeloma by immunofluorescence tests of surface immunoglobulins. Scand J Haematol 21:433–444
63. Kubagawa W, Vogler LB, Capra JD et al (1979) Studies on the clonal origin of multiple myeloma: use of individually specific (idiotype) antibodies to trace the oncogenic event to its earliest point of expression in B-cell differentiation. J Exp Med 150:792–807
64. Schedel I, Peest D, Stunkel K et al (1980) Idiotype-bearing peripheral blood lymphocytes in human multiple myeloma and Waldenstrom's macroglobulinemia. Scand J Immunol 11:437–444
65. Carmagnola AL., Boccadoro M, Massaia M et al (1983) The idiotypic specificities of lymphocytes in human monoclonal gammopathies: analysis with the fluorescence activated cell sorter. Clin Exp Immunol 51:173–177
66. Leonard RCF, MacLennan CM, Smart Y et al (1979) Light chain isotype-associated suppression of normal plasma cell number in patients with multiple myeloma. Int J Cancer 24:385–393
67. Werne A, Joshua DE, Kronenberg H (1984) Light chain isotype associated suppression of surface immunoglobulin expression on peripheral blood lymphocytes in myeloma during plateau phase. Br J Haematol 58:483–489

68. Kraut E (2003) Clinical manifestations and infectious complications of hairy-cell leukaemia. Best Pract Res Clin Haematol 16(1):33–40
69. Offerman MK, Golomb H (1984) Hairy cell leukemia. Curr Probl Cancer 8(7):1–39
70. Golomb H, Hadad L (1984) Infectious complications in 127 patients with hairy cell leukemia. Am J Hematol 16:393–401
71. Stewart DJ, Gp B (1981) Infections in hairy cell leukemia. Cancer 15:801–805
72. Mackowiak P, Demian S, Sutker W et al (1980) Infections in hairy cell leukemia, clinical evidence of a pronounced defect in cell-mediated immunity. Am J Med 68:718–723
73. Bouza E, Burgaleta C, Golde D (1978) Infections in hairy-cell leukemia. Blood 51(5):851–859
74. Kraut EH, Grever MR, Bourouncle B (1994) Long term follow-up of patients with hairy cell leukemia after treatment with 2′′ deoxycoformycin. Blood 84:4061–4063
75. Goodman G, Burian C, Koziol J et al (2003) Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. J Clin Oncol 25(5):891–896
76. Child JA, Cawley JC, Martin S (1979) Microbicidal function of the neutrophils in hairy cell leukemia. Acta Haematol 62:191–198
77. Yam LT, Chaudhry AA, Janckila AJ (1977) Impaired marrow granulocyte reserve and leukocyte mobilization in leukemic reticuloendotheliosis. Ann Intern Med 87:444–446
78. Kjeldsberg CR (1978) Leukocyte mobilization in leukemic reticuloendotheliosis (letter). Ann Intern Med 88:268–269
79. Seshadri R, Brown E, Zipursky A (1976) Leukemic reticuloendotheliosis: a failure of monocyte production. New Engl J Med 295:181–184
80. Ruco LP, Procopio A, Maccanallini V (1983) Severe deficiency of natural killer cell activity in the peripheral blood of patients with hairy cell leukemia. Blood 61:1131–1137
81. Bourguin-Pionquet A, Rouard H, Roudot-Thoraval F (2002) Severe decrease in peripheral blood dendritic cells in hairy cell leukemia. Brit J Haematol 116:595–597
82. Damaj G, Kuhnowski F, Marolleau JP et al (2009) Risk factors for severe infection in patients with hairy cell leukemia: a long-term study of 73 patients. Eur J Haematol 83:246–250
83. Golomb H, Hanauer S (1981) Infectious complications associated with hairy cell leukemia. J Infect Dis 143:639–643
84. Berliner N (1990) T gamma lymphocytosis and T cell chronic leukemias. Hematol Oncol Clin North Am 4:473–487
85. Mohan SR, Maciejewski JP (2009) Diagnosis and therapy of neutropenia in large granular lymphocytic leukemia. Curr Opin Hematol 16:27–34
86. Loughran TP, Starkebaum G (1987) Large granular lymphocytic leukemia: report of 38 cases and review of the literature. Medicine 66:397–405
87. Casazza AR, Duvall CP, Carbone PP (1966) Summary of infectious complications occurring in patients with Hodgkin's disease. Cancer Res 26:1290–1296
88. Colby TV, Richard TH, Roger AW (1981) Hodgkin's disease and autopsy. Cancer 47:1852–1862
89. Romagnani S, Ferrini PLR, Ricci M (1985) The immune derangement in Hodgkin's disease. Semin Hematol 22:41–55
90. Baldwin RW (1972) Immunological aspects of Hodgkin's disease. Proc R Soc Med 65:1113
91. Gupta S (1981) Immunodeficiencies in Hodgkin's disease. Part I: T cell-mediated immunity. Clin Bull 11:58–65
92. Bjorkholm M, Wedelin C, Holm G, Ogenstad S, Johansson B, Mellstedt H (1982) Immune status of untreated patients with Hodgkin's disease and prognosis. Cancer Treat Rep 66:701–709
93. Bjorkholm M (1978) Immunodeficiency in Hodgkin's disease and its relation to prognosis. Scand J Haematol 33(Suppl):7–74

94. Holm G, Mellstedt H, Bjorkholm M, Johansson B, Killander D, Sundblad R, Soderberg G (1976) Lymphocyte abnormalities in untreated patients with Hodgkin's disease. Cancer 37:751–762
95. Hunter CP, Tannenbaum H, Churchill WH, Moloney WC, Schur PH (1997) Immunologic abnormalities in patients with malignant lymphoproliferative diseases. J Natl Cancer Inst 58:11185–11190
96. Franzke A, Koenecke C, Geffers R, Piao W, Hunger JK, Ganser A, Buer J (2006) Classical Hodgkin lymphoma: molecular evidence for specific alterations in circulating T lymphocytes. Tumour Biol 27:329–333
97. Levy R, Kaplan HS (1974) Impaired lymphocyte function in untreated Hodgkin's disease. N Engl J Med 290:181–186
98. Graze PR, Perlin E, Royston I (1976) In vitro lymphocyte dysfunction in Hodgkin's disease. J Natl Cancer Inst 56:239–243
99. Hillinger SM, Herzig GP (1978) Impaired cell-mediated immunity in Hodgkin's disease mediated by suppressor lymphocytes and monocytes. J Clin Invest 61:1620–1627
100. Twomey JJ, Laughter AH, Rice L, Ford R (1980) Spectrum of immunodeficiencies with Hodgkin's disease. J Clin Invest 66:629–637
101. Aisenberg AC (1964) Hodgkin's disease: prognosis, treatment, and etiologic and immunologic considerations. New Engl J Med 270:508–514, 565–570, 617–622
102. Aisenberg AC, Leskowitz S (1963) Antibody formation in Hodgkin's disease. New Engl J Med 268:1269–1272
103. Kelly WD, Lamb DL, Varco RL, Good RA (1960) An investigation of Hodgkin's disease with respect to the problem of homotransplantation. An NY Acad Sci 87:187–202
104. Brown RS, Haynes RA, Foley HT (1967) Hodgkin's disease: immunological, clinical, and histological features of 50 untreated patients. Ann Intern Med 67:291–300
105. Eltringham JR, Kaplan HS (1973) Impaired delayed hypersensitivity responses in 154 patients with untreated Hodgkin's disease. Natl Cancer Inst Monogr 36:107–115
106. Del Giacco GS, Manconi PE, Tognella S, Mantovani G, Grifoni V (1972) Delayed hypersensitivity in Hodgkin's disease. Boll Soc Ital Biol Sper 48:377–381
107. Winkelstein A, Mikulla JM, Sartiano GP, Ellis LD (1974) Cellular immunity in Hodgkin's disease: comparison of cutaneous reactivity and lymphoproliferative responses to phytohemagglutinin. Cancer 34:549–553
108. Shiftan TA, Caviles AP Jr, Mendelsohn J (1978) Spontaneous lymphocyte proliferation and depressed cellular immunity in Hodgkin's disease. Clin Exp Immunol 32:144–152
109. Ford RJ, Tsao J, Kouttab NM, Sahasrabuddhe CG, Mehta SR (1984) Association of an interleukin abnormality with the T cell defect in Hodgkin's disease. Blood 64:386–392
110. Young RC, Corder MP, Haynes HA (1972) Delayed hypersensitivity in Hodgkin's disease: a study of 103 untreated patients. Amer J Med 52:63–72
111. Aisenberg AC (1973) Malignant lymphoma. New Engl J Med 288:883–889
112. Young RC, Corder MP, Berard CW, DeVita VT (1973) Immune alterations in Hodgkin's disease: effect of delayed hypersensitivity and lymphocyte transformation on course and survival. Arch Intern Med 131:446–454
113. Schier WW, Roth A, Ostroff G, Schrift MH (1956) Hodgkin's disease and immunity. Am J Med 20:94–99
114. Jackson SM, Garrett JV, Craig AW (1970) Lymphocyte transformation changes during the clinical course of Hodgkin's disease. Cancer 25:843–850
115. Amlot PL, Slaney JM, Williams BD (1976) Circulating immune complexes and symptoms in Hodgkin's disease. Lancet 1:449–451
116. Brown CA, Hall CL, long J (1978) Circulating immune complexes in Hodgkin's disease. Am J Med 64:289–294
117. Heier HE, Klepp R, Gundersen S (1977) Blood B and T lymphocytes and in vitro cellular immune reactivity in untreated human malignant lymphomas and other malignant tumors. Scand J Haematol 18:137–148

118. Van Rijswijk RE, Sybesma JP, Kater L (1983) A prospective study of the changes in the immune status before, during, and after multiple-agent chemotherapy for Hodgkin's disease. Cancer 51:637–644
119. Bjorkholm M, Holm G, Mellstedt H (1977) Immunologic profile of patients with cured Hodgkin's disease. Scand J Haematol 18:361–368
120. Hancock BW, Bruce L, Dunsmore IR, Ward AM, Richmond J (1977) Follow-up studies on the immune status of patients with Hodgkin's disease after splenectomy and treatment, in relapse and remission. Br J Cancer 36:347–354
121. Hancock BW, Bruce L, Whitham MD, Dunsmore IR, Ward AM, Richmond J (1982) Immunity in Hodgkin's disease: status after 5 years' remission. Br J Cancer 46:593–600
122. Fisher RI, DeVita VT, Bostick F, Vanhaelen C, Howser DM, Hubbard SM, Young RC (1980) Persistent immunologic abnormalities in long-term survivors of advanced Hodgkin's disease. Ann Intern Med 92:595–599
123. Skovmann-Sorensen O, Schroder H, Moller-Larsen A, Haahr S (1981) Cellular and humoral immunity in Hodgkin's disease. I. Patients in continuous long-term remission. Scand J Haematol 27:171–180
124. Pomeroy C, Oken MM, Rydell RE, Filice GA (1991) Infection in the myelodysplastic syndromes. Am J Med 90:338–344
125. Martin S, Baldock SC, Ghoneim A, Child JA (1983) Defective neutrophil function and microbicidal mechanisms in the myelodysplastic disorders. J Clin Pathol 36:1120–1128
126. Cech P, Markert M, Perrin LH (1983) Partial myeloperoxidase deficiency in preleukemia. Blut 47:21–30
127. Scott CS, Cahill A, Bynoe AG, Aihley MJ, Hough D, Roberts BE (1983) Esterase cytochemistry in primary myelodysplastic syndrome and megaloblastic anemia. Br J Haematol 55:411–418
128. Boogaerts MA, Nelissen V, Roelant C, Goosens W (1983) Blood neutrophil function in primary myelodysplastic syndrome. Br J Haematol 55:217–227
129. Ruutu P (1986) Granulocyte function in myelodysplastic syndrome. Scand J Haematol 36(Suppl 45):66–70
130. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R, Stone RM, Nelson D, Powell BL, DeCastro CM, Ellerton J, Larson RA, Schiffer CA, Holland JF (2002) Randomized controlled trial of azacytidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 20:2429–2440
131. Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL, Larson RA (2006) Further analysis of trials with azacytidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the cancer and leukemia group B. J Clin Oncol 3895–3903
132. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, Schoch R, Gattermann N, Sanz G, List A, Gore SD, Seymour JF, Bennett JM, Byrd J, Backstrom J, Zimmerman L, McKenzie D, Beach CL, Silverman LR (2009) Efficacy of azacytidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndrome: a randomized, open-label, phase III study. Lancet Oncol 10:223–232
133. Personal communication, Dr. Kanti Rai. June 1998
134. Cheson BD (1995) Infectious and immunosuppressive complications of purine analog therapy. J Clin Oncol 13:2431–2448
135. Morrison VA, Rai KR, Peterson B et al (2001) Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: intergroup study cancer and leukemia group B 9011. J Clin Oncol 19:3611–3621
136. Anaissie EJ, Kontoyiannis DP, O'Brien S et al (1998) Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 129:559–566

137. Hensel M, Kornacker M, Yammeni S et al (2003) Disease activity and pretreatment, rather than hypogammaglobulinemia, are major risk factors for infectious complications in patients with chronic lymphocytic leukemia. Br J Haematol 122:600–606
138. Steurer M, Pall G, Richards S et al (2006) Single-agent purine analogues for the treatment of chronic lymphocytic leukaemia: a systematic review and meta-analysis. Cancer Treat Rev 32:377–389
139. Leporrier M, Chevret S, Cazin B et al (2001) Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. Blood 98:2319–2325
140. Eichhorst BF, Busch R, Hopfinger G et al (2006) Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 107:885–891
141. O'Brien S, Moore JO, Boyd TE et al (2007) Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 25:1114–1120
142. Kowal M, Dmoszynska A, Lewandowski K et al (2004) Efficacy and safety of fludarabine and cyclophosphamide combined therapy in patients with refractory/recurrent B-cell chronic lymphocytic leukaemia (B-CLL): polish multicentre study. Leuk Lymphoma 45:1159–1165
143. Hainsworth JD, Litchy S, Barton JH et al (2003) Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 21:1746–1751
144. Byrd JC, Peterson BL, Morrison VA et al (2003) Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from cancer and leukemia group B 9712 (CALGB 9712). Blood 101:6–14
145. Keating MJ, O'Brien S, Albitar M et al (2005) Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 23:4079–4088
146. Wierda W, O'Brien S, Wen S et al (2005) Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 23:4070–4078
147. Robak T, Blonski JZ, Urbanska-Rys H, Blasinska-Morawiec M, Skotnicki AB (1999) 2-chlorodeoxyadenosine (cladribine) in the treatment of patients with chronic lymphocytic leukemia 55 years old and younger. Leukemia 13:518–523
148. Byrd JC, Peterson B, Piro L et al (2003) A phase II study of cladribine treatment for fludarabine refractory B cell chronic lymphocytic leukemia: results from CALGB study 9211. Leukemia 17:323–327
149. Robak T, Blonski JZ, Kasznicki M et al (2000) Cladribine with or without prednisone in the treatment of previously treated and untreated B-cell chronic lymphocytic leukaemia: updated results of the multicentre study of 378 patients. Br J Haematol 108:357–368
150. Robak T, Blonski JZ, Kasznicki M et al (2000) Cladribine with prednisone versus chlorambucil with prednisone as first-line therapy in chronic lymphocytic leukemia: report of a prospective, randomized, multicenter trial. Blood 96:2723–2729
151. Dillman RO, Mick R, McIntyre OR (1989) Pentostatin in chronic lymphocytic leukemia: a phase II trial of cancer and leukemia group B. J Clin Oncol 7:433–438
152. Oken MM, Lee S, Kay NE et al (2004) Pentostatin, chlorambucil and prednisone therapy for B-chronic lymphocytic leukemia: a phase I/II study by the Eastern Cooperative Oncology Group study E1488. Leuk Lymphoma 45:79–84
153. Lamanna N, Kalaycio M, Maslak P et al (2006) Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 24:1575–1581

154. Shanafelt TD, Lin T, Geyer SM et al (2007) Pentostatin, cyclophosphamide, and rituximab regimen in older patients with chronic lymphocytic leukemia. Cancer 109:2291–2298
155. Keating MJ, Flinn I, Jain V et al (2002) Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 99:3554–3561
156. Hillmen P, Skotnicki AB, Robak T et al (2007) Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 25:5616–5623
157. Martin SI, Marty FM, Fiumara K et al (2006) Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. Clin Infect Dis 43:16–24
158. Elter T, Borchmann P, Schulz H et al (2005) Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol 23:7024–7031
159. Faderl S, Thomas DA, O'Brien S et al (2003) Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 101:3413–3415
160. O'Brien SM, Kantarjian HM, Thomas DA et al (2003) Alemtuzumab as treatment for residual diseased after chemotherapy in patients with chronic lymphocytic leukemia. Cancer 98:2657–2663
161. Montillo M, Cafro AM, Tedeschi A et al (2002) Safety and efficacy of subcutaneous Campath-1H for treating residual disease in patients with chronic lymphocytic leukemia responding to fludarabine. Haematologica 87:695–700
162. Wendtner CM, Ritgen M, Schweighofer CD et al (2004) Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission: experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 18:1093–1101
163. Rai KR, Byrd JC, Peterson BL, Larson RA (2002) A phase II trial of fludarabine followed by alemtuzumab in previously untreated chronic lymphocytic leukemia (CLL) patients with active disease: cancer and leukemia group B (CALGB) study 19901. Blood 100:205–206a
164. Rai KR, Byrd JC, Peterson BL et al (2003) Subcutaneous alemtuzumab following fludarabine for previously untreated patients with chronic lymphocytic leukemia (CLL): CALGB study 19901. Blood 102:676–677a
165. Morrison VA, Peterson BL, Rai KR et al (2007) Alemtuzumab increases serious infections in patients with previously untreated chronic lymphocytic leukemia (CLL) receiving fludarabine-based therapy: a comparative analysis of 3 cancer and leukemia group B studies (CALGB 9011, 9712, 19901). Blood 110:233a
166. Lin T, Donohue KA, Lucas MS et al (2007) Consolidation therapy with subcutaneous (SC) alemtuzumab results in serious infectious toxicity in previously untreated CLL patients who achieve a complete remission (CR) after fludarabine and rituximab (FR) induction therapy: Interim safety analysis of the CALGB study 10101. Blood 110:232–233a
167. Costa AJH, Costa DB, Shin B, Cooper DL (2004) Pneumococcemia as the presenting feature of multiple myeloma. Am J Heamtol 77:277–281
168. Perri RT, Hebbel R, Oken MM (1981) Influence of treatment and response status on infection risk in multiple myeloma. Am J Med 71:935–938
169. Rayner C, Haynes AP, Thompson JR et al (1991) Perspectives in multiple myeloma: survival, prognostic factors and disease complications in a single center between 1975 and 1988. Q J Med 290:517–525
170. Savage DG, Lindenbaum J, Garrett TJ (1982) Biphasic pattern of bacterial infection in multiple myeloma. An Intern Med 96:47–50
171. Meyers BR, Hirschman SZ, Axelrod JA (1972) Current patterns of infection in multiple myeloma. Am J Med 52:87–92
172. Espersen F, Birgens HS, Hertz JB et al (1984) Current patterns of infection in myelomatosis. Scan J Infect Dis 16:169–173
173. Shaikh BS, Lombard RM, Appelbaum PC et al (1982) Changing patterns of infection in patients with multiple myeloma. Oncology 39:78–82

174. Twomey JT (1973) Infections complicating multiple myeloma and chronic lymphocytic leukemia. Arch Int Med 132:562–565
175. Lortholary O, Ascioglu S, Moreau P et al (2000) Invasive aspergillosis as an opportunistic infection in nonallografted patients with multiple myeloma: a European Organization for Research and Treatment of Cancer. Clin Infect Dis 30:41–46
176. Richardson PG, Sonneveld P, Schuster MW et al (2005) Bortezomib or high dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487–2498
177. Chanan-Khan A, Sonneveld P, Schuster MW et al (2008) Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 26:4784–4790
178. Kim SJ, Kim K, Kim BS et al (2008) Bortezomib and the increased incidence of herpes zoster in patients with multiple myeloma. Clin Lymph Myeloma 8:237–240
179. Bennett C, Vardiman J, Golomb H (1986) Disseminated atypical mycobacterial infection in patients with hairy cell leukemia. Am J Med 80:891–896
180. Weinstein RA, Golomb HM, Grumet G, Gelmann E, Schechter GP (1981) Hairy cell leukemia: association with disseminated mycobacterial infection. Cancer 48:380–383
181. Weinstein RA, Gelmann E, Golomb HM (1978) Disseminated atypical mycobacteria infection in hairy cell leukemia (letter). Lancet 2:1052
182. Rice L, Shenkenberg T, Lynch C, Wheeler TM (1982) Granulomatous infections complicating hairy cell leukemia. Cancer 49:1924–1928
183. Gallo JH, Young GAR, Forrest PR, Vincent PC, Jennis F (1983) Disseminated atypical mycobacteria infection in hairy cell leukemia. Pathology 15:241–245
184. Weeks E, Jones CM, Guinee V (1992) Histoplasmosis in hairy cell leukemia: case report and review of the literature. Ann Hematol 65:138–142
185. Audeh YM, Gruszecki AC, Cherrington A (2003) Hairy cell leukemia with concurrent cryptococcus infection. Am J Hematol 72:223–224
186. Bennett CL, Westbrook CA, Gruber B (1986) Hairy cell leukemia and mucormycosis. Am J Med 81:1065–1067
187. Ma B, Seymour JF, Januszewicz H (2001) Cure of pulmonary *Rhizopus pusillis* infection in a patient with hairy cell leukemia: role of liposomal amphotericin B and GM-CSF. Leuk Lymphoma 42:1393–1399
188. Hoffman M (2006) Clinical presentations and complications of hairy cell leukemia. Hematol Oncol Clin North Am 20:1065–1073
189. Edelman MJ, O'Donnell RT, Meadows I (1997) Treatment of refractory large granular lymphocytic leukemia with 2-chlorodeoxyadenosine. Am J Hematol 54:329–331
190. Fujishima N, Sawada K, Hirokawa M, Oshimi K, Sugimoto K, Matsuda A, Teramura M, Karasawa M, Arai A, Yonemura Y, Nakao S, Omine M, Ozawa K (2008) Long-term responses and outcomes following immunosuppressive therapy in large granular lymphocytic leukemia-associated pure red cell aplasia: a nationwide cohort study in Japan for the PRCA Collaborative Study Group. Haematologica 93:1555–1559
191. Bartlett NL, Longo DL (1999) T-small lymphocytic disorders. Semin Hematol 36:164–170
192. Weide R, Heymanns J, Koppler H, Tiemann M, Huss B, Pfluger KH, Havemann K (1994) Successful treatment of neutropenia in T-LGL leukemia (T gamma-lymphocytosis) with granulocyte colony stimulating factor. Ann Hamatol 69:117–119
193. Loughran TP (1993) Clonal diseases of large granular lymphocytes. Blood 82:1–14
194. Loughran TP, Kidd PG, Starkebaum G (1994) Treatment of large granulocyte lymphocyte leukemia with oral low-dose methotrexate. Blood 84:2164–2170
195. Casazza AR, Duvall CP, Carbone PP (1966) Infection in lymphoma: histology, treatment, and duration in relation to incidence and survival. JAMA 197:118–124
196. Casazza AR, Duvall CP, Carbone PP (1966) Summary of infectious complications occurring in patients with Hodgkin's disease. Cancer Res 26:1290–1296
197. Cohen S, Fisher B, Yoshida T (1974) Serum-migration inhibitory activity in patients with lymphoproliferative disease. N Engl J Med 290:882–886

198. Aisenberg AC (1962) Studies on delayed hypersensitivity in Hodgkin's disease. J Clin Invest 1964–1970
199. Gendel BR, Ende M, Norman SL (1950) Cryptococcosis: a review with special reference to apparent association with Hodgkin's disease. Am J Med 9:343–355
200. Hutter RVP, Collins HS (1962) The occurrence of opportunistic fungus infections in a cancer hospital. Lab Invest 11:1035–1045
201. Shanbrom E, Miller S, Haar H (1960) Herpes zoster in hematologic neoplasias: some unusual manifestations. Ann Intern Med 53:523–533
202. Parker F, Jackson H, Bethea JM, Otis F (1932) Studies of diseases of lymphoid and myeloid tissues; coexistence of tuberculosis with Hodgkin's disease and other forms of malignant lymphoma. Am J M Sci 184:694–699
203. Zimmerman LE, Rappaport H (1954) Occurrence of cryptococcosis in patients with malignant disease of reticuloendothelial system. Am J Clin Path 24:1050–1072
204. Feldman S, Hughes WT, Daniel CB (1975) Varicella in children with cancer: seventy-seven cases. Pediatrics 56:388–397
205. Arvin AM, Pollard RB, Rasmussen LE et al (1980) Cellular and humoral immunity in the pathogenesis of recurrent herpes viral infections in patients with lymphoma. J Clin Invest 68:869–878
206. Whitley RJ (1984) Varicella zoster infections. In: Galasso G, Merigan T, Buchanan R (eds) Antiviral agents and viral infections of man. Raven Press, New York, pp 517–541
207. Schimpff S, Serpick A, Stoler B et al (1972) Varicella-zoster infection in patients with cancer. Ann Intern Med 76:241–254
208. Shambrom E, Miller S, Haar H (1960) Herpes zoster in hematologic neoplasias: some unusual manifestations. Ann Intern Med 53:523–533
209. Wright ET, Winer LH (1961) Herpes zoster and malignancy. Arch Dermat 84:242–247
210. Goffinet DR, Glatstein EJ, Merigan TC (1972) Herpes zoster—varicella infections and lymphoma. Ann Intern Med 76:235–240
211. Mazur MH, Dolin R (1978) Herpes zoster at the NIH: a 20 year experience. Am J Med 65:738–744
212. Arvin AM, Pollard RB, Rasmussen LE et al (1978) Selective impairment of lymphocyte reactivity to varicella-zoster virus antigen among untreated patients with lymphoma. J Infect Dis 137:531–540
213. Sokol SE, Firat D (1965) Varicella-zoster infection in Hodgkin's disease. Am J Med 39:452–463
214. Guinee VF, Guido JJ, Pfalzgraf KA et al (1985) The incidence of herpes zoster in patients with Hodgkin's disease: an analysis of prognostic factors. Cancer 56:642–647
215. Ruckdeschel JC, Schimpff SC, Smyth AC et al (1977) Herpes zoster and impaired cell-associated immunity to the varicella-zoster virus in patients with Hodgkin's disease. Am J Med 62:77–85
216. Cooperative group for the study of immunoglobulin in chronic lymphocytic leukemia (1988) Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. N Engl J Med 319:902–907
217. Morrison VA, Byrd JC, Peterson BL et al (2003) Adding rituximab to fludarabine therapy for patients with untreated chronic lymphocytic leukemia (CLL) does not increase the risk of infection: cancer and leukemia group B (CALGB) study [abstract]. Blood 102:440a
218. O'Brien S, Keating MJ, Mocarski ES (2006) Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma 7:125–130
219. Smith TF, Espy MJ, Mandrekar J et al (2007) Quantitative real-time polymerase chain reaction for evaluating DNAemia due to cytomegalovirus, Epstein-Barr virus, and BK virus in solid-organ transplant recipients. Clin Infect Dis 45:1056–1061

220. O'Brien S, Ravandi-Kashani F, Wierda WG et al (2005) A randomized trial of valacyclovir versus valganciclovir to prevent CMV reactivation in patients with CLL receiving alemtuzumab. Blood 106:830a
221. Oken MM, Pomeroy C, Weisdorf D et al (1996) Prophylactic antibiotics for the prevention of infection in multiple myeloma. Am J Med 100:624–628
222. Health and Public Policy Committee (1986) Position papers: pneumococcal vaccine. Ann Intern Med 104:118–120
223. Salmon SE, Samal BA, Hayes DM et al (1967) Role of gamma globulin for immunoprophylaxis in multiple myeloma. N Engl J Med 277:1336–1340
224. Chapel HM, Lee M, Hargreaves R et al (1994) Randomized trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. Lancet 343:1059–1063

# Infectious Complications of Stem Cell Transplantation

Charulata Ramaprasad and Kenneth J. Pursell

**Abstract**

Hematopoietic stem cell transplantation (HSCT) is an accepted treatment for a variety of hematologic malignancies. The profound immunosuppression these patients experience adversely affects their risk of infection. This risk is much higher than in the general population and requires aggressive diagnostic and therapeutic interventions. The chapter will outline the major infections after HSCT.

**Keywords**

Hematopoietic stem cell transplantation · Immunocompression · Myeloablative conditioning · Non-myeloablative conditioning · Scleraderma · Multiple sclerosis · Hypogammaglobulinemia

## Contents



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## 1 Introduction/Overview

Hematopoietic stem cell transplantation (HSCT) is an accepted therapeutic modality for a variety of life-threatening hematologic and lymphoid malignancies, cancers, and congenital disorders. This intense therapy is also being utilized more recently in the management of non-malignant and severe autoimmune processes such as scleroderma and multiple sclerosis. Nearly 50,000 stem cell transplants are performed annually worldwide (>30,000 autologous transplants and >15,000 allogeneic transplants) [1, 2]. The source of the transplanted cells may be from bone marrow, peripherally harvested stem cells, or umbilical cord blood. Infectious complications are more frequent in recipients of HLA-mismatched transplants and HLA-matched unrelated donor (MUD) transplants compared to HLA-matched related donors. This is largely the result of a higher incidence of graft-versus-host disease (GVHD) associated with these donor sources. Progenitor cells are transfused following a conditioning regimen (either myeloablative or non-myeloablative) that prepares the recipients' marrow. The conditioning regimen 'prepares' the recipient's marrow by eradicating malignant disease, creating physical space in the recipient's marrow to allow engraftment and virtually completely eradicates the recipient's immune system to prevent rejection of the graft. Conditioning regimens are broadly categorized into 'myeloablative' and 'non-myeloablative' (reduced intensity) and have major implications on the time until engraftment, transplant-related morbidity and mortality, and risk of infection. Infections are a major complication of this process that results in profound defects in several arms of the immune system. Following stem cell transplantation, there is an evolving reconstitution of donor-derived immune functions that remain poor for a prolonged period of time [3–5]. Innate immunity is the first to recover following transplantation (epithelial barriers and neutrophils) occurring within 2–3 weeks after infusion of donor cells. It takes months for the recipient to demonstrate adequate numbers of CD8 T-cells and B-cells; however, CD4 T-cells may remain low for

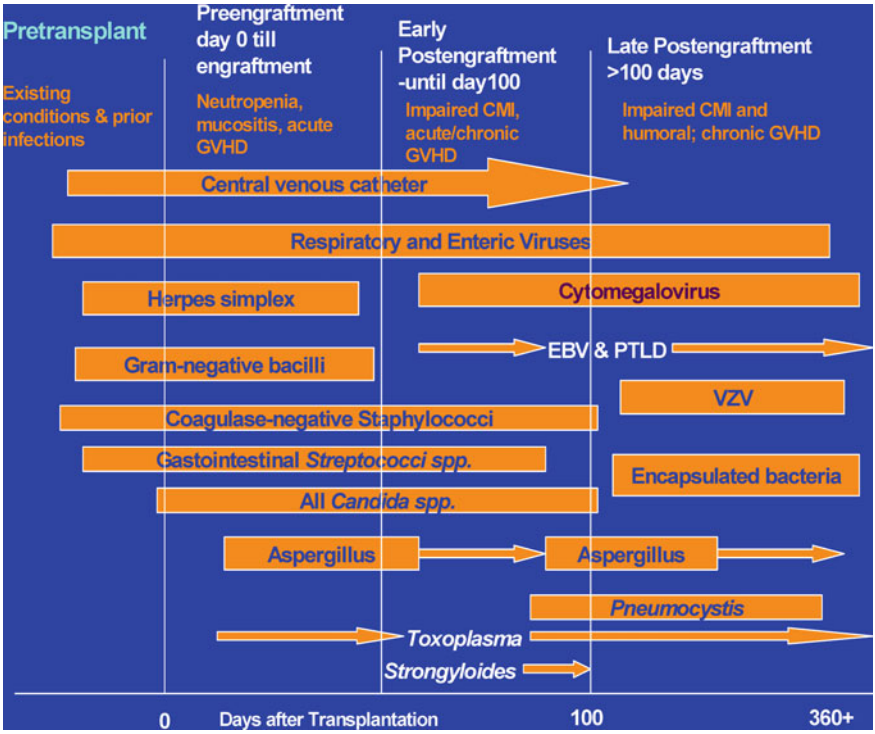


**Fig. 1** General time course of immune defects and infectious complications following hematopoietic stem cell transplantation. *GVHD* graft-versus-host disease; *CMI* cell-mediated immunity; *EBV* Epstein–Barr virus; *PTLD* Post-transplant lymphoproliferative disorder; *VZV* varicella zoster virus

years particularly in the elderly recipient with less thymic reserve. Consequently, B-cell functions and humoral immunity, which is dependent on intact CD4-cell interactions, are depressed for an extended period manifest by hypogammaglobulinemia and infections from encapsulated organisms. In addition, the frequent development of GVHD and the treatment regimens (immunosuppression) used to control this complication significantly increases the risk of infection at all points following transplantation. By convention, the sequential re-acquisition of immune function and the associated immune defects and infectious risks have been demarcated into four general time periods or phases (Fig. 1) [6–10].

1. Pre-transplant Period.
2. Pre-engraftment Period (day 0 until engraftment).
3. Early Post-engraftment Period (engraftment to day +100).
4. Late Post-engraftment Period (>day +100 following engraftment).

## 2 Pre-transplant Period

The patient's underlying disease, the treatments they have received, the amount of immune suppression, and the infectious complications and exposures all contribute to infectious risk during this time frame. The risk of infectious complications in the pre-transplant period is generally low (<20 % of infectious complications), however is quite variable. Localized infections of the skin, oral cavity, and urinary tract are the most common infections. Severe invasive infections and fatalities are very uncommon during this time period [8]. Pre-transplant infectious complications do not negatively influence the transplant or delay engraftment. It should be remembered that certain infections once felt to be contraindications to proceeding with transplantation, particularly aspergillosis, can now be managed appropriately so that successful transplantation is possible [11].

### 2.1 Pre-engraftment Period

This period begins with infusion of the cells, conventionally labeled 'day 0' and extends until marrow engraftment. The primary immune defects occurring during this phase are neutropenia and breaches in primary barriers due to mucositis and the routine use of central venous catheters. The duration of neutropenia/aplasia is usually in the range of 2–3 weeks. The source of the donor cells (peripheral blood vs. bone marrow, related vs. unrelated, matched vs. mismatched) and the absolute number of cells infused are major determinants in hematopoietic recovery. Other factors that can delay engraftment and extend the period of neutropenia (Table 1) include GVHD prophylaxis method (T-cell depleted graft, methotrexate), the development of GVHD, infectious syndromes particularly viral infections, and antimicrobial prophylaxis [e.g., trimethoprim–sulfamethoxazole for PCP prophylaxis and ganciclovir for cytomegalovirus (CMV) prevention]. Bacterial infections dominate this period of neutropenia with most organisms isolated derived from the recipient's gut (enteric gram-negative and gram-positive) and/or skin commensals (gram-positive) which include hospital-acquired skin organisms with increased antimicrobial resistance, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). As mentioned, central venous catheters are almost universally employed, which can lead to more unusual bacterial isolates in blood cultures if these vascular devices become infected. Herpes simplex virus (HSV) commonly reactivates during this time period prompting the routine use of acyclovir prophylaxis in patients with serologic evidence of past infection. Patients with delay in engraftment and a prolonged duration of neutropenia are susceptible to opportunistic fungal infections, particularly from *Candida* and *Aspergillus*. *Candida* infections typically present as bloodstream infections arising from contamination of central venous catheters while *Aspergillus* infections most often manifest as nodular pulmonary infiltrates with or without surrounding hypoattenuation on CT scanning. During this phase of transplantation, there have been reports of up to a 20 % incidence of *Clostridium*

**Table 1** Factors influencing marrow recovery/engraftment

| |
|---|
| *Source of cells* |
| Related versus unrelated |
| Matched versus mismatched |
| Marrow versus peripheral stem cells versus cord |
| *Absolute number of stem cells transfused* |
| *Type of GVHD prophylaxis* |
| Methotrexate |
| T-cell depletion |
| *Viral infections* |
| CMV |
| HHV-6 |
| *Antimicrobial prophylaxis* |
| Trimethoprim–sulfamethoxazole |
| Ganciclovir/valganciclovir |

*difficile* associated diarrhea (CDAD) as a complication of the ubiquitous application of broad-spectrum antibiotics [12]. Recent outbreaks in North America and Western Europe of hypersecreting variants of *C. difficile* (BI/NAP1/027 strain) with elaboration of high levels of toxin A and toxin B leading to more severe disease and complications raise serious concern of spread to this susceptible patient population [13] (see Chapter Enteric Infections).

## 2.2 Early Post-engraftment Period

Following engraftment and resolution of neutropenia comes a roughly 4–6-month period of early immune reconstitution. Impaired T-cell functions leading to defective cell-mediated immunity (CMI) are the hallmark immune defect of this phase of transplantation. This is the period where CMV typically reactivates and when prophylactic/preemptive strategies need to be targeted to manage this potentially fatal complication. These strategies include serial monitoring for the emergence of CMV viremia (e.g., CMV PCR analysis) and rapid employment of effective antiviral treatment (e.g., valganciclovir, foscarnet) to suppress viral replication and prevent progression to end-organ disease. The major event contributing to continued increased infectious risk is the development of GVHD. Both the pathophysiology of GVHD and the therapeutic management of this complication combine to render the transplant recipient susceptible to numerous infectious complications. Invasive aspergillosis, which historically has been a complication of the prolonged neutropenia of the pre-engraftment phase, is now more commonly encountered during this phase of transplantation. Also, there is an increasing emergence of non-*Aspergillus* mold infections

as well, particularly the Zygomycetes. Central venous catheters tend to remain in place during this phase and bacteremia and fungemia due to *Candida* spp. continue to be encountered. At our institution, the majority of central venous catheter infections in this patient population occur outside the hospital setting (unpublished). Other opportunistic infections that take advantage of the marked CMI defects include *Pneumocystis jirovecii* (PCP) and respiratory and gastrointestinal viral infections.

### 2.3 Late Post-engraftment Period

This phase of transplantation occurs around 100 days after infusion of donor cells. This time frame corresponds to the recognition of chronic GVHD, if it is present. The transplant recipient who does not develop chronic GVHD can expect to restore reasonable immune function in 1–2 years. Chronic GVHD may prolong immune recovery by years and lead to combined deficiencies in CMI and humoral immunity with hypogammaglobulinemia. Infectious complications including bacteremia, aspergillosis, pneumonia, and adenoviral infections are much more frequently seen in patients being treated for chronic GVHD, especially when higher doses of corticosteroids are used [14]. The humoral defects predispose the patient to infections with encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) especially of the respiratory tract. Prophylaxis with penicillin is routinely used at our institution in patients with chronic GVHD (quinolones are used in the penicillin allergic patient). Invasive mold infections have become a major infectious complication during this time frame in patients with severe GVHD receiving aggressive immunosuppressive management. As noted above, invasive *Aspergillus* infections are now more commonly diagnosed in these later phases of transplantation because of the emergence of GVHD. Dermatomal reactivation of varicella zoster virus (VZV) occurs in up to 50 % of patients and can progress to life-threatening disseminated infections. Of note, with the continued augmented immunosuppression attendant with chronic GVHD, there is an increasing incidence of 'late' reactivation of CMV. CMV reactivation historically has occurred in the early phase of immune reactivation; however, it is now being seen at much later periods owing to the continued immunosuppression associated with GVHD and effective preemptive anti-viral prophylaxis [15]. The inability to mount specific anti-CMV T-cell responses is associated with the development of late CMV disease [16, 17].

## 3 Infectious Syndromes Following Stem Cell Transplantation

Stem cell transplant recipients may present with one of numerous infectious syndromes after transplantation. These include febrile neutropenia, infected vascular catheters, pneumonia, sinusitis, hemorrhagic cystitis, rash, diarrhea, and

meningitis/encephalitis. Several principles apply to the care of these patients. First, knowledge of time from transplant, type of transplant, graft-versus-host disease, immunosuppression, and antimicrobial prophylaxis are critical to generating a differential diagnosis. Second, the social and personal histories of transplant recipients, including travel history, occupation, and hobbies, are essential. Finally, diagnostic procedures, when safe and feasible, should be aggressively pursued, given the broad spectrum of infectious pathogens to which these patients are susceptible, the high attributable morbidity and mortality of these infections, and the complications that arise from their therapies.

## 3.1 Febrile Neutropenia

Febrile neutropenia frequently complicates stem cell transplantation. For example, in one study of autologous stem cell transplant recipients not receiving anti-bacterial prophylaxis, neutropenic fever was seen in 83 % of patients. In this same study, 5 % of patients suffered from severe sepsis [18]. The high attributable mortality in patients with febrile neutropenia mandates prompt therapy with broad-spectrum anti-bacterial medications with an anti-pseudomonal B-lactam. Cefepime and carbapenems and/or piperacillin–tazobactam are frequently used [19–24]. The prevalence of extended spectrum B-lactamase and AmpC producing organisms, as well as local resistance data, should be taken into consideration when deciding upon an empirical antimicrobial therapy. A glycopeptide should be added if there is suspicion for a resistant gram-positive infection or the presence of mucositis. After the prompt administration of anti-bacterial therapy, a thorough search for an infectious source should be undertaken. In patients with febrile neutropenia unresponsive to anti-bacterial therapy after 72 h, empirical anti-mold therapy is recommended [19, 25] (see Chapter Neutropenic Fever and Sepsis: Evaluation and Management).

Use of fluoroquinolones for prophylaxis in patients who are afebrile, neutropenic, and have hematologic malignancies has been shown to reduce all-cause mortality, infection-related death, and fever [26]. As multi-drug-resistant pathogens continue to emerge, continued vigilance for the presence of these organisms is needed given the high anti-microbial exposure in stem cell transplant patients. The administration of prophylactic granulocyte transfusion to prevent febrile neutropenia has also been evaluated, and although this practice did lower infection-related mortality, it had no impact on all-cause mortality [27]. A study of allogeneic stem cell transplant recipients showed a decrease in days of fever and days of intravenous antibiotics, but no impact on hospital days or day 100 survival [28]. Colony-stimulating factors decrease febrile neutropenia, infections, and hospital length. However, they do not confer a survival benefit, and concerns about their effects on residual leukemic cells remain [29, 30]. Several biomarkers, such as procalcitonin, C-reactive protein, and vascular endothelial growth factor, have been evaluated as prognostic indicators in febrile neutropenia, but are not routinely employed [31, 32]. Low citrulline, a marker of mucosal barrier injury, is seen in autologous transplant patients with bacteremia [33].

## 3.2 Infected Vascular Catheters

Patients undergoing stem cell transplant have increased risk of catheter-related blood stream infections [34]. Gram-positive, gram-negative, mycobacterial, and fungal pathogens have all been reported. Training of health care workers in the proper use of central venous catheters is of paramount importance and has been shown to significantly decrease risk of catheter-associated blood stream infections [35]. Patient education is similarly important as patients often go home after transplantation with a catheter in place. An outbreak in an outpatient stem cell transplant unit of gram-negative blood stream infections was associated with increased baths (in contrast to showers) and patient self-administration of intravenous infusions [36]. Several catheter-specific interventions have been tried to decrease infection rates. The use of chlorhexidine/silver sulfadiazine catheters reduces catheter colonization but not related blood stream infections or fever in stem cell transplant recipients [37]. Urokinase rinses, which dissolve fibrin, have been shown to decrease coagulate-negative staphylococcal catheter-related blood stream infections in patients undergoing intensive cytotoxic chemotherapy for hematologic malignancy [38]. Guidelines for the management of central venous catheter infections have recently been published [39].

## 3.3 Pneumonia

The differential diagnosis for post-stem cell transplant pneumonia is broad. Infectious pathogens can be bacterial, viral, fungal, or tuberculous, and risk varies according to time from transplant. In the pre-engraftment time period, bacterial, fungal (e.g., *Aspergillus fumigatus*, but increasingly other *Aspergillus* species and mold infections), and respiratory viruses predominate. Immediately post-engraftment, respiratory viruses, CMV, toxoplasmosis, *P. jirovecii*, and *Aspergillus* are prevalent. Late post-engraftment, the differential diagnosis includes respiratory viruses, encapsulated bacteria, toxoplasmosis, aspergillosis, and *P. jirovecii*. In general, the endemic mycoses such as histoplasmosis and blastomycosis are rare, but they have been reported [40–43]. The incidence of tuberculosis is variable (less than one to almost 10 %) and depends on the incidence of disease in the population. *Nocardia* is also seen [44] (see Chapter Respiratory Infections).

## 3.4 Sinusitis

Sinusitis, especially from fungal causes, can be invasive and rapidly fatal in stem cell transplant recipients. Any patient with symptoms of sinusitis, including facial pain, facial swelling, tooth pain, palate or nasal necrosis or pallor, should be emergently evaluated by otolaryngology. Broad-spectrum anti-bacterial and anti-mold coverage should be initiated immediately. GVHD host disease is a

predisposing factor to rhinosinusitis, as is total body irradiation [45–47]. The course of sinusitis in transplant patients can be complicated, and vigilance for related intracranial pathology, such as cavernous sinus thrombosis, should be high [48]. Gram-negative pathogens (especially *Pseudomonas*) are isolated in more than half of the cultures obtained, with gram-positive bacterial and fungal organisms recovered in a significant minority. Cultures are negative in almost 1/3 of samples obtained, largely due to empiric broad-spectrum antibiotic use at the time of sampling. The spectrum of fungal pathogens involved in sinusitis continues to broaden. The agents of mucormycosis and *Aspergillus* are common, although other pathogens such as *Scedosporium* are increasingly reported [49–51].

## 3.5 Hemorrhagic Cystitis

The causes of hemorrhagic cystitis can be infectious or non-infectious. Non-infectious causes include radiation and cyclophosphamide, and recently, genetic polymorphisms in cyclophosphamide metabolism genes have been associated with hemorrhagic cystitis [52]. Common causes of infectious hemorrhagic cystitis are BK virus, adenovirus, and CMV [53, 54]. Diagnosis is made using polymerase chain reaction testing on urine or by histopathology. Hemorrhagic cystitis can lead to life-threatening blood loss and ureteral obstruction from blood clots and is one of the several syndromes associated with BK reactivation in the uroepithelial tract [55]. Treatment options for BK virus and adenovirus are limited. Several therapeutic strategies are being investigated, including treatment of BK virus with low-dose cidofovir (1 mg/kg) or intravesicular cidofovir [56, 57]. Leflunomide, ciprofloxacin, and intravenous immune globulin are also being studied for BK virus [58]. Urologic consultation should be obtained in these patients. Several newer therapies to stop bleeding, including intravesicular hyaluronic acid for a child with CMV and likely BK virus grade III hemorrhagic cystitis [59], fibrin glue therapy in five patients with refractory BK virus or CMV hemorrhagic cystitis [60], and palifermin (a human keratinocyte growth factor), have all been used successfully [61].

## 3.6 Rash

There are both infectious and non-infectious etiologies of rash after stem cell transplant. GVHD and drug reactions are common non-infectious causes. Rarer causes, such as microangiopathy, have also been reported [62]. Bacteria or fungal endocarditis or catheter-related septic emboli should always be considered in a bacteremic or fungemic patient, and surveillance for extent of embolic disease is important. *Nocardia* has been reported to cause subcutaneous nodules [44, 63], as have atypical mycobacteria, such as *Mycobacterium szulgai* and *M. fortuitum* [64, 65]. Viral causes of rash include HSV (local or disseminated) and VZV

(primary disease or reactivation) [66]. These typically cause vesicular lesions, and acyclovir or its derivatives can be used for therapy. In patients who worsen or do not improve on acyclovir, resistance should be considered. CMV, which can cause ulcerative lesions, is treated with ganciclovir. If resistance is present, foscarnet, or cidofovir can be used. Human herpesvirus 6 (HHV-6) can cause a maculopapular rash [67]. Fungal pathogens can also result in rash. For example, disseminated candidiasis can result in macules, papules, or nodules, usually on the trunk and extremities [68], as can Fusarium [69]. *Cryptococcus* can result in nodules or a cellulitic appearance. Skin manifestations of all of these pathogens are frequently atypical. As such, culture and biopsy are crucial to establish a definitive diagnosis (see Chapter Dermatologic Infections in Cancer Patients).

## 3.7 Diarrhea

Non-infectious causes of diarrhea include GVHD, chemotherapy-induced mucosal injury, and immunosuppression [70]. Common infectious causes include CMV and *C. difficile* [12, 71]. Rarer causes include diphyllobothriasis (in patients with a history of eating raw or undercooked fish) [72] and cryptosporidiosis [73]. Travel and social history are important to the differential diagnosis. Suspect strongyloidiasis in patients from an endemic area or unexplained eosinophilia during the pre-transplant evaluation, as post-transplant immunosuppression can lead to hyperinfection syndrome [74]. *Shigella* and *Salmonella* are more common in the developing world [75].

Neutropenic enterocolitis is characterized by fever and abdominal pain. Its pathogenesis not well understood, but likely arises from a combination of mucosal injury, lack of host defenses, and neutropenia. The incidence is as high as 5 %, with a high attributable mortality. Broad-spectrum antibiotics should be initiated and urgent surgical consult obtained [76] (see Chapter Enteric Infections).

## 3.8 Neurologic Syndromes

An infectious etiology is responsible for a minority of post-HSCT neurologic syndromes [77]. Infectious neurologic complications can have bacterial, fungal, or viral etiologies. Neurologic imaging and lumbar puncture (when safe) should always be performed. Bacterial meningitis can arise from typical pathogens such as pneumococcus, meningococcus, or *Listeria*. Drug resistance should be considered given the high antibiotic exposure in these patients [78–81]. Viral causes of encephalitis include HHV-6 [82], VZV (which has been reported in the absence of skin lesions) [83], West Nile virus [84, 85], HSV, and JC virus. Fungal etiologies include *Cryptococcus*, which is more common after allogeneic than autologous transplant [86]. Toxoplasmosis should be considered, and pre-transplant donor and recipient serologies should obtained (see Chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients).

## 4 Major Infectious Pathogens After SCT

In addition to infectious syndromes, there are several major infectious pathogens than warrant discussion.

### 4.1 Bacteria

*Pneumococcus* Several large studies have quantified the risk of invasive pneumococcal disease after stem cell transplantation. HSCT patients have more than 25 times the risk of the general population for pneumococcal infection. It is more commonly seen in the late post-transplant phase owing to persistent humoral immunity defects. Trimethoprim–sulfamethoxazole resistance rates are high (almost 50 %) [87]. GVHD is risk factor for disease. Overall mortality approaches 20 % [88].

*Staphylococcus* Coagulase-negative *Staphylococcus* is the most common cause of central venous catheter infections. Vancomycin is traditionally used as therapy; isolates are also sensitive to daptomycin [89]. *S. aureus*, including methicillin-resistant isolates, can be treated with vancomycin, daptomycin, or linezolid, although a B-lactam should be used if the isolate is sensitive. GVHD and length of hospital stay are the main risk factors for late staphylococcal infection after transplant [90]. The attributable mortality for *S. aureus* bacteremia in particular is high, and metastatic disease is common. If *S. aureus* is known or suspected, methicillin resistance should be covered until susceptibilities are known. Bacteremia should always be treated with intravenous antibiotics.

*Pseudomonas* The problem of emerging drug resistance seen in gram-positive organisms such as *S. aureus* is also present in numerous gram-negative pathogens, including *P. aeruginosa*. A recent study of gram-negative bacteremia found that *P. aeruginosa* constituted 22 % of all gram-negative bacteremia in stem cell transplant recipients (*Klebsiella pneumoniae* and *Escherichia coli* were 19 and 17 %, respectively). Thirty seven percentage of gram-negative isolated were multi-drug resistant (resistant to at least two of the following: a 3rd or 4th generation cephalosporin, a carbapenem, or piperacillin–tazobactam). This has profound implications for the selection of empirical gram-negative therapy [91]. In critical ill patients, dual coverage until susceptibilities are known should be considered.

### 4.2 Fungi

*Candida* Risk factors for *Candida albicans* infection include use of broad-spectrum antibiotics, breakdown of mucosal membranes, central venous catheterization, and neutropenia. The widespread use of fluconazole as *Candida* prophylaxis during neutropenia has decreased morbidity and mortality from invasive *Candida* infections considerably. This has also resulted in the increased

prevalence of non-*albicans Candida* such as *C. kruseii* (which is intrinsically resistant to fluconazole) and fluconazole-resistant *C. glabrata.* Other *Candida* species, such as *C. parapsilosis*, are seen in the setting of parenteral nutrition [92].

*Aspergillus and other angioinvasive molds* With the use of fluconazole prophylaxis, invasive mold infections, particularly invasive aspergillosis, have become dominant fungal pathogens in the stem cell transplant population. Disease prevalence ranges from 5 to 15 % [93, 94]. Risk factors include advanced age, allogeneic transplant, GVHD, neutropenia, and viral infections. The emergence of viral infections as risk factors for invasive aspergillosis has been a significant and relatively recent development, with hazard ratios for lower respiratory tract viral infection and CMV 4.2 and 2.8, respectively [95]. The increasing prevalence of non-*fumigatus Aspergillus* species, zygomycetes (especially in those patients on voriconazole prophylaxis), and *Scedosporium apiospermum* [50], combined with the toxicities of several of the anti-mold therapies, makes aggressive pursuit of diagnosis with biopsy, culture, or non-culture based means essential [96–103].

## 4.3 Viruses

*Cytomegalovirus* CMV seropositive recipients of grafts from seronegative donors represent those at highest risk for disease. With increasing and successful use of prophylaxis and preemptive strategies after HSCT, CMV reactivation is now being seen at later time points. Lack of CMV-specific T-cell-mediated immunity after transplant increases risk of CMV, particularly late disease [10, 104]. High-dose acyclovir and valacyclovir can be used as prophylactic agents. Intravenous ganciclovir and oral valganciclovir are also active and could be used as prophylaxis, but marrow toxicity limits long-term use [104, 105]. If acyclovir or valacyclovir is used as prophylactic medications, they must be combined with preemptive monitoring strategies with weekly CMV monitoring (pp65 antigen or CMV PCR).

Early detection of viremia and associated end-organ disease is essential for preventing severe CMV-associated complications. End-organ disease usually manifests as gastroenteritis or pneumonitis, with retinitis and encephalitis less frequently described in this population. Retinitis, when it is seen, is often present in the late post-transplant course. Viremia and end-organ disease are both treated with intravenous ganciclovir. Intravenous immune globulin has been used as adjuvant therapy for pneumonitis [104]. Mortality is high, even with appropriate therapy. Standardized therapy recommendations for gastrointestinal CMV disease are lacking, although most would agree that longer therapy and maintenance with ganciclovir is necessary. IVIG is not usually given for gastrointestinal disease. Additionally, it is critical to distinguish this manifestation from GVHD. Colonoscopy should be pursued if safe. Recurrence rates of invasive disease are high in the HSCT population, necessitating ongoing surveillance [10].

*Herpes simplex viruses* After primary HSV infection, latency is established, with reactivation occurring during periods of immunosuppression. HSV-1 and HSV-2 frequently reactivate and can cause disease after HSCT, although disease attributable to HSV-1 is more common [106]. Reactivation of HSV was common prior to routine anti-viral prophylaxis (around 80 %), which is now given routinely to seropositive patients. Cutaneous and mucosal lesions (including oropharyngeal and esophageal) are the most common manifestations, although dissemination to the brain, lungs, and liver can occur. Intravenous acyclovir therapy should be used for visceral disease or severe mucocutaneous disease, while oral acyclovir, valacyclovir, or famciclovir can be used for less serious disease. Diagnosis can be made by culture, immunofluorescence, or PCR.

*Varicella zoster virus* After primary infection, VZV establishes latency in the dorsal root ganglia and reactivates during periods of immunosuppression as herpes zoster [106]. Prior to the use of prophylaxis, 50 % of those HSCT patients surviving 6 months developed herpes zoster, with high attributable morbidity and mortality. VZV manifests locally as a vesicular rash, with serious risk of dissemination to brain, lungs, and liver. Prophylaxis of seropositive allogeneic recipients is recommended for 1 year. Initial treatment of disease should be with intravenous acyclovir, although oral therapy can be used to finish therapy. Diagnosis can be made by culture, immunofluorescence, or PCR.

*Epstein–Barr Virus (EBV)* Primary infection with EBV occurs in childhood or adolescence. Reactivation after transplantation is usually subclinical; however, numerous EBV-related tumors can arise after transplant. Unlike previously noted viral infections, prophylaxis against EBV reactivation is not recommended as it has no impact on prevention of EBV-related post-transplant lymphoproliferative disorders (PTLD). Monitoring by PCR is recommended in high-risk patients, and preemptive therapy with agents such as rituximab can be considered [106]. Serial monitoring of EBV DNA levels by PCR may be useful is ascertaining which patients may progress to EBV-associated PTLD [107].

*Human herpesvirus 6* HHV-6 exposure usually occurs during childhood. It reactivates frequently after HSCT; therefore, its detection in the blood alone is of unclear clinical significance. Encephalitis is the most common clinical manifestation but still remains quite rare—there are approximately 40 reported cases in the literature. Prophylaxis against HHV-6 reactivation is not recommended. Encephalitis can be treated with foscarnet or ganciclovir [108]. PCR can detect viral DNA in peripheral blood or CSF. Interesting, HHV-6 has the ability to integrate into the host's chromosome, although this happens in the vast minority of cases.

*Adenovirus* The incidence of adenovirus infection is between 5 and 21 % after HSCT [54]. Cystitis and enteritis results in low mortality, but adenovirus pneumonia and hepatitis are often fatal. Cidofovir has in vitro activity and has been used at both low and high doses though despite treatment, mortality from invasive disease is very high. Of 687 patients who received allogeneic stem cell transplants, adenovirus was isolated from 64 patients. It was most commonly found in stool (49 patients), respiratory specimens (22 patients), and urine. Eleven of these patients met the criteria for invasive disease (3 had pneumonia, 1 had hepatitis, 4 had

hemorrhagic colitis, and 3 had hemorrhagic cystitis). Eight of the 11 patients received T-cell-depleted grafts, and all 3 with pneumonia died despite therapy.

*Respiratory Viruses* Respiratory syncytial virus (RSV) causes typical upper respiratory tract infection symptoms [109]. It progresses to pneumonia in 30–40 % patients and in this form may be fatal. Co-pathogens are identified 30 % of the time. Ribavirin has been use for treatment with mixed results. Lymphopenia is a major risk factor for progression to lower tract disease within the first 3 months of HSCT.

Parainfluenza also presents initially as an upper tract infection. It has four serotypes, with serotype three being the most common. Lymphopenia and use of corticosteroids are the risk factors for progression to lower tract disease, and like RSV, it is often isolated with a co-pathogen. Mortality from parainfluenza pneumonia is around 35 %. The data on aerosolized ribavirin and IVIG in parainfluenza are retrospective in nature and it is unclear whether their use is beneficial.

Influenza has a lower incidence than RSV and parainfluenza and importantly can be prevented and attenuated with vaccination although response rates to vaccines are low in the HSCT population. Anti-viral treatment is generally instituted in all HSCT patients who test positive, and chemoprophylaxis in immunocompromised hosts can be considered in the setting of an outbreak. Yearly information about circulating strains and their susceptibility should be incorporated into treatment decisions, given the recent issues with resistance and the emergence of the novel H1N1 strain during 2009.

Finally, human metapneumovirus was recently discovered. It is structurally similar to RSV. Risk factors for disease acquisition and progression are unclear. There are no established treatment guidelines, although ribavirin has in vitro activity.

## References

1. Tabbara IA, Zimmerman K, Morgan C, Nahleh Z (2002) Allogeneic hematopoietic stem cell transplantation: complications and results. Arch Intern Med 162:1558–1566
2. Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354:1813–1826
3. Storek J, Geddes M, Khan F et al (2008) Reconstitution of the immune system after hematopoietic stem cell transplantation in humans. Semin Immunopathol 30:425–437
4. Storek J, Dawson MA, Storer B et al (2001) Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. Blood 97:3380–3389
5. Geddes M, Storek J (2007) Immune reconstitution following hematopoietic stem-cell transplantation. Best Pract Res Clin Haematol 20:329–348
6. Meyers JD (1986) Infection in bone marrow transplant recipients. Am J Med 81:27–38
7. Wingard JR (1999) Opportunistic infections after blood and marrow transplantation. Transpl Infect Dis 1:3–20
8. Sable CA, Donowitz GR (1994) Infections in bone marrow transplant recipients. Clin Infect Dis 18:273–281 (quiz 82–84)
9. LaRocco MT, Burgert SJ (1997) Infection in the bone marrow transplant recipient and role of the microbiology laboratory in clinical transplantation. Clin Microbiol Rev 10:277–297
10. Hiemenz JW (2009) Management of infections complicating allogeneic hematopoietic stem cell transplantation. Semin Hematol 46:289–312
11. Hill BT, Kondapalli L, Artz A et al (2007) Successful allogeneic transplantation of patients with suspected prior invasive mold infection. Leuk Lymphoma 48:1799–1805

12. Bobak D, Arfons LM, Creger RJ, Lazarus HM (2008) *Clostridium difficile*-associated disease in human stem cell transplant recipients: coming epidemic or false alarm? Bone Marrow Transplant 42:705–713
13. Blossom DB, McDonald LC (2007) The challenges posed by reemerging *Clostridium difficile* infection. Clin Infect Dis 45:222–227
14. Yamasaki S, Heike Y, Mori S et al (2008) Infectious complications in chronic graft-versus-host disease: a retrospective study of 145 recipients of allogeneic hematopoietic stem cell transplantation with reduced- and conventional-intensity conditioning regimens. Transpl Infect Dis 10:252–259
15. Hebart H, Einsele H (2004) Clinical aspects of CMV infection after stem cell transplantation. Hum Immunol 65:432–436
16. Boeckh M, Leisenring W, Riddell SR et al (2003) Late *Cytomegalovirus* disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood 101:407–414
17. Moins-Teisserenc H, Busson M, Scieux C et al (2008) Patterns of *Cytomegalovirus* reactivation are associated with distinct evolutive profiles of immune reconstitution after allogeneic hematopoietic stem cell transplantation. J Infect Dis 198:818–826
18. Hamalainen S, Kuittinen T, Matinlauri I, Nousiainen T, Koivula I, Jantunen E (2009) Severe sepsis in autologous stem cell transplant recipients: microbiological aetiology, risk factors and outcome. Scand J Infect Dis 41:14–20
19. Freifeld AG, Bow EJ, Sepkowitz KA et al (2011) Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infections Diseases Society of America. Clin Infect Dis 52:e56–e93
20. Harter C, Schulze B, Goldschmidt H et al (2006) Piperacillin/tazobactam vs ceftazidime in the treatment of neutropenic fever in patients with acute leukemia or following autologous peripheral blood stem cell transplantation: a prospective randomized trial. Bone Marrow Transplant 37:373–379
21. Bow EJ, Rotstein C, Noskin GA et al (2006) A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. Clin Infect Dis 43:447–459
22. Sanz MA, Bermudez A, Rovira M et al (2005) Imipenem/cilastatin versus piperacillin/tazobactam plus amikacin for empirical therapy in febrile neutropenic patients: results of the COSTINE study. Curr Med Res Opin 21:645–655
23. Cherif H, Bjorkholm M, Engervall P et al (2004) A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. Scand J Infect Dis 36:593–600
24. Raad II, Escalante C, Hachem RY et al (2003) Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. Cancer 98:1039–1047
25. Neuburger S, Maschmeyer G (2006) Update on management of infections in cancer and stem cell transplant patients. Ann Hematol 85:345–356
26. Gafter-Gvili A, Paul M, Fraser A, Leibovici L (2007) Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. J Antimicrob Chemother 59:5–22
27. Massey E, Paulus U, Doree C, Stanworth S (2009) Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev 1:CD005341
28. Oza A, Hallemeier C, Goodnough L et al (2006) Granulocyte-colony-stimulating factor-mobilized prophylactic granulocyte transfusions given after allogeneic peripheral blood progenitor cell transplantation result in a modest reduction of febrile days and intravenous antibiotic usage. Transfusion 46:14–23

29. Levenga TH, Timmer-Bonte JN (2007) Review of the value of colony stimulating factors for prophylaxis of febrile neutropenic episodes in adult patients treated for haematological malignancies. Br J Haematol 138:146–152
30. Battiwalla M, McCarthy PL (2009) Filgrastim support in allogeneic HSCT for myeloid malignancies: a review of the role of G-CSF and the implications for current practice. Bone Marrow Transplant 43:351–356
31. Hamalainen S, Juutilainen A, Matinlauri I et al (2009) Serum vascular endothelial growth factor in adult haematological patients with neutropenic fever: a comparison with C-reactive protein. Eur J Haematol 83(3):251–257
32. Prat C, Sancho JM, Dominguez J et al (2008) Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leuk Lymphoma 49:1752–1761
33. Herbers AH, Blijlevens NM, Donnelly JP, de Witte TJ (2008) Bacteraemia coincides with low citrulline concentrations after high-dose melphalan in autologous HSCT recipients. Bone Marrow Transplant 42:345–349
34. Sariosmanoglu N, Ugurlu B, Turgut NH et al (2008) Use of tunnelled catheters in haematological malignancy patients with neutropenia. J Int Med Res 36:1103–1111
35. Chaberny IF, Ruseva E, Sohr D et al (2009) Surveillance with successful reduction of central line-associated bloodstream infections among neutropenic patients with hematologic or oncologic malignancies. Ann Hematol 88:907–912
36. Toscano CM, Bell M, Zukerman C et al (2009) Gram-negative bloodstream infections in hematopoietic stem cell transplant patients: the roles of needleless device use, bathing practices, and catheter care. Am J Infect Control 37:327–334
37. Maaskant JM, De Boer JP, Dalesio O, Holtkamp MJ, Lucas C (2009) The effectiveness of chlorhexidine-silver sulfadiazine impregnated central venous catheters in patients receiving high-dose chemotherapy followed by peripheral stem cell transplantation. Eur J Cancer Care (Engl) 18:477–482
38. van Rooden CJ, Schippers EF, Guiot HF et al (2008) Prevention of coagulase-negative staphylococcal central venous catheter-related infection using urokinase rinses: a randomized double-blind controlled trial in patients with hematologic malignancies. J Clin Oncol 26:428–433
39. Mermel LA, Allon M, Bouza E et al (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 49:1–45
40. Vail GM, Young RS, Wheat LJ, Filo RS, Cornetta K, Goldman M (2002) Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. Transpl Infect Dis 4:148–151
41. Jones O, Cleveland KO, Gelfand MS (2009) A case of disseminated histoplasmosis following autologous stem cell transplantation for Hodgkin's lymphoma: an initial misdiagnosis with a false-positive serum galactomannan assay. Transpl Infect Dis 11:281–283
42. Peterson MW, Pratt AD, Nugent KM (1987) Pneumonia due to Histoplasma capsulatum in a bone marrow transplant recipient. Thorax 42:698–699
43. Serody JS, Mill MR, Detterbeck FC, Harris DT, Cohen MS (1993) Blastomycosis in transplant recipients: report of a case and review. Clin Infect Dis 16:54–58
44. Freites V, Sumoza A, Bisotti R et al (1995) Subcutaneous *Nocardia* asteroides abscess in a bone marrow transplant recipient. Bone Marrow Transplant 15:135–136
45. Ortiz E, Sakano E, De Souza CA, Vigorito A, Eid KA, Chronic GVHD (2006) Predictive factor for rhinosinusitis in bone marrow transplantation. Braz J Otorhinolaryngol 72:328–332
46. Thompson AM, Couch M, Zahurak ML, Johnson C, Vogelsang GB (2002) Risk factors for post-stem cell transplant sinusitis. Bone Marrow Transplant 29:257–261

47. Savage DG, Taylor P, Blackwell J et al (1997) Paranasal sinusitis following allogeneic bone marrow transplant. Bone Marrow Transplant 19:55–59
48. de Medeiros CR, Bleggi-Torres LF, Faoro LN et al (2001) Cavernous sinus thrombosis caused by zygomycosis after unrelated bone marrow transplantation. Transpl Infect Dis 3:231–234
49. Beltrame A, Sarmati L, Cudillo L et al (2009) A fatal case of invasive fungal sinusitis by Scopulariopsis acremonium in a bone marrow transplant recipient. Int J Infect Dis 13:e488–e492
50. Machado CM, Martins MA, Heins-Vaccari EM et al (1998) *Scedosporium apiospermum* sinusitis after bone marrow transplantation: report of a case. Rev Inst Med Trop Sao Paulo 40:321–323
51. Schlemmer F, Lagrange-Xelot M, Lacroix C, de La Tour R, Socie G, Molina JM (2008) Breakthrough Rhizopus infection on posaconazole prophylaxis following allogeneic stem cell transplantation. Bone Marrow Transplant 42:551–552
52. Rocha V, Porcher R, Fernandes JF et al (2009) Association of drug metabolism gene polymorphisms with toxicities, graft-versus-host disease and survival after HLA-identical sibling hematopoietic stem cell transplantation for patients with leukemia. Leukemia 23:545–556
53. Ison MG (2006) Adenovirus infections in transplant recipients. Clin Infect Dis 43:331–339
54. Symeonidis N, Jakubowski A, Pierre-Louis S et al (2007) Invasive adenoviral infections in T-cell-depleted allogeneic hematopoietic stem cell transplantation: high mortality in the era of cidofovir. Transpl Infect Dis 9:108–113
55. Rajpoot DK, Gomez A, Tsang W, Shanberg A (2007) Ureteric and urethral stenosis: a complication of BK virus infection in a pediatric renal transplant patient. Pediatr Transplant 11:433–435
56. Savona MR, Newton D, Frame D, Levine JE, Mineishi S, Kaul DR (2007) Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. Bone Marrow Transplant 39:783–787
57. Bridges B, Donegan S, Badros A (2006) Cidofovir bladder instillation for the treatment of BK hemorrhagic cystitis after allogeneic stem cell transplantation. Am J Hematol 81:535–537
58. Rinaldo CH, Hirsch HH (2007) Antivirals for the treatment of polyomavirus BK replication. Expert Rev Anti Infect Ther 5:105–115
59. Cipe FE, Soygur T, Dogu F, Erdogan O, Bozdogan G (2009) Ikinciogullari A. Treatment with intravesical hyaluronic acid. Pediatr Transplant, Late onset hemorrhagic cystitis in a hematopoietic stem cell recipient
60. Tirindelli MC, Flammia G, Sergi F et al (2009) Fibrin glue for refractory hemorrhagic cystitis after unrelated marrow, cord blood, and haploidentical hematopoietic stem cell transplantation. Transfusion 49:170–175
61. Czibere A, Bruns I, Graef T et al (2007) Treatment of severe hemorrhagic cystitis after allogeneic stem cell transplantation with palifermin, a recombinant human keratinocyte growth factor. Biol Blood Marrow Transplant 13:872–874
62. Choi CM, Schmaier AH, Snell MR, Lazarus HM (2009) Thrombotic microangiopathy in haematopoietic stem cell transplantation: diagnosis and treatment. Drugs 69:183–198
63. Hodohara K, Fujiyama Y, Hiramitu Y et al (1993) Disseminated subcutaneous *Nocardia* asteroides abscesses in a patient after bone marrow transplantation. Bone Marrow Transplant 11:341–343
64. Frisk P, Boman G, Pauksen K, Petrini B, Lonnerholm G (2003) Skin infection caused by *Mycobacterium szulgai* after allogeneic bone marrow transplantation. Bone Marrow Transplant 31:511–513
65. Okano A, Shimazaki C, Ochiai N et al (2001) Subcutaneous infection with *Mycobacterium fortuitum* after allogeneic bone marrow transplantation. Bone Marrow Transplant 28:709–711

66. Onozawa M, Hashino S, Haseyama Y et al (2009) Incidence and risk of postherpetic neuralgia after varicella zoster virus infection in hematopoietic cell transplantation recipients: hokkaido hematology study group. Biol Blood Marrow Transplant 15:724–729
67. Ljungman P, Singh N (2006) Human herpesvirus-6 infection in solid organ and stem cell transplant recipients. J Clin Virol 37(Suppl 1):S87–S91
68. Pedraz J, Delgado-Jimenez Y, Perez-Gala S, Nam-Cha S, Fernandez-Herrera J, Garcia-Diez A (2009) Cutaneous expression of systemic candidiasis. Clin Exp Dermatol 34:106–110
69. Busemann C, Kruger W, Schwesinger G et al (2009) Myocardial and aortal involvement in a case of disseminated infection with Fusarium solani after allogeneic stem cell transplantation: report of a case. Mycoses 52:372–376
70. Selbst MK, Ahrens WA, Robert ME, Friedman A, Proctor DD, Jain D (2009) Spectrum of histologic changes in colonic biopsies in patients treated with mycophenolate mofetil. Mod Pathol 22:737–743
71. Schulenburg A, Turetschek K, Wrba F et al (2004) Early and late gastrointestinal complications after myeloablative and nonmyeloablative allogeneic stem cell transplantation. Ann Hematol 83:101–106
72. Detrait M, Poirier L, Roy DC et al (2009) Diphyllobothriasis, a rare cause of profuse diarrhea following autologous transplantation. Bone Marrow Transplant 44:131–132
73. Manivel C, Filipovich A, Snover DC (1985) Cryptosporidiosis as a cause of diarrhea following bone marrow transplantation. Dis Colon Rectum 28:741–742
74. Wirk B, Wingard JR (2009) Strongyloides stercoralis hyperinfection in hematopoietic stem cell transplantation. Transpl Infect Dis 11:143–148
75. Kang G, Srivastava A, Pulimood AB, Dennison D, Chandy M (2002) Etiology of diarrhea in patients undergoing allogeneic bone marrow transplantation in South India. Transplantation 73:1247–1251
76. Davila ML (2006) Neutropenic enterocolitis. Curr Opin Gastroenterol 22:44–47
77. Batlle M, Oriol A, Ribera JM et al (2005) Neurologic complications following hematopoietic stem cell transplantation. Study of 14 patients. Med Clin (Barc) 125:697–699
78. Buxmann H, Soerensen J, Koehl U et al (2003) Meningitis due to multiple-resistant penicillin- and cefotaxime-intermediate *Streptococcus pneumoniae* in a German child after bone marrow transplantation. Infection 31:425–427
79. de Almeida SM, Teive HA, Brandi I et al (2003) Fatal Bacillus cereus meningitis without inflammatory reaction in cerebral spinal fluid after bone marrow transplantation. Transplantation 76:1533–1534
80. Matsubara H, Makimoto A, Higa T et al (2003) Successful treatment of meningoencephalitis caused by methicillin-resistant *Staphylococcus aureus* with intrathecal vancomycin in an allogeneic peripheral blood stem cell transplant recipient. Bone Marrow Transplant 31:65–67
81. Girmenia C, Iori AP, Bernasconi S et al (2000) Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. Eur J Clin Microbiol Infect Dis 19:711–714
82. Yoshida H, Matsunaga K, Ueda T et al (2002) Human herpesvirus 6 meningoencephalitis successfully treated with ganciclovir in a patient who underwent allogeneic bone marrow transplantation from an HLA-identical sibling. Int J Hematol 75:421–425
83. Leveque N, Galambrun C, Najioullah F, Bleyzac N, Pages MP, Bertrand Y (2006) Two cases of varicella zoster virus meningitis found in pediatric patients after bone marrow transplantation despite valaciclovir prophylaxis and without skin lesions. J Med Virol 78:514–516
84. Robertson KB, Barron MA, Nieto Y (2004) West Nile virus infection in bone marrow transplant patients. Bone Marrow Transplant 34:823–824
85. Hiatt B, DesJardin L, Carter T, Gingrich R, Thompson C, de Magalhaes-Silverman M (2003) A fatal case of West Nile virus infection in a bone marrow transplant recipient. Clin Infect Dis 37:e129–e131

86. Mendpara SD, Ustun C, Kallab AM, Mazzella FM, Bilodeau PA, Jillella AP (2002) Cryptococcal meningitis following autologous stem cell transplantation in a patient with multiple myeloma. Bone Marrow Transplant 30:259–260
87. Kumar D, Humar A, Plevneshi A et al (2008) Invasive pneumococcal disease in adult hematopoietic stem cell transplant recipients: a decade of prospective population-based surveillance. Bone Marrow Transplant 41:743–747
88. Engelhard D, Cordonnier C, Shaw PJ et al (2002) Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. Br J Haematol 117:444–450
89. Kratzer C, Rabitsch W, Hirschl AM, Graninger W, Presterl E (2007) In vitro activity of daptomycin and tigecycline against coagulase-negative *Staphylococcus* blood isolates from bone marrow transplant recipients. Eur J Haematol 79:405–409
90. Mihu CN, Schaub J, Kesh S et al (2008) Risk factors for late *Staphylococcus aureus* bacteremia after allogeneic hematopoietic stem cell transplantation: a single-institution, nested case-controlled study. Biol Blood Marrow Transplant 14:1429–1433
91. Oliveira AL, de Souza M, Carvalho-Dias VM et al (2007) Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. Bone Marrow Transplant 39:775–781
92. De La Rosa GR, Champlin RE, Kontoyiannis DP (2002) Risk factors for the development of invasive fungal infections in allogeneic blood and marrow transplant recipients. Transpl Infect Dis 4:3–9
93. Pagano L, Caira M, Nosari A et al (2007) Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study–Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clin Infect Dis 45:1161–1170
94. Grow WB, Moreb JS, Roque D et al (2002) Late onset of invasive *Aspergillus* infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant 29:15–19
95. Martino R, Pinana JL, Parody R et al (2009) Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT. Bone Marrow Transplant 44:749–756
96. Ghiasian SA, Maghsood AH, Mirhendi SH (2006) Disseminated, fatal Trichosporon asahii infection in a bone marrow transplant recipient. J Microbiol Immunol Infect 39:426–429
97. Shi JM, Cai Z, Huang H et al (2009) Role of CT-guided percutaneous lung biopsy in diagnosis of pulmonary fungal infection in patients with hematologic diseases. Int J Hematol 89:624–627
98. Herbrecht R, Denning DW, Patterson TF et al (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415
99. Lionakis MS, Kontoyiannis DP (2005) Sinus zygomycosis in a patient receiving voriconazole prophylaxis. Br J Haematol 129:2
100. Kontoyiannis DP, Lionakis MS, Lewis RE et al (2005) Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 191:1350–1360
101. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP (2005) Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41:60–66
102. Rachwalski EJ, Wieczorkiewicz JT, Scheetz MH (2008) Posaconazole: an oral triazole with an extended spectrum of activity. Ann Pharmacother 42:1429–1438
103. Schulenburg A, Sperr W, Rabitsch W, Knobl P, Thalhammer F (2005) Brief report: practicability and safety of amphotericin B deoxycholate as continuous infusion in neutropenic patients with hematological malignancies. Leuk Lymphoma 46:1163–1167
104. Ljungman P (2008) CMV infections after hematopoietic stem cell transplantation. Bone Marrow Transplant 42(Suppl 1):S70–S72

105. Kline J, Pollyea DA, Stock W et al (2006) Pre-transplant ganciclovir and post transplant high-dose valacyclovir reduce CMV infections after alemtuzumab-based conditioning. Bone Marrow Transplant 37:307–310
106. Styczynski J, Reusser P, Einsele H et al (2006) Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the second European Conference on Infections in Leukemia. Bone Marrow Transplant 43:757–770
107. Aalto SM, Juvonen E, Tarkkanen J et al (2007) Epstein-Barr viral load and disease prediction in a large cohort of allogeneic stem cell transplant recipients. Clin Infect Dis 45:1305–1309
108. Ljungman P, de la Camara R, Cordonnier C et al (2008) Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 42:227–240
109. Boeckh M (2008) The challenge of respiratory virus infections in hematopoietic cell transplant recipients. Br J Haematol 143:455–467

# Infections Associated with Solid Malignancies

Sarah H. Sutton

**Abstract**

Although solid tumors comprise the vast majority of cancers, the incidence of serious infectious complications in this population is much less than in patients with hematologic malignancies. Most infections involving patients with solid tumors comprise two groups. First, patients acquire infections as a result of the cancer itself, due to either mass effect that interrupts normal function or destruction of the normal barriers to infection. Second, patients acquire infections as a complication of the treatments they receive, such as chemotherapy, radiation, surgery, or medical devices. Advances in the management of cancer have resulted in a gradual stepwise improvement in survival for patients with most types of solid tumors. Much of this improvement has been attributed to advances in cancer screening, diagnosis, and therapeutic modalities. In addition, improvements in the prevention, diagnosis, and treatment of infections have likely contributed to this prolonged survival. This review highlights select articles in the medical literature that shed light on the epidemiology and pathophysiology of infections in patients with solid tumors. In addition, this review focuses upon the diagnosis and treatment of these infections and their recent advances.

**Keywords**

Neoplasm · Infection · Bacterial infections · Soft tissue infections · Respiratory tract infection · Intraabdominal infection · Bacillus Calmette-Guérin · *Clostridium septicum* · *Streptococcus bovis*

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## Contents



## 1 Introduction

Solid tumors are defined by The National Cancer Institute (NCI) as non-cystic masses, both benign and malignant, and include the carcinomas, lymphomas, and sarcomas; these cancers represent the vast majority of malignancies in adults. All ten of the most common new cancer diagnoses in US adults are solid tumors [1]. For US men alone, 9 of the top 10 cancers are solid tumors. Prostate cancer, the most common male cancer, has an incidence 10 times greater than leukemia, which ranks ninth in incidence [1]. Although solid tumors account for the vast majority of cancers in adults, the incidence of severe infectious complications in these patients is much lower than in patients with hematologic malignancies. Nevertheless, patients with solid tumors complicated by infection comprise a large portion of hospitalized cancer patients with infections—mainly as a result of the high frequency of these cancers. It is necessary to interpret with caution most

studies that include both patients with solid tumors and patients with hematologic malignancies. Many of these studies are retrospective, represent hospitalized patients only, and represent single institutions. Such studies are hampered by the high prevalence of patients with solid tumors and the variable representation of hematologic patients in each inpatient setting. Unless explicitly stated in these articles, the incidence of infectious complications of solid tumors compared to those with hematologic malignancies should not be estimated.

## 2 Immune Defects Among Patients with Solid Tumors

The function of the immune system is a major factor in determining the spectrum of infections to which cancer patients are vulnerable. Absent in most solid tumor patients is a distinct defect in the white blood cells or their products caused by the cancer itself, as in patients with leukemia. Instead, comorbidities, time to cancer diagnosis, and secondary effects of cancer subtly influence the strength of the immune system. Comorbidities such as chronic obstructive pulmonary disease (COPD) and poor dentition may increase infection risk at presentation and throughout therapy. Because solid tumor patients often have indolent presentations and prolonged treatment courses, malnutrition and cancer cachexia may be severe. Malnutrition weakens both the innate and adaptive immune responses. Both the innate and the adaptive immune systems may be altered somewhat in the patient with a solid tumor, although the impact of cancer and its therapies upon the innate immune system is better understood.

The innate immune system, which includes the skin and mucosal barriers to infection as well as phagocytes, natural killer cells, and complement, is damaged in those with solid tumor as a direct and indirect result of the cancer as well as from its therapies. Specific to each cancer type, tumor location, size, and the presence or absence of metastasis, solid tumors may increase the risk of infection by their mass effect. When the physiologic flow of biliary or pancreatic fluids, enteral contents, or urinary fluids is disrupted or obstructed, abscess, bacteremia or, in the case of enteral obstruction, an aspiration event may result. Also, the cancer itself may disrupt the normal physical barriers to infection such as skin or mucosa. Thus, infection may develop as a result of an injured physiologic barrier. For example, patients with colon cancer are at increased risk of bacteremia, peritonitis, or colon perforation as a result of such a defect. Many patients with solid tumors undergo surgical interventions, and a growing number undergo procedures performed in interventional radiology. Normal physiologic barriers are often crossed, leaving normally sterile tissues and organs vulnerable to colonization and infection by pathogens. The local injury, ischemia, and necrosis caused by radiation therapy may further increase the risk of infection.

Chemotherapy and radiation may result in decreased number of circulating neutrophils. A subset of solid tumor patients receive intensive chemotherapy that is complicated by neutropenia, but typically the period of neutropenia is brief. As a result of the brevity of neutropenia, many neutropenic solid tumor patients are

considered low risk for significant infectious morbidity and mortality. The duration of neutropenia alters the frequency of serious infection as well as its spectrum. Short periods of neutropenia place patients at risk for gram-positive and gram-negative bacterial infections and fungal infections. Prolonged neutropenia is extremely rare in solid tumor patients in the absence of hematopoietic stem cell transplantation (HSCT); as a result, solid tumor patients are much less prone to diseases such as invasive aspergillosis (IA), mucormycosis, *Pneumocystis jiroveci*, and disseminated cytomegalovirus (CMV) infection.

In the 1970s, when the critical importance of empiric treatment of neutropenic fever was proven, it was recognized that cancer patients had significant infectious morbidity and mortality even with normal granulocyte counts. For solid tumor patients, the portion of febrile episodes that had an infectious etiology identified was a significant minority. In a prospective study of 1,001 fever episodes in hospitalized pediatric and young adult hematology–oncology patients undergoing chemotherapy, Pizzo et al. [2] attempted to identify an infectious source for each febrile episode. Work-up included history, physical, urinalysis, blood cultures, and chest X-ray. Among non-neutropenic patients, Pizzo et al. [2] identified infectious sources in solid tumor patients in 17 of 112 episodes (15 %), in 7 of 40 (17 %) lymphoma patients, and 12 of 56 (21 %) leukemia patients. In a review of hospitalized bacteremic and fungemic episodes in patients with solid and liquid tumors at a tertiary cancer center, investigators reported a 26.6 % mortality rate for 192 non-neutropenic episodes of sepsis in solid tumor patients [3]. As treatment regimens for these malignancies become more aggressive, the role of infection in these patients is likely to grow.

The presence of a solid tumor may have deleterious effects upon the adaptive immune system, but these are poorly understood. For example, depressed CD4 and CD8 lymphocyte counts have been measured in solid tumor patients [4], but the clinical significance of these abnormalities remains unclear. Severe lymphopenia appears to increase the risk of developing two very rare but life-threatening infections among solid tumor patients, *P. jivoreci* pneumonia and IA.

In summary, patients with solid tumors at presentation represent a heterogeneous population of underlying immunocompromise; modern cancer therapy typically combines multiple modalities that commonly injure the immune system further.

## 3 Healthcare-Associated Infections

Patients with solid tumors are at risk of becoming colonized with resistant organisms often associated with healthcare settings. Modern cancer treatment commonly includes multiple modalities—chemotherapy, surgery, and radiation—and takes place in both inpatient and outpatient healthcare settings. As a result of antibiotic therapy and increased exposure to healthcare settings and healthcare workers, solid tumor patients are at increased risk of becoming colonized with *Clostridium difficile,* methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant

enterococci (VRE), *Candida* spp., and resistant gram-negative organisms. Recent increasing resistance among gram-negative organisms is particularly alarming. For example, heathcare-associated *Klebsiella pneumoniae* with carbapenemases and multi-drug-resistant *Pseudomonas aeruginosa* are becoming widespread. Selection of empiric antibiotics should be based on the vulnerabilities of the host, the clinical presentation, and the antibiograms of the institution and setting (intensive care unit, ward, or clinic). The presence of highly drug-resistant pathogens in healthcare settings has increased the importance of obtaining appropriate cultures upon initial presentation of an acutely ill oncology patient. The possibility of clinical failure of routine broad empiric antibiotic coverage is growing.

## 4 Bloodstream Infections

Spanning almost all patients with cancer is the elevated risk of bloodstream infections. For solid tumor patients, the risk of significant bacteremia and fungemia is lower than for patients with hematologic malignancies. Mayo and Wenzel [5] found that nosocomial bloodstream infections were 15 times less likely in solid tumor patients than leukemia patients. Elting et al. [6] reported that polymicrobial sepsis was 16 times less common per patient admission in patients with solid tumors than patients with acute leukemia. Chronic venous access devices (Fig. 1) are the source of most bacteremia and fungemia in cancer patients. Raad et al. [7] followed all cancer patients at a single tertiary cancer center over a 14-month period that had paired quantitative blood cultures drawn, one from a central venous catheter and one from a peripheral vein. They found 169 cancer patients with bacteremia or fungemia, 56 % of which were catheter-related. The majority of patients with both solid malignancies and liquid malignancies had gram-positive isolates. The source of gram-negative isolates, however, differed significantly between patients with solid tumors and those with hematologic malignancies. Sixty percent of the gram-negative isolates from solid tumor patients were catheter-related; in contrast, only 19 % of hematologic patients had isolates that appeared to come from the catheter ($p = 0.01$) [7]. In a large retrospective study, Ghanem et al. [8] compared complications of cancer patients with *S. aureus* catheter-related bacteremia. Solid tumor patients were more likely to have septic thrombosis; hematologic cancer patients were more likely to have sepsis, multiorgan failure, and death. Aggressive infection control and technologic advances in long-term venous devices will further reduce the rate of healthcare-related bacteremia and fungemia [9].

In addition to catheter-related bloodstream infections, cancer patients are susceptible to non-catheter-related bloodstream infections. A retrospective study at a tertiary care center found solid tumor patients comprised 63 % of the 122 cancer patients with *Streptococcus pneumoniae* bacteremia, including 14 % with lymphomas [10]. A significant majority of these bacteremic episodes were considered community-acquired. Most had evidence of pneumonia at presentation, suggesting the respiratory tract was the primary source of infection.

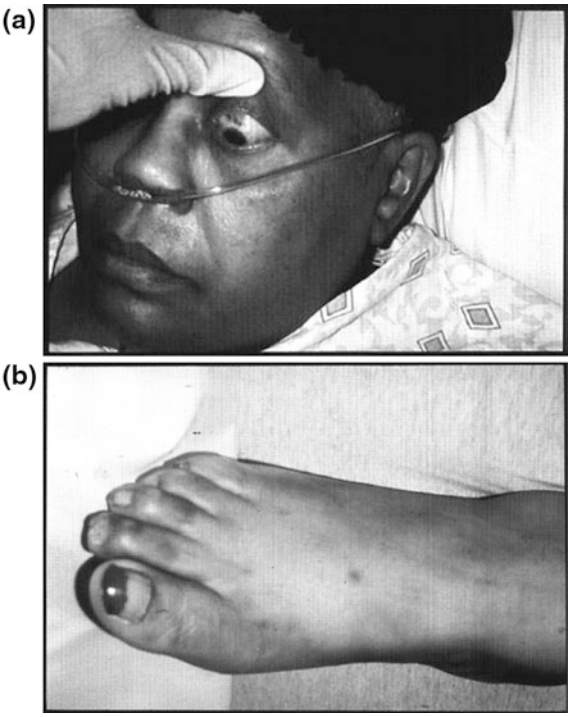


**Fig. 1** A 62-year-old woman with recurrent breast cancer following surgery, radiation, and chemotherapy was admitted to the hospital with several days of malaise, myalgias, and blurred vision. She was febrile to 39.4 °C and pus could be expressed from her percutaneously inserted central venous catheter (*PICC*) site. Conjunctival hemorrhages (**a**) and purpuric skin lesions (**b**) were evident. Retinal exam also identified multiple chorioretinal abscesses. PICC line site, catheter tip, and blood cultures were positive for methicillin-resistant *Staphylococcus aureus.* A transesophageal echocardiogram showed no evidence of cardiac valvular vegetations. Nevertheless, a presumptive diagnosis of endocarditis was made, and she responded to 6 weeks of intravenous vancomycin

## 5 Neutropenic Fever

Evaluation of solid tumor patients with neutropenic fever requires timely face-to-face healthcare evaluation, laboratory work including blood cultures, chest X-ray, and thoughtful medical decision making. Urgent empiric antibiotic therapy is instituted while the initial evaluation is performed, and a decision about hospitalization must be made. For the febrile neutropenic cancer patient, empiric antibiotics should include coverage of gram-positive bacteria and gram-negative bacteria, including *P. aeruginosa*. The 2010 Infectious Disease Society of America (IDSA) *Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer* [11] emphasizes that individualized risk of serious infectious complication plays a large role in determining the initial level of care and mode of

antimicrobial treatment; most of the patients who are potentially low risk are patients with solid tumors. Low-risk patients are likely to have neutropenia for less than 7 days, have no hypotension, have few or no comorbidities, have normal renal and hepatic function, have no evidence of disseminated or local infection upon acute evaluation, and are able to take oral medications. Low-risk patients may receive brief courses of parenteral antibiotics if fever resolves quickly and no evidence of focal or disseminated infection is identified; the patient then may be changed to oral antibiotics until the neutropenia resolves [11]. If a source of infection is identified, the organism and site of the infection determines the length and route of antimicrobial therapy. Antibiotic coverage is also typically continued until the ANC is >500 cells/$mm^3$ and rising. Because their risk of severe infectious morbidity and mortality is substantially lower than for high-risk patients, low-risk patients may be candidates for oral antibiotic therapy, as inpatients or outpatients, as long as daily evaluation by the healthcare team is assured. If a low-risk patient receives oral antibiotics, typically ciprofloxacin and amoxicillin–clavulanate, but fevers persist for 48 h, inpatient re-evaluation is necessary and intravenous antibiotics should be instituted [11]. Historically, low-risk patients have not received antibacterial or antifungal prophylaxis; results of the 2005 SIGNIFICANT trial represent progress in our understanding of antibiotic prophylaxis for inpatients on chemotherapy for a wide range of solid tumors [12]. In the SIGNIFICANT trial, a large prospective randomized double-blind placebo-controlled study of exclusively patients with solid tumors, patients receiving oral levofloxacin during *anticipated* periods of chemotherapy-related neutropenia had fewer episodes of fever and fewer probable infections when compared to placebo [12]. Of note, less than 10 % of the patients enrolled had chronic central lines, few had prior chemotherapy courses, and few had prior radiation therapy; thus, one should be cautious about generalizing these encouraging results to patients with central lines or extensive previous cancer therapy. Furthermore, the impact of use of prophylaxis on the development of resistance could not be evaluated. In an era of increasing fluoroquinolone use, the efficacy and/or benefit of such prophylactic regimens may decrease with time.

## 6 Infectious Complications of Lung Cancer Patients and Pulmonary Complications of Patients with Solid Tumors

Lung cancer is the second most common new cancer diagnosis in the United States, behind prostate cancer for men and breast cancer for women [1]. In 2007, the number of men and women living in the United States with lung cancer or a history of lung cancer was approximately 370,617 [1]. Infection plays a potentially critical role in the outcome of patients with lung cancer. The lung must continue to function as an organ of gas exchange during and after cancer therapy. Exposure to the external environment, and the attendant risk of exposure to infectious pathogens, must be maintained for gas exchange to occur. In addition, the lung serves as a vast vascular bed, and hematogenous seeding by bacteria and fungi can occur,

although infrequently. The lung's defenses against these insults may be impaired by lung cancer and its treatment.

The lung cancer patient has altered host defenses in several ways. Host defenses of the respiratory system diminish with age [13, 14], and most lung cancer develops in older adults. According to the NCI, approximately 70 % of cases are diagnosed among those 65 years or older [1]. Age-dependent changes that predispose to respiratory infections include an increased tendency to aspirate, decreased cough reflex, decreased mucociliary clearance, and increased oropharyngeal colonization by aerobic gram-negative bacilli [15]. Increasing age is also associated with decreased cellular and humoral immunity. In addition, there are changes that are associated with the cancer itself. The most apparent is local bronchial obstruction by a tumor mass, leading to impaired clearance of respiratory secretions. Lung cancer, particularly with advanced disease, has also been associated with diminished delayed cutaneous hypersensitivity reactions [16]. The lung cancer patient may present with one or more serious comorbidities such as COPD, malnutrition, and persistent tobacco use, each of which can prolong the need for ventilatory support or require tracheostomy. Such complications can increase pulmonary and non-pulmonary infection risks. Finally, treatment of lung cancer can increase infection risk. Most patients with stage I and II non-small-cell carcinoma of the lung undergo surgery. In a study of 103 such patients, the risk of post-thoracotomy pneumonia was 22 % [17]. Small cell lung cancer patients, and recently some non-small-cell lung cancer patients, have disease that can be responsive to chemotherapy and radiation; therapy-related immunosuppression and injury can increase infection risk, particularly in the lung. Monoclonal antibodies and receptor blockers such as bevacizumab and cetuximab are now being used in some non-small-cell lung cancers as single agents or as components of combination chemotherapy. Both of these drugs have been associated with increased risk of infections. Bevacizumab has been associated with increased risk of intestinal perforation when used in combination with other agents [18]. Skin reactions occur frequently in patients who receive cetuximab; these patients may be at increased risk of colonization and thus infection with *S. aureus* [18].

## 6.1 Bacterial Infections

Pneumonia is a common diagnosis among patients with solid tumors. Etiologies include community-acquired organisms such as *Legionella* spp. [19], *S. pneumoniae*, and *Haemophilus influenzae*. Among atypical organisms, *Legionella* spp. are known to cause severe life-threatening pneumonia. Having a cancer diagnosis as well as receiving corticosteroids was associated with an elevated case fatality rate in a recent Spanish study of adults with *Legionella* pneumonia [20]. The risk of legionellosis in solid tumor patients, both community-acquired and healthcare-associated, is not known.

Lung cancer patients are predisposed to develop focal lung infections secondary to bronchial obstruction by the tumor. In a review of 579 hospitalized patients with

lung cancer at a Japanese university hospital over 15 years, 139 (24 %) developed respiratory infections, most of which were bacterial [21]. Patients with extensive disease were more likely to develop pulmonary infection than those with cancer at early stages. Twenty-seven percent of the pneumonias were post-obstructive by chest radiograph [21]. Several older studies documented the simultaneous diagnoses of lung cancer and bacterial pneumonia, lung abscess, or empyema. Strang and Simpson [22] reported 70 patients with lung abscesses among 1,930 patients with a lung cancer diagnosis in Great Britain over an 11-year period, an incidence of 3.6 %. In many cases, partial obstruction by tumor led to post-obstructive atelectasis and pneumonia. In a minority of cases, infection occurred secondarily within an area of tumor necrosis. Rarely, when an abscess was found distant to the tumor, aspiration was thought to be its etiology. Patients generally presented with the abrupt onset of cough productive of sputum, fever, and chest pain. A subset presented in a more indolent manner, with weight loss and anorexia as prominent symptoms. Sputum cultures were usually polymicrobial. In contrast to most patients with simple abscesses who improved with penicillin, most patients with cancer and abscess did not show clinical benefit or radiologic improvement after penicillin therapy alone [22].

Post-obstructive pneumonias are thought to develop secondary to partial obstruction of an airway with overgrowth of bacteria distal to the obstruction; however, this may be simplistic. Other factors likely contribute to the risk of pneumonia associated with an endobronchial tumor. The organisms recovered from lung abscesses secondary to obstructing tumor are frequently more virulent than those recovered from primary lung abscesses. In a review of 97 lung abscesses, Perlman and associates [23] found that *S. aureus* and gram-negative enteric organisms were recovered from patients with underlying lung cancer more often than those without lung cancer. Cultures from primary abscesses (non-cancer patients) were more likely to reflect normal upper respiratory flora, especially alpha-hemolytic streptococci. This shift to more virulent organisms in the lung abscesses of cancer patients likely results from aspiration of altered oropharyngeal flora. Oropharyngeal colonization changes during illness, probably due to alterations in epithelial cell surface receptors, resulting in increased proliferation of aerobic gram-negative rods. Empyema occasionally complicates post-obstructive pneumonia. In a review of 105 cases of empyema, only 7 (6.7 %) were associated with post-obstructive pneumonia secondary to bronchogenic carcinoma [24]. Kohno et al. [21] reported only 2 empyemas among 148 episodes of pulmonary infection in hospitalized patients with lung cancer.

Empiric therapy for post-obstructive pneumonia or abscess should include coverage of *S. aureus,* aerobic gram-negative bacilli, and anaerobes. A variety of antibiotic regimens may be appropriate and should be guided by the results of sputum gram stains (and later cultures), previous antibiotic exposure (especially recent), and knowledge of local (community and institutional) antibiotic susceptibility patterns. Usual lung abscess treatment (e.g., clindamycin) may be adequate if cultures fail to identify aerobic gram-negative bacilli. Prolonged therapy may be required when bronchial obstruction prevents adequate drainage of the infected lung.

## 6.2 Mycobacterial Infection

The frequency of mycobacterial disease may be increased in patients with cancer. In a retrospective review at M. D. Anderson in Houston, Texas, the incidence of mycobacterial disease among their cancer patients was 65 cases per 100,000 persons, in comparison with 45 cases per 100,000 among Texans age 45–65 years old [25]. Kaplan et al. [26] reviewed 201 cases of tuberculosis (TB) that developed in cancer patients at Sloan-Kettering Cancer Center over 20 years. Lung cancer patients had the highest prevalence, 920 per 100,000, among solid tumor patients, which was second only to Hodgkin's disease overall. Lung cancer and head and neck cancer patients were more likely to present with tuberculosis at the time of cancer diagnosis; patients with the other neoplasms were more likely to develop tuberculosis while receiving cancer therapy [26]. A recent study from MD Anderson Cancer Center concluded that foreign-born cancer patients, head and neck cancer patients, and hematologic cancer patients are at elevated risk of developing reactivation tuberculosis; the risk of reactivation TB was not increased among routine solid tumor patients when the two former groups were excluded [27]. The Center for Disease Control and Prevention's (CDC) guideline for treatment of patients with latent TB recognizes the most inclusive 5-mm cutoff for positive PPDs for those with an abnormal chest X-ray suggestive of prior pulmonary TB, the foreign-born from TB-endemic countries, and those who are receiving immunosuppressive therapy [28]. The guideline recognizes as positive those who have a PPD at $\geq$10 mm among patients with leukemia, lymphoma, carcinoma of the head and neck, and lung cancer [28]. The remaining individuals, including patients with many other types of solid tumors, qualify for a positive PPD at $\geq$15 mm [28].

Historically, two mechanisms of tuberculosis reactivation in lung tumor patients have been invoked: First, tumor can break down granulomas harboring sequestered mycobacteria or second, malignancy-associated cachexia may impair cell-mediated immunity, resulting in reactivation [29]. As therapy for lung cancer has become more aggressive, chemotherapy-related immunosuppression may contribute to reactivation. In a population with high baseline rates of tuberculosis, autopsy data revealed that corticosteroids plus antineoplastic agents increased the incidence of mycobacterial infection compared with antineoplastic agents alone [30]. Of the 304 Japanese patients who died with lung cancer, five died of tuberculosis [30]. In the majority of these cases, there had been evidence of latent tuberculosis at the time of lung cancer diagnosis. Four of the five deaths secondary to active tuberculosis involved patients who had recent corticosteroids added to their chemotherapy.

A high index of suspicion for tuberculosis in a cancer patient is indicated if the patient's history or epidemiological background suggests prior exposure or if unexplained or rapidly progressive pulmonary symptoms, signs, or chest X-ray findings develop. Increased concern for mycobacterial infection may be warranted in a cancer patient with fevers and new pulmonary infiltrates if glucocorticoids are part of a patient's active or recent medications. At diagnosis of solid tumor disease, we recommend that a tuberculin skin test be placed. Gamma interferon

release assays such as the QuantiFERON®-TB Gold (QFT-G) have not been validated for patients with lung cancer and other solid tumors. One should consider sending biopsy material and respiratory specimens for acid-fast bacilli (AFB) stain and culture regardless of tuberculin skin test status or QFT-G result. If the patient is determined to have latent tuberculosis, treatment with daily isoniazid along with pyridoxine for 9 months is indicated. If a patient has been previously adequately treated for latent tuberculosis, a repeat course of isoniazid is not recommended. Whenever AFB are identified on smears or histopathology or when mycobacteria are identified in respiratory cultures, therapy for presumed active pulmonary tuberculosis is indicated. Some of these smears or cultures will prove to represent contamination of specimens by non-pathogenic mycobacteria (e.g., *M. gordonae)* and therapy can be discontinued. Some others may prove to represent true infection caused by atypical organisms (e.g., *M. kansasii* or *M. avium-intracellulare*) and therapy can be altered appropriately.

## 6.3 Fungal Infection

*Aspergillus* spp. causes three general types of disease: invasive, allergic, and saprophytic. Solid tumor patients who are not stem cell transplant recipients are not considered at high risk of developing IA. As a result, the significance of isolating an *Aspergillus* species from a respiratory specimen must be evaluated individually. Furthermore, because of the low incidence of IA in this population, most solid tumor patients do not receive empiric antifungal prophylaxis. In a retrospective collection of all the cases of IA in solid tumor patients spanning 1993–2003 at a tertiary cancer center, there were only 13 proven or probable cases [31]. Nine of the 13 had pulmonary disease. Excluded were 14 cases in which patients had positive *Aspergillus* spp. in respiratory specimens but were asymptomatic or in which a copathogen was isolated that explained the patient's presentation. Risk factors for development of IA were exposure to glucocorticoids within 30 days of diagnosis and lymphopenia. Recent neutropenia was not a risk factor for developing IA, unlike for those with hematologic malignancies. Radiologic findings were either nodular or cavitary infiltrates. Almost all of these patients responded well to antifungal agents, with much lower 6-week mortality than is seen in leukemia patients. Less than one percent of autopsies of solid tumor patients performed during the same period were found to have IA, in contrast to over 17 % of those with hematologic malignancies [31].

Cases of focally invasive *Aspergillus* infection are scattered throughout the literature, represented in individual case reports of relatively immunocompetent lung cancer patients. In these cases, necrotic tumor itself serves as the substrate in which *Aspergillus* spp. germinates, colonizes, and/or invades. Saprophytic colonization near or within the tumor appears to be the most common presentation in relatively immunocompetent lung cancer patients. Smith and Bveneck [32] noted that these focal *Aspergillus* spp. infections rarely cause life-threatening hemorrhage and uncommonly form fungal balls, in contrast to post-tuberculous aspergilloma.

Symptoms from a growing tumor may result in an earlier recognition of *Aspergillus* spp. infection than post-tuberculous cases, before complications associated with more long-standing infection can develop. As a result, aspergillomata forming in the presence of lung cancers have rarely been described. In one case, misdiagnosis contributed to development of a fungal ball over several months. A 61-year-old male presented with hemoptysis and a multiloculated cystic lung lesion; over the next several months, while the patient was treated empirically for tuberculosis, a fungal ball developed within the cystic cavity [33]. At lobectomy, a mass of *A. fumigatus* was found within a previously undiagnosed necrotic, cavitating adenocarcinoma. No evidence of tuberculosis was identified. Only rarely is focal fungal disease detected at the site of the tumor prior to any cancer therapy.

Most IA infections in solid tumor patients, however uncommon, are much more aggressive, developing in the setting of intensive immunosuppression associated with chemotherapy and/or radiation therapy. *Aspergillus* spp. pneumonia may vary according to the intensity of chemotherapy and duration of neutropenia. At Memorial Sloan-Kettering Cancer Center, a retrospective study noted twice as many *Aspergillus* spp. infections during 1969–1970 as during 1964–1965 [34]. Of the 93 collected cases of *Aspergillus* spp. infection in cancer patients, 14 involved solid tumor patients. Like the affected leukemia and lymphoma patients, the solid tumor patients who developed invasive *Aspergillus* spp. were more likely to have leukopenia or a history of recent chemotherapy or corticosteroid therapy. A common presentation was the abrupt onset of unremitting fever and pulmonary infiltrates that did not respond to broad-spectrum antibacterial therapy.

The role of corticosteroids, whether exogenous or endogenous, in the development of IA is illustrated by the following cases. Borkin et al. [35] reported a case of a 53-year-old male with history of adenocarcinoma of the left lung, following resection, who presented with brain metastasis. He was placed on dexamethasone; 5 weeks later, he developed fever and right chest pain while hospitalized for brain irradiation. Chest X-ray showed a dense right lower lobe infiltrate. He developed respiratory distress over 2 days and subsequently died after massive hemoptysis. Sputum cultures grew *A. fumigatus,* among other pathogens. Autopsy revealed necrotizing pneumonia of the right lung; microscopically, vascular invasion by fungal hyphae was seen. No evidence of malignancy was found in the lung. Smith et al. [36] reported a case of a 47-year-old male who presented with a 3-month illness associated with a 19-kg weight loss and a 2-week history of cough. He was found to be grossly cushingoid in appearance. A chest X-ray demonstrated a right hilar mass, a focal infiltrate, and lymphadenopathy. Hemoptysis prompted a transbronchial biopsy that revealed invasive pulmonary aspergillosis. Small cell carcinoma was found on bone marrow examination. The Cushing syndrome was attributed to ectopic hormone secretion by tumor. Following his death on the ninth day of hospitalization, autopsy showed widespread fungal abscesses.

Animal models have demonstrated the impact of corticosteroids on clearance of an aerosol challenge of *Aspergillus* spores [37]. The macrophages of untreated control mice effectively phagocytized the spores and the animals remained healthy.

The macrophages of mice receiving corticosteroids failed to effectively phagocytize spores. The *Aspergillus* spores germinated and produced invasive hyphae; hemorrhagic bronchopneumonia developed and the majority of animals died.

Sputum cultures that demonstrate *Aspergillus* spp. in an immunocompetent patient with deteriorating pulmonary status or new infiltrates should prompt a more thorough investigation for evidence of invasive disease. In severely immunosuppressed individuals with deteriorating pulmonary status or new infiltrates, recovery of *Aspergillus* spp. from the respiratory tract should prompt empiric antifungal therapy. If possible, immunosuppressive therapy should be discontinued. Liposomal amphotericin is often given empirically until mucormycosis is ruled out. Voriconazole is the usual therapy for IA. Mucormycosis is extremely rare in patients with solid tumors unless they are undergoing HSCT.

Other fungal infections have been noted rarely in patients with lung cancer, but no clear association has been made. These have included blastomycosis [38], candidal infections, and cryptococcosis. In a survey of 170 Veterans Affairs hospitals over 12 years, 198 cases of blastomycosis were found; only 3 had underlying bronchogenic carcinoma and 2 had metastatic lung lesions [39]. Isolation of *Candida* spp. from the lung has proved to be airway colonization in most cases. Thirty-one cases of *Candida* pneumonia, however, were documented by autopsy over a 20-year period at the MD Anderson Cancer Center [40]. Sixteen (52 %) of these cases had underlying solid tumors; the remainder had hematologic malignancies. Associated with the development of *Candida* pneumonia were broad-spectrum antibiotics (28 patients), corticosteroid therapy (15 patients), and neutropenia (9 patients).

## 6.4 *Pneumocystis jiroveci* Pneumonia

The risk of acquiring *P. jiroveci* pneumonia (PCP) in non-AIDS patients appears to be highest in patients with hematologic malignancies, chronic high-level glucocorticoid exposure, or lymphopenia. PCP is a rare but recognized risk in immunosuppressed solid tumor patients. In a recent retrospective study of cancer patients at MD Anderson Cancer Center, the incidence of PCP pneumonia for solid tumor patients was 16 cases per 100,000 patients; the incidence for patients with hematologic malignancies (including lymphoma) was approximately eleven times greater [41]. Yale and Limper [42], in a review of 116 non-AIDS patients with PCP at the Mayo Clinic, reported that 13 % had underlying solid tumors, 30 % had hematologic malignancies, 25 % had received organ transplants, and 22 % had inflammatory disorders. The underlying solid tumors included brain tumors, lung carcinoma, breast carcinoma, colon carcinoma, renal cell carcinoma, and melanoma.

Accumulated evidence from human and animal studies documents that chronic corticosteroid administration is a significant risk factor for PCP. The animal model of PCP is based on the fact that rats routinely develop progressive PCP when treated with corticosteroids [43, 44]. A review of 142 PCP cases in non-AIDS cancer patients at Memorial Sloan-Kettering Cancer Center reported that 31 % had

underlying solid tumors and 67 % had hematologic malignancies [45]. Eighty-seven percent of these patients had been on corticosteroids within 3 months of PCP diagnosis. Sixty-eight percent of the solid tumor patients who developed PCP in the aforementioned study by Torres et al. [41] had received corticosteroids in the month prior to PCP diagnosis. In some patients, the development of symptomatic PCP may be associated with tapering of chronic steroids [46, 47]. The mechanism by which chronic steroid use predisposes to PCP is unclear. Chronic corticosteroid therapy causes CD4 cell depletion and impaired macrophage function, which may allow the development of PCP infection while limiting the host inflammatory response. Withdrawal of steroids may remove the anti-inflammatory effects before the immunosuppressive effects have resolved, leading to clinical exacerbation.

In general, the presentation of PCP in non-AIDS patients is more acute than in AIDS patients, yet the load of organisms in the lung is lower. Kovacs et al. [48] found that prior to presentation, non-AIDS patients had a median duration of pulmonary symptoms of 5 days (range, 1–42 days), whereas AIDS patients had a median duration of 28 days (range, 1–270 days). Non-AIDS patients were more likely to have fever and severe hypoxemia and showed a wider range of respiratory rates. In the report by Henson et al. [46], brain tumor patients with PCP had pulmonary symptoms a median of 7.4 days before admission (range, 1–30 days). Of 10 patients, 8 had dyspnea and 6 had fever. Chest X-rays upon admission varied from normal ($n = 1$), to an isolated focal infiltrate ($n = 2$), to diffuse or bilateral infiltrates ($n = 7$). Lactate dehydrogenase levels were elevated, ranging from 336 to 1,284 U/L (median 510 U/L). Non-AIDS patients with PCP, and specifically those with solid tumors, have a 10-fold lower organism load than AIDS patients with PCP [49]. While the low organism load may reduce the diagnostic yield of bronchoscopy, it does not appear to reduce the severity of illness. In the series reported by Yale and Limper [42], 7 of 15 patients with PCP and underlying solid tumors developed respiratory failure and died. In Kovacs et al. [48], the survival of AIDS and non-AIDS patients presenting with PCP was not significantly different (57 and 41 %, respectively).

Solid tumor patients with severe cell-mediated immunosuppression, for example, those who are severely malnourished, HSCT recipients, and those who receive chronic corticosteroids, are candidates for PCP prophylaxis (trimethoprim-sulfamethoxazole, dapsone, atovaquone, or monthly aerosolized pentamidine). Individuals receiving chronic steroid therapy, especially high-dose therapy, should continue on PCP prophylaxis during steroid tapering [50].

## 6.5 Viral Infection

Viral pneumonia is a rare cause of infectious complications in solid tumor patients. Camazine et al. [51] reported three cases of herpes simplex virus (HSV) type 1 pneumonia occurring in patients who had undergone recent thoracotomy for carcinoma involving the lung. A 52-year-old female presented with fever and

hypoxemia on postoperative day two following thoracotomy for pulmonary metastasis of rectal carcinoma, a 72-year-old male developed fever and hypoxemia on postoperative day three after thoracotomy for squamous cell carcinoma of the lung, and a 72-year-old male with mesothelioma presented with fever, hypoxemia, and respiratory failure on postoperative day four. Two of the three patients developed diffuse interstitial infiltrates; one developed a focal, progressive infiltrate. Respiratory cultures were positive for HSV and, in one case, CMV as well; no other pathogens were isolated. Bronchial washings revealed intranuclear inclusions consistent with HSV infection. All three patients responded promptly to acyclovir. The authors recommended delaying cardiothoracic surgery in the presence of perioral HSV lesions.

Significant immunosuppression, similar to that experienced by organ transplant patients and HSCT patients, appears to be necessary to develop pneumonia secondary to CMV, respiratory syncytial virus (RSV), parainfluenza virus, and adenovirus. Solid tumor patients undergoing HSCT are at risk for these infections.

Although non-transplant solid tumor patients do not appear to have increased susceptibility to severe influenza infection, all cancer patients are encouraged to receive annual influenza vaccination. The antibody response to influenza vaccination in solid tumor patients appears to be variable yet fairly comparable to non-cancer patients [52, 53]. Routine annual vaccination is recommended, and *S. pneumoniae* vaccination is recommended.

## 6.6 Non-infectious Causes of Pulmonary Infiltrates in Solid Tumor Patients

Radiation pneumonitis typically presents 3–4 months after irradiation with insidious onset of non-productive cough, fever, and shortness of breath [54]. Symptoms frequently become apparent when corticosteroids are tapered [55]. Physical findings are uncommon but include pulmonary consolidation, pleural friction rub, or pleural effusion [55]. When patients become symptomatic, radiologic changes are evident and are almost always precisely limited by the edges of the radiation field. During the period 2–4 months after irradiation, many more individuals develop abnormalities on chest X-ray than develop symptoms. Ground glass opacification or haze is common in the early stages [55], possibly followed by dense infiltrates. Because radiation pneumonitis can respond dramatically to steroids, diagnosis is clinically important. Some chemotherapeutic agents, such as actinomycin D and adriamycin, have been associated with reactivation of radiation pneumonitis [56].

Other non-infectious causes of pulmonary infiltrates in patients with lung cancer include congestive heart failure, pulmonary emboli, pulmonary hemorrhage, adult respiratory distress syndrome, drug toxicity, chemical aspiration, and progression of tumor.

## 6.7 Evaluation and Management

Delay in starting empiric antibiotics for pneumonia and sepsis has been associated with increased morbidity and mortality; as a result, broad antibiotic coverage is typically started in a patient with fever, respiratory distress, and/or pulmonary infiltrates, regardless of whether a patient has cancer. Commonly, lung cancer patients would receive coverage for MRSA, MSSA, expanded gram-negative coverage, anaerobes, and atypical pneumonia organisms.

There have been recent advances in non-invasive methods of determining the etiology of pulmonary infections in solid tumor patients; for patients with moderate immunocompromise such as patients with a solid tumor and chronic corticosteroids, an early invasive study should not be delayed awaiting these results. *S. pneumoniae* urinary antigen and *L. pneumophila* urinary antigen have become routine tests for patients with acute pneumonia who can produce urine. Similarly, Histoplasma urine antigen and Blastomyces urine antigen should be sent, particularly if nodular infiltrates, cavities, and mediastinal lymphadenopathy are present. Serum and respiratory assays have not been validated as a test to detect IA in solid tumor patients. The precise role of PCR for PCP is under investigation. Because routine PCR is extremely sensitive, such that even colonization with PCP is detected, the technique of real-time PCR, which quantitates the load of PCP, shows promise [57–59]. PCR testing of oropharyngeal washings, blood, and serum is also under investigation [59]. Interferon-gamma release assays for *M. tuberculosis* such as QFT-G have yet to be validated among immunocompromised hosts such as solid tumor patients.

The urgency with which diagnosis of pulmonary infiltrates in a lung cancer patient must be made depends upon the level of immunosuppression. The relatively immunocompetent patient with lung cancer is more likely to develop focal infiltrates. These patients may benefit from a CT scan of the chest with intravenous contrast to better define the extent of disease and facilitate obtaining a biopsy. Sputum for gram stain, culture, AFB smear, mycobacterial culture, and fungal culture should be obtained. A tuberculin skin test should be placed. Video-assisted transthoracic surgery (VATS) (if the lesion is located peripherally), bronchoscopy with bronchoalveolar lavage (BAL), and transbronchial biopsy (TBB) are options for rapid diagnosis. If tissue is obtained, aerobic, anaerobic, fungal, and mycobacterial studies, as well as cytology, are indicated. Because fungi can colonize the airways of relatively immunocompetent individuals, reviewing the biopsy with a pathologist may be necessary to determine whether tissue invasion is present, indicating disease.

Diffuse pulmonary infiltrates typically occur in lung cancer patients with severe immunosuppression. A lung cancer patient who is severely malnourished, neutropenic, or receiving high-dose corticosteroid therapy who develops pulmonary infiltrates should undergo an urgent diagnostic procedure. Diffuse pulmonary infiltrates are more likely to be secondary to infection when the patient has received chemotherapy, when fever develops with the radiographic changes, and

when the radiographic changes occur rapidly [60]. Nevertheless, clinical presentation is not predictive enough to direct therapy with confidence. In the setting of diffuse pulmonary infiltrates and immunosuppression, an invasive diagnostic procedure (BAL, TBB, or open lung biopsy (OLB)) should be considered early in the clinical course. Meanwhile, specimens of blood and sputum (if accessible) should be sent for bacterial, fungal, and mycobacterial cultures. Because viruses commonly cause diffuse pulmonary infiltrates in the setting of severe immunosuppression, a nasopharyngeal, oropharyngeal swab, or lower respiratory sample should be sent for a PCR-based viral panel including influenza, parainfluenza, and RSV. A broad panel now available tests the latter three viruses plus adenovirus, metapneumovirus, and rhinovirus. Bronchoscopy with BAL is often utilized as the first-line diagnostic procedure in the immunosuppressed patient with new diffuse pulmonary infiltrates. Specific studies of solid tumor patients have not been performed, so recommendations must be derived from reports in which leukemia and lymphoma patients predominate [61]. When the patient is severely immunosuppressed, specimens should be sent for gram stain and quantitative culture, acid-fast stain and mycobacterial culture, fungal stain and culture, *Pneumocystis* direct fluorescent antibody (DFA) and culture, *Legionella* DFA staining and culture, HSV and CMV PCR, possibly cultures for *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae,* and a respiratory virus PCR panel. Because BAL generally dilutes lower respiratory tract secretions by a factor of 1:10–1:100, the diagnostic threshold for bacterial culture is $10^4$ CFU/mL. However, some organisms, including *M. tuberculosis, Legionella* spp., and *Nocardia* spp., should be considered pathogens whenever isolated. A sample should also be sent for cell count with differential and for cytopathology. The cell count and differential may be used to assess specimen adequacy. For example, squamous and bronchial epithelial cells accounting for >1 % of the total cells suggests contamination by oropharyngeal flora. Detection of plentiful hemosiderin-laden macrophages by direct microscopy suggests pulmonary hemorrhage.

BAL appears to have a good yield in the diagnosis of PCP, tuberculosis, CMV, and aspergillosis [62]. TBB is more invasive than BAL alone but improves the diagnostic yield in some infectious and non-infectious processes. However, TBB is associated with an increased risk of pneumothorax and hemorrhage. OLB is associated with greater morbidity than either BAL or TBB but may be considered when BAL and TBB fail to provide a diagnosis or are contraindicated because of respiratory instability or bleeding risk. For abscesses or nodular masses in the periphery of the lung, VATS may be a less invasive alternative.

## 7 Infectious Complications of Breast Cancer

Breast cancer is the leading cause of new cancer cases diagnosed each year in females in the United States; over 2.5 million US women are living who have or have had breast cancer [1]. Most infectious complications in breast cancer patients involve skin and soft tissue that has been altered by surgery and/or irradiation.

These infections occur both immediately postoperatively and later, from months to several years after cancer therapy. Lumpectomy followed by local radiation has been proven to be as effective as mastectomy for early stages of breast cancer; this finding represented a major step forward in breast conservation surgery.

Additional developments in breast cancer care are three-fold: First, increasingly, patients with a wide range of disease stages are now receiving some combination of chemotherapy, radiation, and surgery; second, innovative diagnostic and surgical techniques are being developed and validated that conserve lymphatic drainage; third, a greater variety of breast reconstruction techniques is available and more is understood about how the timing of reconstruction influences clinical outcomes [63]. The goals of these advances are to improve the cure rate and to minimize complications of disfigurement, pain, disuse, and infection. Sentinel lymph node biopsy, a diagnostic technique that takes place at the time of cancer diagnosis, identifies a subset of patients who appear to have no local lymph node metastasis. This subset of patients does not undergo ipsilateral lymph node dissection and thus has a reduced risk of lymphedema and subsequent cellulitis. Axillary reverse mapping (ARM) is a relatively new technique that compliments sentinel lymph node biopsy [64]. In ARM, a liquid dye is injected in the ipsilateral arm thereby mapping the individual patient's lymphatic channels through subcutaneous tissue. When possible, subsequent surgery can be strategically planned to minimize lymphatic damage. Limited clinical data are available regarding the impact of combined-modality therapy on infection rates [65, 66], although chemotherapy and radiation can theoretically delay wound healing and impede wound drainage.

## 7.1 Early Postoperative Infectious Complications of Breast Cancer Patients

Despite the fact that most breast cancer surgery is classified as clean, acute wound infection rates in the range of five times the rate of other clean surgeries have been reported [67]. A 2006 Cochrane review concluded that preoperative antibiotic prophylaxis successfully reduces postoperative wound infections across a wide range of breast cancer surgeries and among patients receiving various other therapies [68]. Disruption of the skin integrity and contamination by skin flora accounts for most wound infections within the first 6 weeks after breast surgery [67]. By far the most common organisms involved in these wound infections are streptococcal species, *S. aureus,* and coagulase-negative staphylococci (CoNS) [67, 69]. A surveillance study of surgical wound infections revealed that variable wound infection rates appear to be dependent on the type of breast cancer procedure performed [67]. More extensive surgery resulted in higher wound infection rates: simple breast biopsies had a rate of 2.3 %, lumpectomy with lymph node dissection had a wound infection rate of 6.6 %, and mastectomies had a rate of 19 % ($P < 0.05$). In addition, variation in surgical technique, such as drain type (e.g., closed suction, Jackson-Pratt) and placement (e.g., new skin incision separate from the cancer incision vs. through the wound), also influenced infection rates

[67]. Alternatively, other investigators have reported similar wound infection rates for modified radical mastectomy and lumpectomy. For example, Vinton et al. [70] reviewed 387 modified radical mastectomies and 173 lumpectomies between 1983 and 1989. The wound infection rates were not significantly different for modified radical mastectomy (15 %) and lumpectomy (13 %). The impact of the shift toward more conservative surgery on breast cancer wound infection rates is unclear in part because the postoperative population is so heterogeneous. Some patients receive lumpectomy and immediate reconstruction; others receive lumpectomy with radiation and delayed reconstruction; some receive a two-staged reconstruction with expanders then prosthetic implants and others receive a muscle flap procedure; patients with advanced disease receive mastectomy, extensive lymph node dissection, and extensive chemotherapy. Reduction in infection risk will most likely stem from technological advances that further conserve tissue and lymphatic drainage and potentially minimize implantation of prostheses; well-designed comparative studies will be needed.

## 7.2 Late-Onset Infectious Complications of Breast Cancer

A subset of breast cancer patients experience skin and soft tissue infections months to years after therapy concludes. Impaired local immunity and lymphedema, both clinically apparent and unapparent, are the underlying predisposing factors for these infections. Historically, the most common late infection in postmastectomy patients was upper extremity cellulitis ipsilateral to the breast cancer surgery and lymph node dissection. A classic presentation is sudden onset of a painful and erythematous rash that spreads rapidly on the involved upper extremity, with or without fever. Blood cultures, positive in only a minority of cases, may yield skin flora. Many, but not all, of the patients who experience one or more episodes of cellulitis had obvious preexisting chronic swelling and lymphedema of the ipsilateral upper extremity. Lymphedema was a common complication after radical and, less frequently, modified radical mastectomy. The incidence of chronic lymphedema following these surgeries has been estimated at 15 % [71]. Risk factors for the development of lymphedema included the following: a greater number of lymph nodes removed, delayed postoperative wound healing, cellulitis, radiodermatitis, hematoma, seroma formation, and skin flap necrosis [71].

The rates of upper extremity cellulitis following lumpectomy, radiation therapy, and chemotherapy are unavailable but appear to be lower than those following radical or modified radical mastectomy. Clinical lymphedema appears to be a marker for increased risk of cellulitis, but subclinical abnormalities of lymphatic drainage can also predispose to infection. Bertelli et al. [72] reported that 7 of 21 patients with ipsilateral upper extremity cellulitis following breast cancer surgery did not have clinically detectable lymphedema. Breast cancer patients who experience a single episode of cellulitis appear to be at risk of recurrence; in one series, 11 of 15 patients with cellulitis after breast cancer surgery had more than one episode [73]. A breast cancer patient, especially one who experiences

difficulties with wound healing postoperatively should be considered at life-long risk of developing upper extremity cellulitis. Improved understanding about the development of postoperative lymphedema in breast cancer patients [74] may eventually identify those who are at increased risk of developing this condition.

Osteomyelitis and septic arthritis of the shoulder ipsilateral to the involved breast is a very rare infectious complication of breast cancer and therapy. This complication is apparently also linked to preexisting lymphedema, presenting years after breast cancer surgery. Chaudhuri et al. [75] described five cases in which ipsilateral humeral osteomyelitis and septic arthritis presented 2–12 years after breast cancer surgery. All five patients had received a radical or modified radical mastectomy followed by radiation therapy. A striking characteristic of these cases was indolent presentation—ipsilateral shoulder pain and restricted movement for four or more months, without fever. Four patients had an erythrocyte sedimentation rate (ESR) of >100 mm/h. Radiologic studies confirmed the diagnosis of osteomyelitis: all five patients had positive bone scans, three of the five patients had findings of osteomyelitis on plain radiographs, and none had findings consistent with radiation necrosis. In the latter disease, the bony changes are defined radiologically by the prior radiation field. It is unclear whether these serious late complications, osteomyelitis and septic arthritis, will occur following tissue-conserving surgeries.

Despite the shift in management of breast cancer to more conservative surgery, skin and soft tissue infections continue to be the major delayed complication of breast cancer. Instead of ipsilateral arm cellulitis, focal cellulitis of the involved breast has been reported following lumpectomy with axillary lymph node dissection. Rescigno et al. [76] documented 20 episodes of breast cellulitis in 11 patients. The authors estimated the incidence of this complication among patients after lumpectomy to be 2.5–3.0 %. Time from completing radiation to first episode of cellulitis ranged from 9 days to 4 years (median, 4.3 months). Each of these patients presented acutely with rapidly spreading erythema, warmth, and tenderness of the breast. The original site of erythema was often removed from the surgical scar. In 8 cases, erythema spread beyond the breast tissue to the back, shoulder, or arm. Fever or breast swelling was present in some, but not all, patients. Six cases required hospitalization. Two patients experienced repeated episodes of chronic recurrent cellulitis. Episodes of acute and recurrent breast cellulitis responded to antibiotics directed against gram-positive cocci (e.g., oxacillin, cefazolin). Finally, four patients experienced chronic persistent cellulitis, which did not fully resolve despite prolonged antibiotic therapy. This apparent non-infectious erythema may be to radiation-induced inflammation [77]. This latter condition is treated with corticosteroids.

Late development of breast abscesses may be unique to the breast cancer patients who received lumpectomy and radiation. Keidan et al. [78] reviewed 112 lumpectomies, finding seven breast abscesses that developed 1.5–8 months following surgery. This 6 % abscess incidence was higher than expected for clean surgery. Aspirated fluid grew *S. aureus* in three cases and *S. epidermidis* in three cases. Postsurgical manipulation, such as previous seroma aspiration, was a risk

factor for abscess development. Notably, each of the seven patients with breast abscess had received local irradiation. Irradiation may result in impaired lymphatic drainage and local ischemia, which may increase the risk of infection. Axillary node dissection likely contributes to poor lymphatic drainage.

## 7.3 Management of Soft Tissue Infections in Breast Cancer Patients

New onset of erythema in the breast tissue or ipsilateral upper extremity in a patient with history of breast cancer is most likely cellulitis. However, non-infectious causes of skin erythema should also be considered, especially when erythema occurs within the radiation field or when it persists after a trial of antibiotic therapy. Radiation changes alone can cause chronic, sometimes progressive, inflammation. In addition, "radiation recall" of the chest has been reported when patients receive chemotherapy agents long after their radiation course [79]. Differential diagnosis of a focal breast mass in a breast cancer patient following recent surgery includes fat necrosis [80], which often presents as a tender hard mass with or without appreciable inflammation, tumor recurrence, benign cyst, and sterile seroma. An ultrasound should be performed to evaluate an area of focal induration. If fluid is detected, an aspirate should be sent for cytology, gram stain, and culture. If the tender mass does not have a fluid component, a biopsy is necessary to differentiate tumor recurrence, fat necrosis, and phlegmon. In the setting of long-standing chronic lymphedema, Stewart–Treves syndrome, a very rare type of angiosarcoma, develops either in the ipsilateral arm of patients following mastectomy or, in the era of lumpectomy with irradiation, in the irradiated field of the breast, chest wall, or shoulder [81, 82]. Angiosarcomas involving skin as well as breast tissue have been noted with a wide range of soft tissue irregularities including edema, nodules, vesicles, papules, macules, and ulceration [81, 82]. In those who develop angiosarcomas within the radiation field, the mean interval between radiation therapy and sarcoma diagnosis is 5 years [81, 82] earlier than the lymphedema-induced angiocarcoma cases. This lesion is highly metastatic and has a high mortality despite aggressive measures. Skin biopsy or breast biopsy should be considered if the appearance of the involved region does not resolve with a seemingly appropriate course of antibiotic therapy.

The underlying pathophysiology of most infectious complications of breast cancer patients is damaged local host defense secondary to surgery and radiation therapy, namely an impaired skin barrier, injured microcirculation, and impaired lymphatic drainage. If infection involves an indwelling foreign body (e.g., tissue expander, mesh, or prosthetic implant), the material will likely serve as a nidus for bacteria or *Candida* species; successful eradication of infection will likely require device removal. Patients usually present with acute onset of erythema, increased warmth, pain, possibly with drainage, fever, and leukocytosis. The infections tend to be local, involving skin, underlying dermis, and possibly fat. Because the infections tend to be focal, blood cultures are rarely positive but should be performed. Tissue

samples for culture are also rarely positive; unless there is fluctuance, tissue aspiration is not recommended so as to avoid further damage to the skin barrier. When cultures are positive, isolated pathogens are almost always gram-positive; thus, in most cases, antistaphylococcal coverage is adequate. The patient should be treated with antistaphylococcal coverage, such as nafcillin, cefazolin, clindamycin, or vancomycin. Local frequencies of healthcare-associated MRSA as well as of community-associated MRSA should influence the choice of empiric vancomycin. Often oral antibiotics, such as clindamycin, trimethoprim-sulfamethoxazole, and doxycycline, may be used to complete a course once swelling and erythema have been reduced. Rarely, a patient presenting with an acute implant-associated infection will appear septic, with hypotension, tachycardia, flushing of skin, and malaise. In such a situation, it is prudent to remove the implant promptly. In the absence of sepsis, the decision whether a prosthesis must be removed can take place over a series of days or even weeks; a patient can be treated initially with antibiotics while the prosthesis remains in place, the extent of the infection is evaluated, and the virulence of the organism(s) is determined.

Any patient who has undergone lymph node dissection should be educated about protecting the ipsilateral arm from trauma, pressure, or damage. Patients are advised to avoid phlebotomy, intravenous catheters, blood pressure monitoring [83], sunburn, or trauma in the upper extremity ipsilateral to previous breast cancer surgery. The use of compression garments and elevation of the affected arm can reduce lymphedema. Early aggressive therapy of cutaneous fungal infections can minimize local skin breakdown [84]. Those who experience poor wound healing initially, develop clinical lymphedema, or experience an episode of cellulitis should take measures to prevent repeated episodes. Selected patients with recurrent cellulitis may benefit from chronic suppressive oral antibiotic therapy.

## 8 Infectious Complications of Abdominal and Pelvic Cancer

Malignant tumors do not honor mucosal barriers. As a consequence, infectious complications of solid tumors in the abdomen and pelvis appear to occur mainly secondary to mucosal invasion of tumor, with subsequent local abscess formation or dissemination. The gastrointestinal tract serves as the dominant source of bacteria within the abdomen and pelvis. When the gastrointestinal tract is intact, a sterile peritoneum lays within millimeters of colonic luminal contents bearing a bacterial density of $10^{11}$ organisms per gram of dry weight [85]. Tumor invasion of gastrointestinal structures allows contamination of previously sterile structures, spaces, or fluids. As a result, the infections that result from cancers in the abdomen and pelvis are often polymicrobial. In a 10-year review of polymicrobial septicemia in cancer patients, Elting et al. [6] found three types of underlying malignancies most frequently: hematologic malignancy in 47 %, genitourinary cancers in 16 %, and gastrointestinal cancers in 13 %. In addition, bacterial flora within the gastrointestinal lumen may shift toward more virulent organisms secondary to exposure to healthcare settings, antibiotics, chemotherapy, and radiation therapy. Normal

gastrointestinal anatomy and function work together as incomplete barriers between contiguous parts of the gastrointestinal system. For instance, an intact ileocecal valve and proper peristalsis serves as a partial barrier protecting the small bowel from colon contents; the valve and peristalsis separate the mainly aerobic small bowel luminal contents, bearing only $10^4$–$10^6$ bacteria per milliliter, from colonic contents, most of which is anaerobic [85]. Solid tumors can disrupt normal digestion and structures, resulting in a host susceptible to serious bacterial and fungal infection.

## 8.1 *Streptococcus bovis* Bacteremia and Endocarditis

The relationship between *Streptococcus bovis* bacteremia and colon carcinoma was uncovered during the 1970s. Klein et al. [86] reported two patients with adenocarcinoma of the colon who developed *S. bovis* endocarditis. They showed that fecal carriage of *S. bovis* in patients with colon carcinoma was significantly greater (56 %) than in healthy controls (10 %), patients with non-gastrointestinal carcinomas, and patients with other gastrointestinal disorders. The authors recommended evaluation for colon carcinoma in all cases of *S. bovis* endocarditis. Subsequently, these same investigators prospectively evaluated 29 patients with 30 episodes of *S. bovis* endocarditis [87]. Twelve patients were found to have colonic neoplasms, three of which were malignant; three other patients had undiagnosed colonic masses and ten had diverticulosis. Of note, the majority of the patients with colonic neoplasms and endocarditis did not have neoplasms that invaded the muscularis mucosa. The presence of a friable intraluminal mass or diverticuli, which also bleed easily, may allow bacteria access to the bloodstream. Similarly, of 53 cases of *S. bovis* endocarditis, Grinberg et al. [88] found 75 % of patients had benign or malignant neoplasms on colonoscopy; the majority were benign. Following the reported association of *S. bovis* and colon carcinoma, there have been case reports of patients with endocarditis involving other streptococci (e.g., *S. sanguis, S. agalactiae*) who were found to have colonic neoplasms [89, 90] and gastric carcinoma [91].

The diagnosis of *S. bovis* bacteremia and endocarditis is based on recovery of the organism from blood cultures. Once a blood culture isolate is identified as *S. bovis,* it is necessary to establish whether endocarditis is likely by performing serial blood cultures and transesophageal echocardiography. In addition, the lower gastrointestinal tract should be evaluated for the presence of disease. Colonoscopy or a barium enema may be performed; if a barium enema is negative, however, a colonoscopy is indicated.

## 8.2 *Clostridium septicum* Myonecrosis and Bacteremia

*Clostridium septicum,* a sporulating gram-positive, toxin-producing anaerobic rod, is an uncommon pathogen in humans. In a review of 114 cases of clostridial infection by Gorbach and Thadepalli [92], only three were caused by *C. septicum.* In a literature review, Kornbluth et al. [93] reviewed four studies of clostridial

infection: of a total of 612 clinical isolates of *CIostridium* spp, only six (1.3 %) were *C. septicum.* An association between malignancy and *C. septicum* non-traumatic myonecrosis has been noted, although this rapidly fatal disease is extremely rare. Particularly vulnerable to these acute, life-threatening bacterial infections are those with leukemia or occult colon or rectal carcinoma [93–95]. In a literature review covering 42 years, Kornbluth et al. [93] identified 162 cases of *C. septicum* infection; 47 % had hematologic malignancies and 34 % had colorectal carcinoma. Occult malignancies were found in 37 %.

The most common sites of underlying adenocarcinoma in patients with *C. septicum* disease are the cecum and distal ileum. Tumor invasion into the mucosa is thought to allow access of the organism to the bloodstream. In a review of the published literature, Kaiser et al. [96] described 23 cases of distant clostridial myonecrosis, 12 of which had underlying colon or rectal carcinoma. *Clostridium perfringens* was isolated in approximately half of these cases, causing a syndrome indistinguishable from that caused by *C. septicum.* The 12 patients with underlying colorectal cancer had mucosal breakdown at the ileum, colon, or rectum documented at surgery or autopsy. Seventeen of the 23 patients died, many within a few hours of admission. Of 59 cases with *C. septicum* bacteremia reviewed by Koransky et al. [95], 21 had solid tumors, 14 of which were colon cancers. Of the 28 patients autopsied, a colonic lesion was documented in 17. Seven autopsies demonstrated evidence of "fecal peritonitis from bowel perforation or gangrene." Case reports of blood-borne *C. septicum* infection associated with colon cancers are the following: septic arthritis [97, 98], septic shock [99], aortitis [100], meningitis and cerebritis [101], and polymicrobial abscess within a hepatic metastasis [102]. Host factors such as diabetes mellitus [93, 103, 104], granulocytopenia [95], and atherosclerosis [95] may increase the risk of developing *C. septicum* infection. Skin damage (e.g., necrosis, cellulitis, and bullae formation) is thought to develop from toxins produced by *C. septicum*.

The presentation of a patient with *C. septicum* myonecrosis is strikingly sudden and severe. He or she reports an acute intense, focal pain, usually of an extremity. The painful site may initially look normal, but within hours, the involved skin becomes discolored and edematous, bullae form, and the discolored area enlarges rapidly [93]. Some patients present with diffuse abdominal pain as the most prominent initial symptom [93]. As a late finding, the subcutaneous tissue becomes crepitant [105]. Patients progress rapidly from a toxic presentation to shock and ultimately death, often within 48 h.

It is critical to rapidly diagnose *C. septicum* myonecrosis on clinical grounds both in patients with and without known malignancies. Blood cultures should be obtained before initiating antibiotics. Gram stain and culture of percutaneous tissue aspirates and bullae aspirates should be performed emergently [96]; identification of short, plump gram-positive rods suggests clostridial infection in the appropriate clinical setting. Because gas on X-ray may be a late finding, performing such studies should not delay debridement. Surgical debridement is necessary on an emergent basis. Patients may require multiple surgeries over several days following presentation. High-dose penicillin G is the traditional drug

of choice for *C. septicum* infection. Clindamycin is favored by some investigators because its mechanism of action may inhibit clostridial toxin production and more effectively halt the progression of established disease. Initial antibiotic management is typically broad, covering gram-negative, staphylococcal, and anaerobic organisms, until the diagnosis is confirmed by culture results and the extent of intraabdominal disease is known. The patient should be aggressively treated for sepsis and monitored closely for hemodynamic deterioration. It is unclear whether patients benefit from adjunctive hyperbaric oxygen therapy.

## 8.3 Pyogenic Abscesses

Pyogenic liver abscess is another extremely rare entity that can complicate gastrointestinal malignancies. There appear to be two typical presentations for pyogenic liver abscesses in patients with gastrointestinal malignancies. First, abscesses may herald the discovery of a previously undiagnosed, usually advanced, luminal or pancreaticobiliary malignancy. Secondly, pyogenic liver abscesses occur in patients with known malignancies, many of whom have undergone recent gastrointestinal procedures. In a review of 20 cases of pyogenic liver abscess, five had underlying gastrointestinal carcinomas [106]. Patients frequently presented with fever of unknown origin. Most pyogenic liver abscesses associated with colon carcinomas were polymicrobial and included anaerobes and enteric gram-negative rods. Organisms presumably spread from areas of mucosal breakdown to the liver via the portal circulation. Pancreaticobiliary malignancy may obstruct the biliary tract, resulting in ascending cholangitis and then in multiple hepatic abscesses.

The development of one or more liver abscesses in a known cancer patient is extremely rare. A review of liver abscess in cancer patients at the NCI yielded only 37 patients over 35 years [107]. The etiology of these abscesses was bacterial in 17 and fungal in 20. Twelve of the 17 patients with bacterial liver abscesses had solid tumors; the remaining five had hematologic malignancies. Most bacterial abscesses were polymicrobial, with gram-negative and anaerobic organisms recovered on culture. Marcus and associates [107] found that recent gastrointestinal instrumentation was a strong risk factor for liver abscess development. Ten of the 17 patients with bacterial abscesses had undergone either a surgical or radiologic procedure on the gastrointestinal system, such as surgical resection of liver metastases and biliary stent placement. Similarly, invasive procedures involving the colon may increase the risk of liver abscess by seeding the portal vein with bacteria: For instance, a pyogenic liver abscess was reported after colonoscopy with removal of a malignant polyp [108]. Hepatic and splenic abscesses have occurred after invasive procedures for hepatocellular carcinoma. Okada et al. [109] reported a *K. pneumoniae* pyogenic liver abscess following percutaneous ethanol injection into liver lesions. Isobe et al. [110] reported a case of probable multiple splenic abscesses in a cirrhotic woman with hepatocellular carcinoma who developed fever and acute left upper quadrant pain 1 day after percutaneous ethanol injection. Whereas breakdown of the mucosal barrier of the gut or pancreaticobiliary system is the basis of pyogenic liver abscess

in the undiagnosed colon carcinoma patient, in the known cancer patient undergoing therapy, recent gastrointestinal instrumentation appears to be the primary risk factor.

Pyogenic hepatic abscesses should be suspected in a patient with fever, malaise, right upper quadrant pain, and/or jaundice or in a patient with persistent unexplained fever. Liver abscesses may be identified by CT scan or by ultrasound. Blood cultures should be obtained upon admission and when the patient is febrile. If a patient with a pyogenic abscess has no clear pancreaticobiliary obstruction, a search for a lesion within the lumen of the gastrointestinal tract should be considered. Treatment of pyogenic liver abscesses is controversial and evolving. Many continue to rely on surgical or percutaneous drainage [111]. Some patients have done well with prolonged antibiotic therapy alone, following percutaneous aspiration and identification of the infecting organisms and their antimicrobial susceptibilities [112]. Empiric broad-spectrum antibiotics, including gram-negative and anaerobic coverage, are indicated initially; choices such as piperacillin/tazobactam, ticarcillin/clavulanate, imipenem cilistatin, or meropenem are among the many appropriate initial regimens. Use of an aminoglycoside can often be avoided or used only in the initial days of therapy while awaiting culture results. Antibiotic coverage should be tailored to the results of antimicrobial susceptibility testing, if available. Because polymicrobial infections are common in these infections, retaining broad coverage agent gram-negative and anaerobic bacteria is usually indicated on the assumption that more organisms may be involved than can readily be identified. Periodic imaging studies can be used to monitor the resolution of the abscesses; up to 4 months of antibiotic therapy may be warranted.

## 8.4 Gynecologic Cancers

In a retrospective study of infectious morbidity on a university gynecologic oncology service, Brooker et al. [113] found 20 (6 %) of 494 patients had a serious infection on admission and 54 patients (11 %) developed serious infections during hospitalization. The infection rate per admission varied by cancer origin: 8 % for cervical cancer, 7 % for uterine cancer, 3 % for ovarian cancer, and 21 % for vulvar cancer. Bacteremia in gynecologic cancers may be caused by a single organism or be polymicrobial, with the primary tumor the likely portal of entry [6]. Infections associated with gynecologic cancer involve organisms such as streptococci, enterococci, *Enterobacteriaceae*, anaerobes, and staphylococci. In general, the organisms involved in gynecologic infections are normal flora of the vagina, gastrointestinal tract, and skin.

Infectious complications of gynecologic cancers at diagnosis highlight the changes in endogenous mucosal flora that may take place when cancer develops. When infection complicates stage I cervical cancer, the infection is typically limited to the vagina, covering only the surfaces of the tumor itself [114]. The abnormal neoplastic tissue allows bacterial overgrowth of normal flora to take place. Streptococcal species are usually isolated from the purulent debris. Rose and Wilson [115] presented a case of *S. aureus* toxic shock syndrome in a patient with

previously undiagnosed advanced cervical cancer. The cervical cancer was believed to be the portal of entry for staphylococcal toxins to reach the bloodstream.

In patients with advanced cervical disease, obstruction may contribute to the development of adnexal infections. Barton et al. [116] described three unusual cases in which patients presented with cervical cancer complicated by tuboovarian abscesses. In two cases, the patients were initially overstaged secondary to inflamed adnexal masses, which were later found to be free of cancer. The third patient developed an acute abdomen secondary to a ruptured tuboovarian abscess shortly after detection of an exophytic cervical mass.

Patients with cervical disease that has invaded surrounding tissues by direct extension may be more likely to develop pyometra (pus in the uterus) [114]. Some patients with pyometra present with the classic triad of purulent vaginal drainage, fever, and lower abdominal pain [117]. Pyometra, however, can often be asymptomatic, presenting without fever or pelvic pain [114] and does not necessarily develop secondary to obstruction at the cervical os. Typical organisms are aerobic and anaerobic streptococci [114].

Spontaneous peritonitis is an unusual infectious complication of gynecology–oncology patients. Peritonitis may occur if a pyometra ruptures. A collection of 15 cases in the literature of spontaneous perforation of pyometra found that one-third of the patients had malignant disease [117]. All 15 patients presented with fever, 53 % with vomiting, and 20 % with atypical genital bleeding. The most common organisms in peritoneal fluid were *Escherichia coli, Bacteroides* species, and polymicrobial. Douvier et al. [118] reported two cases of perforation of the uterus at the site of endometrial carcinoma, resulting in peritonitis. Very advanced, usually undiagnosed, carcinoma of the cervix has been associated with spontaneous rupture into the retroperitoneum [114]. The severity of infectious complications at cancer diagnosis appears to correlate with the extent of tumor invasion and secondary obstruction; because the majority of gynecologic cancers in the United States are now diagnosed when disease is localized, complications such as peritonitis are extremely rare at the time of cancer detection.

Surgery, chemotherapy, and/or radiation therapy contribute to infectious complications of gynecology–oncology patients. Under such abnormal conditions, a normally benign vaginal commensal can proliferate, invade the bloodstream, and cause sepsis. For example, Andriessen et al. [119] reported a non-neutropenic patient who presented with sepsis following chemotherapy for metastatic choriocarcinoma; multiple blood cultures grew *Lactobacillus acidophilus.* A gallium scan showed only diffuse uptake in her uterus. Connor et al. [120] reported a case in which a patient became septic 2 days following surgery and was found to have a *Lactobacillus* spp. pelvic abscess and bacteremia. In a retrospective study of infections associated with gynecologic cancers, cervical cancer had the highest surgical infection rate (22 %); examples of such infections were peritonitis, pelvic hematomas, groin abscesses, and drainage tube infections [113]. Similar types of infections were documented as complications of uterine and ovarian cancers. Prior radiation therapy and surgery appeared to be risk factors for infection in patients with cervical and uterine cancers (Fig. 2). Preexisting subclinical pelvic infections,

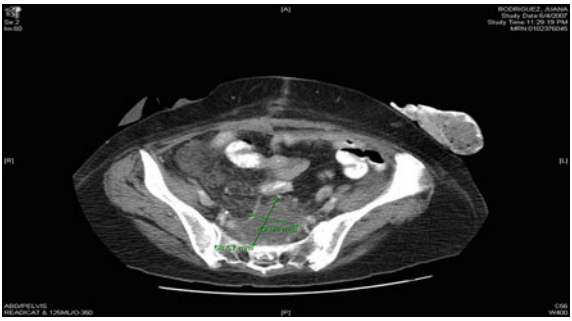

**Fig. 2** This is a 56-year-old female with past medical history of cervical cancer treated two years previously with chemotherapy and radiation therapy who presented with new onset pelvic pain. She was diagnosed with locally-invasive recurrent cervical cancer and underwent pelvic exenteration with placement of ileal conduit and loop colostomy. At postoperative day 7 she began having daily fevers associated with shaking chills. She denied other complaints and her physical exam was unremarkable. This pelvic CT scan with oral and i.v. contrast, performed postoperative day 13, revealed new rim enhancement of presacral fluid. Interventional Radiology placed a drain. Gram stain of the reddish fluid obtained contained few Gram negative rods. Anaerobic culture grew many *Bacteroides* species. Fevers resolved with drainage and a course of metronidazole

invasive diagnostic procedures, and invasive devices of supportive care (nasogastric tubes, urinary catheters, and central lines) may also contribute to the development of postoperative infections [113]. Complications of pelvic irradiation for cervical cancer, such as fistula formation and small bowel obstruction or perforation, are rare and may be associated with previous pelvic inflammatory disease [121]. Graham [122] suggested that two additional factors contributed to gynecologic surgical infections: First, removed organs and tissue create dead space that fills with blood and serum, an excellent culture medium, and, second, bowel obstruction or ileus can result in poor nutritional status preoperatively and postoperatively. Ovarian carcinoma is the most common gynecologic cancer to be treated with chemotherapy; these patients are at risk for the infectious complications associated with neutropenia.

Infections associated with gynecologic cancers can be life-threatening. Empiric antibiotics for a febrile patient with suspected advanced gynecologic cancer should cover anaerobes and aerobic gram-negative bacilli. *Candida* spp. may play a role in some infections because they are part of normal and abnormal vaginal flora. Enterococci and group B streptococci may also be involved in gynecologic infections, particularly abscesses. Cultures of blood, vagina, pyometra, and abscess drainage may help guide therapy.

## 8.5 Bacillus Calmette-Guérin Dissemination

Dissemination of intravesicular bacillus Calmette-Guérin (BCG) is an unusual outcome of a unique anticancer therapy commonly used in bladder cancer. The antineoplastic mechanism of action of this *Mycobacterium bovis* strain is thought

to be as an immune modulator. Cases of disseminated BCG have been rare. Lamm et al. [123] found granulomatous hepatitis and/or pneumonitis in 0.7 % of bladder cancer patients receiving intravesicular BCG therapy. *M. bovis* is presumed to spread hematogenously from the bladder.

The time from installation to symptomatic presentation appears to be highly variable, ranging from hours to several months after exposure. Proctor et al. [124] presented a case of an elderly male who experienced fever and rigors 5 h after installation. A blood culture from that day grew *M. bovis.* The patient developed mild hepatitis, hyperbilirubinemia, and AFB-positive hepatic granulomas. The patient improved on isoniazid and rifampin for 12 months plus 2 months of initial ethambutol. In contrast, Hakim and colleagues [125] reported a case in which an elderly bladder cancer patient presented with a *M. bovis* psoas abscess 9 months after BCG therapy. Katz et al. [126] reported a case of a man who presented with lumbar vertebral osteomyelitis and psoas abscess approximately 4 months after completing a year of BCG therapy. Cultures from bone and abscess fluid grew *M. bovis.* Subsequent vertebral surgery revealed necrotic bone with AFB-positive caseating and non-caseating granulomas. He responded well to abscess drainage and isoniazid and rifampin.

Other cases of BCG infection that are consistent with hematogenous spread include the following: acute prosthetic knee arthritis [127], septic arthritis of the elbow [128], pancreatic and psoas abscesses [129], lumbar discitis [130], mycotic aneurysms of large arteries, both native and prosthetic [131], and pulmonary infections [132]. Pulsed field gel electrophoresis has been used to confirm that the instilled organism is identical to the infecting pathogen [132]. Infectious arthritis, which should be treated with antituberculous drugs, should be differentiated from BCG-associated reactive polyarthritis [133, 134] or Reiter's syndrome [135], which is treated with anti-inflammatory agents.

One needs to have a high index of suspicion that BCG may be the cause of infection in a febrile patient who is receiving or has received BCG therapy for bladder cancer. Attempts should be made to isolate and identify the organism because prolonged, potentially toxic treatment is required. When BCG disseminates, therapy requires prolonged antituberculous medication and drainage of any abscess. *M. bovis* is intrinsically resistant to pyrazinamide. Most cases in the literature reported cure when patients were treated with isoniazid and rifampin for 6–9 months. A patient who suffers from invasive BCG infection should not receive any additional BCG therapy.

## 9 Infectious Complications of Head and Neck Cancer

Infections occur commonly in patients with head and neck cancer. Because patients typically become symptomatic at late stages of disease, they often present when large tumors obstruct airways or inhibit swallowing. Tumor involvement of the oral mucosa, a reservoir of substantial numbers of bacteria, provides a ready source of pathogens. Dry mouth, a common side effect of radiation and surgery to

the head and neck, contributes to alterations in oral flora, shifting to colonization of yeast and bacterial pathogens. Local infection, aspiration, and aspiration pneumonia are common. In the late stages of disease, many patients experience profound weight loss secondary to cachexia and restricted intake. The resulting malnutrition and related immunosuppression, as well as frequent COPD, liver disease, and poor dental hygiene, further diminish the ability of these patients to effectively fight infection. As in other solid tumor patients, surgery, radiation therapy, and chemotherapy further impair local and systemic host defenses. The combination of these factors results in a significant risk of infection.

Recently, there have been considerable stepwise advances in the basic science of and management of head and neck patients. First, we now have evidence that human papillomavirus may play a significant role in the pathogenesis of many head and neck cancer patients. This development may ultimately lead to interventions that decrease the incidence via vaccination, enhance early detection, or contribute to new therapies for this disease. Next, understanding the role of growth factors in the development of cancers has led to the development of cetuximab, a monoclonal antibody that inhibits epidermal growth factor receptor (EGFR); this agent has been administered alone or in combination with radiation or chemotherapy in head and neck cancer cases that failed standard chemotherapy. Use of cetuximab has been associated with small increases in infectious complications in randomized controlled trials [136, 137]. Third, there have been significant advances in clinical research in the treatment of advanced head and neck cancer; the goals of these advances are to improve the rate of cure and to reduce damage to organs of the head and neck [138]. For advanced head and neck cancer, concurrent chemoradiation has been shown to have a survival advantage over radiation alone. These combined therapies appear to be associated with increased hematologic and mucosal damage. Coincident advances in radiation therapy and surgery have decreased the potential for infectious complications, however. Focused irradiation modalities such as intensity-modulated radiation therapy have resulted in reduced damage to the swallowing reflex and salivary gland function [138, 139]. The advantages of intensity-modulated radiation therapy are two-fold: First, increased doses of irradiation are focused on the precise three-dimensional shape of the tumor; second, normal tissue is spared. Similar reduction in toxicity has been seen by administering multiple doses per day over fewer days (hyperfractionation). Advances in surgical approaches have resulted in maintaining saliva production, retaining the swallowing reflex, and sparing the larynx when possible [139]. Overall, such advances have decreased the risk of serious infectious complications in patients with head and neck cancer.

## 9.1 Infections After Radiation Therapy

Head and neck cancer patients commonly receive treatment with chemotherapy, radiation, and surgery. Radiation can result in delayed healing, posing an increased risk of wound infection. In addition, radiation can dramatically reduce saliva

production, causing an alteration in oral flora favoring more virulent organisms [140–142]. Microbial samples from plaque and saliva of patients before and after irradiation revealed significant increases in *Streptococcus mutans, Lactobacillus* spp., *Candida* spp., *Staphylococcus* spp., enteric gram-negative bacilli, and anaerobes [142]. A progressive drop in salivary production was identified, beginning within 2 weeks of bilateral parotid gland irradiation and decreasing to 6 % of initial flow rates in patients by 3 months; at that time, dental caries were noted with increased frequency [143]. Fungal infections cause a great deal of morbidity in the head and neck patient following irradiation [141], including increased pain and difficulty with speech [144]. Irradiation to the mouth or the larynx changes the skin flora and the mouth flora for up to 6 months, resulting in significant overgrowth by a variety of yeast.

## 9.2 Postoperative Wound Infections

Most surgery for head and neck cancer, because it involves the upper respiratory and gastrointestinal tract, is considered to be contaminated or clean contaminated. During surgery and throughout the healing process, most wounds are in intimate contact with the mucosal surfaces or secretions, of the oropharynx and respiratory tract. Salivary bacterial counts are in the range of $10^8$–$10^9$/mL [145]. Anaerobes account for 90 % of the bacteria in the oral cavity; the remainder are aerobic gram-positive and gram-negative organisms. Contamination by oral flora during and after surgery contributes greatly to the high rate of wound infections after head and neck surgery. Infection rates of over 80 % have been recorded when prophylactic antibiotics were not used.

The impact of anaerobic organisms in the pathogenesis of wound infections in head and neck cancer became evident during the 1980s, coinciding with improved techniques of isolating anaerobic bacteria. Sawyer [146] clarified the need for anaerobic coverage in most head and neck cancer surgeries by demonstrating a significantly reduced infection rate following prophylaxis with metronidazole and cefazolin when compared with recent historical controls using cefazolin alone. A prospective, randomized trial in head and neck cancer patients confirmed improved infection rates with cefazolin and metronidazole (9.5 % infection rate vs. 18.6 % infection rate for cefazolin alone) [147]. The majority of head and neck postoperative wounds are polymicrobial. Brook and Hirokawa [148] cultured 24 postoperative wounds of head and neck cancer patients, finding that 88 % of the wounds were mixed anaerobic and aerobic flora. *Peptostreptococcus* spp., *Bacteroides* spp. (*non-fragilis*), and *Fusobacterium* spp. were the most commonly identified anaerobes.

Increased risk of wound infection can be attributed to the extent of disease, duration of surgery, and technical constraints. While tumor removal is of primary importance, surgeons attempt to preserve the airway, cough reflex, diaphragm function, speech, facial muscles and nerves, hormonal function, lymphatic drainage, and saliva production [149]. Seroma and hematoma formation can contribute

to the risk of abscess; effective hemostasis and use of drains can minimize bleeding and edema. Patients with advanced disease often require removal of large amounts of tissue, thereby exposing extensive wounds. Technical decisions that influence perfusion of a graft or skin flap can have significant impact on infection risk. Tandon et al. [150] found that patients who underwent a muscle flap procedure, which reflects extensive disease, had increased risk of infection. Eight of 12 patients who underwent a pectoralis major flap developed wound infections. Robbins et al. [151] reviewed 400 head and neck patients who underwent surgery and found a wound infection rate of 20 %. The presence of advanced disease, duration of surgery greater than 6 h, placement of a flap, as well as the absence of anaerobic coverage perioperatively, were found to be significant risk factors for wound infections. Brown et al. [152] recorded an overall 7 % wound infection rate among 245 head and neck patients receiving perioperative antibiotics; the subset of patients with stage IV disease had a 15 % risk of wound infection. Similarly, those patients who underwent a myocutaneous flap procedure had an infection rate of 36 % whereas those receiving simpler procedures had a risk of 6 %. These investigators also identified probable errors in surgical decision making or technique in 10 of the 17 patients who developed wound infections, many of which resulted in flap or skin graft failure from ischemia, bleeding, tension, or trauma. Some risk factors for wound infection in head and neck cancer patients may be difficult to modify, namely the extent of disease at presentation and the technical and physical constraints that result.

## 9.3 Non-wound Infections in Head and Neck Patients

The lower respiratory tract is the primary site of non-wound infections in head and neck cancer patients. These infections are a major cause of morbidity and mortality in this patient group. Hussain et al. [153] reviewed 12 months of admissions to a university head and neck cancer service. Eighty-six infections were documented among 102 febrile episodes in 67 patients. Forty-three percent of the infections were attributed to pneumonia or tracheobronchitis. Eighteen percent of deaths were directly attributed to pneumonia. Papac [154] reported 78 infectious complications among 191 patients with advanced head and neck cancer hospitalized on a medical oncology service at a Veterans Affairs hospital. Of 111 reported deaths, pneumonia was the most frequent cause of death (26 %), twice as common as the next leading cause of death, tumor or metastasis. Pneumonia was the most common non-wound infection in a study of perioperative morbidity among patients with head and neck cancer [155]. Twenty-two of 225 patients experienced lower respiratory tract infections. Of the 22 patients, 19 developed postoperative pneumonia and three had tracheobronchitis. Duration of surgery greater than 6.2 h increased the risk of non-wound infection from 4.5 to 15.3 %. Having a greater than 70 pack-year history of smoking and receiving a blood transfusion perioperatively also significantly increased the risk of pulmonary infection. Length of stay for those with pneumonia increased from a mean of 19.6 days to 23 days

($P < 0.05$). Other sources of non-wound infections were the urinary tract ($n = 3$), septic phlebitis ($n = 1$), and acute sinusitis ($n = 1$).

### 9.4 Management of Infections in Head and Neck Cancer

At the time of diagnosis of head and neck cancer, some steps can be taken to prevent infectious complications. Because tuberculosis can become reactivated in these patients, it is prudent to test for evidence of past and present infection with a PPD or QFT-G. Isoniazid with pyridoxine prophylaxis should be strongly considered for those who have latent tuberculosis, despite their advancing age and possible underlying liver disease. Monitoring for adherence and potential toxicity is indicated. Pneumococcal vaccination prior to instituting therapy and annual influenza vaccination may be protective.

Anticipating problems involving the oral cavity is critical to minimizing infectious complications during and after radiation therapy, and to a lesser extent, during and after surgery. Before receiving radiation therapy or undergoing surgery, a head and neck cancer patient should have a complete dental evaluation, including dental X-rays [149, 156]. Carious teeth should be removed or restored. Institution of oral hygiene can reduce the risk of subsequent infectious complications. Patients should use salivary substitutes throughout the day and receive regular fluoride treatments [156]. Some investigators recommend selective decontamination with topical antibiotics during the weeks of irradiation. The patient should be well educated regarding the benefits of rigorous oral hygiene during and after radiation.

Postoperative management is critical in the efforts to reduce morbidity in these patients. In the event of a postoperative wound infection, aerobic and anaerobic cultures should be sent. Empiric antibiotic therapy covering anaerobes, gram-negative bacilli, and aerobic gram-positive cocci is appropriate. Infected fluid collections should be drained. Coleman [149] urged prompt exploration of the surgical wounds if fistulae or necrosis (or other evidence of infection) develop. The index of suspicion of infection should be heightened if the patient has received preoperative irradiation. Should a fistula form near or overlying the carotid sheath, an emergency exploration should be performed; infection of the carotid artery in a previously irradiated site can result in septic emboli or carotid artery rupture with exsanguination [149]. Attempts to prevent aspiration in a patient with advanced head and neck cancer are often futile. Pneumonia is relatively common and often responds to empiric broad-spectrum antibiotics.

## 10 Conclusions

Two broad categories of infection in patients with solid tumors can be described. The first category includes a heterogeneous group of infections which are directly attributable to the tumor. These infections develop because the neoplastic process

causes focal injury, breaks down normally intact barriers, or causes local obstruction. The most prevalent example is postobstructive pneumonia which complicates lung cancer. Many of the remaining infections in this category are quite rare, such as pyogenic liver abscess in hepatocellular carcinoma and *C. septicum* myonecrosis in patients with colon cancer; these infections are reported in the literature as case reports or case series. The second major category of infections is attributed to the effects of cancer treatment: surgery, chemotherapy, and radiation therapy. Examples include neutropenic fever, lymphedema-associated breast cellulitis in breast cancer patients following lumpectomy, intraabdominal sepsis following attempted resection of a solitary hepatic metastasis, and catheter-related sepsis in a patient with head and neck cancer. Some therapies designed to improve cancer morbidity and mortality, such as chemotherapy for some postsurgical non-small-cell lung cancer patients or new biologic chemotherapeutic agents for head and neck patients, may result in increased rates of severe infectious complications. Other innovations in cancer therapy, such as tissue-sparing head and neck surgical techniques and sentinel lymph node biopsy in breast cancer, will likely result in reduced infectious complications. Advances in the management of solid malignancies, technological advances in the management of the infectious disease complications, and the presence of observant clinicians have and will continue to result in the improved quality of life and increased longevity for patients with solid malignancies.

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## References

1. U.S. Cancer Statistics Working Group (2011) United States Cancer Statistics: 1999–2006 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute 2010. Available at www.cdc.gov/uscs. Accessed 3 May 2011
2. Pizzo PA, Robichaud KJ, Wesley R, Commers JR (1982) Fever in the pediatric and young adult patient with cancer: a prospective study of 1,001 episodes. Medicine. 61:153–165
3. Singer C, Kaplan MH, Armstrong D (1977) Bacteremia and fungemia complicating neoplastic disease: a study of 364 cases. Am J Med 62:731–742
4. Mathe G, Meyer P, Brienza S et al (1992) Retrospective study correlating clinical infectious history and peripheral blood T-cell subpopulations in cancer, GvH and HIV+ patients. Biomed Pharmacother 46:17–19
5. Mayo JW, Wenzel RP (1982) Rates of hospital-acquired bloodstream infections in patients with specific malignancy. Cancer 50:187–190
6. Elting LS, Bodey GP, Fainstein V (1986) Polymicrobial septicemia in the cancer patient. Medicine 65:218–225
7. Raad I, Hachem R, Hanna H et al (2007) Sources and outcome of bloodstream infections in cancer patients: the role of central venous catheters. Eur J Clin Microbiol Infect Dis 26:549–556

8. Ghanem GA, Boktour M, Warneke C et al (2007) Catheter-related *Staphylococcus aureus* bacteremia in cancer patients: high rate of complications with therapeutic implications. Medicine (Baltimore) 86:54–60
9. Crnich CJ, Maki DG (2002) The promise of novel technology for the prevention of intravascular device–related bloodstream infection. II. Long-term devices. Clin Infect Dis 34:1362–1368
10. Kumashi P, Girgawy E, Tarrand J, Rolston K et al (2005) *Streptococcus pneumoniae* bacteremia in patients with cancer: disease characteristics and outcomes in the era of escalating drug resistance (1998–2002). Medicine 84:303–312
11. Freifeld AG, Bow EJ, Sepkowitz KA et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:e56–e93
12. Cullen M, Steven N, Billingham L et al (2005) Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. Simple investigation in neutropenic individuals of the frequency of infection after chemotherapy +/− antibiotic in a number of tumors (SIGNIFICANT) trial group. N Engl J Med 353:988–998
13. Meyer KC (2001) The role of immunity in susceptibility to respiratory infection in the aging lung. Respir Physiol 128:23–31
14. Meyer KC (2004) Lung infections and aging. Ageing Res Rev 3:55–67
15. Krumpe PE, Knudson RJ, Parsons G, Reiser K (1985) The aging respiratory system. Clin Geriatr Med 1:143–175
16. Brugarolas A, Takita H (1973) Immunologic status in lung cancer. Chest 64:427–430
17. Busch E, Verazin G, Antkowiak JG et al (1994) Pulmonary complications in patients undergoing thoracotomy for lung carcinoma. Chest 105:760–766
18. Salvana EM, Salata RA (2009) Infectious complications associated with monoclonal antibodies and related small molecules. Clin Microbiol Rev 22:274–290
19. Jacobson KL, Miceli M, Tarrand J et al (2008) Legionella pneumonia in cancer patients. Medicine 87:152–159
20. Dominguez A, Alvarez J, Sabria M et al (2009) Factors influencing the case-fatality rate of Legionnaires' disease. Int J Tuberc Lung Dis 13:407–412
21. Kohno S, Koga H, Oka M et al (1994) The pattern of respiratory infection in patients with lung cancer. Tohoku J Exp Med 173:405–411
22. Strang C, Simpson JA (1953) Carcinomatous abscess of the lung. Thorax 8:11–25
23. Perlman LV, Lerner E, D'Esopo N (1969) Clinical classification and analysis of 97 cases of lung abscess. Am Rev Respir Dis 99:390–398
24. Snider GL, Saleh SS (1968) Empyema of the thorax in adults: review of 105 cases. Dis Chest 54:410–415
25. Feld R, Bodey GP, Groschel D (1976) *Mycobacteriosis* in patients with malignant disease. Arch Intern Med 136:67–70
26. Kaplan MH, Armstrong D, Rosen P (1974) Tuberculosis complicating neoplastic disease: a review of 201 cases. Cancer 33:850–858
27. Kamboj M, Sepkowitz KA (2006) The risk of tuberculosis in patients with cancer. Clin Infect Dis 42:1592–1595
28. Centers for Disease control and Prevention (2000) Targeted tuberculin testing and treatment of latent tuberculosis. MMWR 49(6):1–54
29. Snider GL, Placik B (1969) The relationship between pulmonary tuberculosis and bronchogenic carcinoma: a topographic study. Am Rev Resp Dis 99:229–236
30. Nagata N, Nikaido Y, Kido M et al (1993) Terminal pulmonary infections in patients with lung cancer. Chest 103:1739–1742
31. Ohmagari N, Raad II, Hachem R, Kontoyiannis DP (2004) Invasive aspergillosis in patients with solid tumors. Cancer 101:2300–2302

32. Smith FB, Bveneck B (1991) Localized A*spergillus* infestation in primary lung carcinoma: clinical and pathological contrasts with post-tuberculous intracavitary aspergilloma. Chest 100:554–556
33. De Vuyst P, De Troyer A, Yerault J et al (1980) Aspergilloma in a necrotic bronchial adenocarcinoma. Eur J Respir Dis 61:213–217
34. Meyer RD, Young LS, Armstrong D, Yu B (1973) Aspergillosis complicating neoplastic disease. Am J Med 54:6–15
35. Borkin MH, Arena FP, Brown AE, Armstrong D (1980) Invasive aspergillosis with massive fatal hemoptysis in patients with neoplastic disease. Chest 7(8):835–839
36. Smith JM, Hampton JR, Webb RW (1979) Disseminated aspergillosis, Cushing's syndrome, and oat cell carcinoma of the lung. Chest 76:112–113
37. Sidransky H, Friedman L (1959) The effect of cortisone and antibiotic agent on experimental pulmonary aspergillosis. Am J Pathol 35:169–183
38. Hasan FM, Jarrah T, Nassar V (1978) The association of adenocarcinoma of the lung and blastomycosis from an unusual geographical location. Br J Dis Chest 72:242–246
39. Kaplan W, Clifford MK (1964) Blastomycosis. I. A review of 198 collected cases in Veterans administration hospitals. Am Rev Resp Dis 89:659–672
40. Haron E, Vartivarian S, Anaissie E et al (1993) Primary *Candida* pneumonia: experience at a large cancer center and review of the literature. Medicine 72:137–142
41. Torres A, Chemaly RF, Storey R et al (2006) Influence of type of cancer and hematopoietic stem cell transplantation on clinical presentation of *Pneumocystis jiroveci* pneumonia in cancer patients. Eur J Clin Microbiol Infect Dis 25:382–388
42. Yale SH, Limper AH (1996) *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illnesses and prior corticosteroid therapy. Mayo Clinic Proc 71:5–13
43. Frenkel JK, Good JT, Shultz JA (1966) Latent *Pneumocystis* infection in rats, relapse, and chemotherapy. Lab Invest 15:1559–1577
44. Walzer PD, LaBine M, Redington TJ, Cushion MT (1984) Lymphocyte changes during chronic administration of and withdrawal from corticosteroids: relation to *Pneumocystis carinii* pneumonia. J Immunol 133:2502–2508
45. Sepkowitz KA, Brown AE, Telzak EE et al (1992) *Pneumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. JAMA 267:832–837
46. Henson JW, Jalaj JK, Walker RW et al (1991) *Pneumocystis carinii* pneumonia in patients with primary brain tumors. Arch Neurol 48:406–409
47. Poplin EA, Gordon CJ, Piskorowski TJ, Chandrasekar PH (1991) *Pneumocystis carinii* pneumonia in patients with solid tumors without acquired immune deficiency syndrome. Cancer 68:193–194
48. Kovacs JA, Hiemenz JW, Macher AM et al (1984) *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 100:663–671
49. Limper AH, Offord KP, Smith TF, Martin WJ (1989) *Pneumocystis carinii* pneumonia: differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis 140:1204–1209
50. Sepkowitz KA (1996) *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome: who should receive prophylaxis? Mayo Clin Proc 71:102–103
51. Camazine B, Antkowiak JG, Nava MER et al (1995) Herpes simplex viral pneumonia in the postthoracotomy patient. Chest 108:876–879
52. Ring A, Marx G, Steer C, Harper P (2002) Influenza vaccination and chemotherapy: a shot in the dark? Support Care Cancer 10:462–465
53. Nordoy T, Aaberge IS, Husebekk A et al (2002) Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and *Streptococcus pneumoniae*. Med Oncol 19:71–78

54. Coggle JE, Lambert BE, Moores SR (1986) Radiation effects in the lung. Environ Health Perspect 70:261–291
55. Gross NJ (1977) Pulmonary effects of radiation therapy. Ann Intern Med 86:81–92
56. McInerney DP, Bullimore J (1977) Reactivation of radiation pneumonitis by adriamycin. Br J Radio 50:224–227
57. Azoulay E, Bergeron A, Chevret S et al (2009) Polymerase chain reaction for diagnosing *Pneumocystis* pneumonia in non-HIV immunocompromised patients with pulmonary infiltrates. Chest 135:655–661
58. Fujisawa T, Suda T, Matsuda H et al (2009) Real-time PCR is more specific than conventional PCR for induced sputum diagnosis of *Pneumocystis* pneumonia in immunocompromised patients without HIV infection. Respirology 14:203–209
59. Durand-Jolya I, Chabéa M, Soulaa F et al (2005) Molecular diagnosis of *Pneumocystis* pneumonia. FEMS Immunol Med Microbiol 45:405–410
60. Schwarz MI, Whitcomb ME, Goldman AL (1973) The spectrum of diffuse pulmonary infiltration in malignant disease. Chest 64:88–93
61. Pisani RJ, Wright AJ (1992) Clinical utility of bronchoalveolar lavage in immunocompromised hosts. Mayo Clin Proc 67:221–227
62. Shure D (1989) Transbronchial biopsy and needle aspiration. Chest 95:1130–1138
63. Pomahac B, Recht A, May JW et al (2006) New trends in breast cancer management. Is the era of immediate breast reconstruction changing? Ann Surg 244:282–288
64. Noguchi M (2010) Axillary reverse mapping for breast cancer. Breast Cancer Res Treat 119:529–535
65. Nahabedian MY, Tsangaris T, Bahram M, Manson PN (2003) Infectious complications following breast reconstruction with expanders and implants plastic and reconstructive surgery. Plast Reconstr Surg 112:467–476
66. Brewer VH, Hahn KA, Rohrbach BW, Bell JL, Baddour LM (2000) Risk factor analysis for breast cellulitis complicating breast conservation therapy. Clin Infect Dis 31:654–659
67. Rotstein C, Ferguson R, Cummings KM et al (1992) Determinants of clean surgical wound infections for breast procedures at an oncology center. Infect Control Hosp Epidemiol 13:207–214
68. Bunn F, Cunningham ME, Handscomb K (2006) Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. Cochrane Database Syst Rev 2:CD005360
69. Sauter ER, Eisenberg BL, Hoffman JP et al (1993) Postmastectomy morbidity after combination preoperative irradiation and chemotherapy for locally advanced breast cancer. World J Surg 27:237–242
70. Vinton AL, Traverso LW, Jolly PC (1991) Wound complications after modified radical mastectomy compared with tylectomy with axillary lymph node dissection. Am J Surg 161:584–588
71. Mozes M, Papa MZ, Karasik A, Reshef A, Adar R (1982) The role of infection in post-mastectomy lymphedema. Surg Ann 14:73–83
72. Bertelli G, Venturini M, Forno G, Macchiavello F, Dini D (1992) An analysis of prognostic factors in response to conservative treatment of postmastectomy lymphedema. Surg Gynecol Obstet 175:455–460
73. Simon MS, Cody RL (1992) Cellulitis after axillary lymph node dissection for carcinoma of the breast. Am J Med 93:543–548
74. Stanton AW, Modi S, Mellor RH et al (2009) Recent advances in breast cancer related lymphedema of the arm: lymphatic pump failure and predisposing factors. Lymphat Res Biol 7:29–45
75. Chaudhuri K, Lonergan D, Portek I, McGuigan L (1993) Septic arthritis of the shoulder after mastectomy and radiotherapy for breast carcinoma. J Bone Joint Surg Br 75:318–321
76. Rescigno J, McCormick B, Brown AE, Myskowski PL (1994) Breast cellulitis after conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys 29:163–168

77. Olivotto IA, Weir L, Kim-Sing C (1995) In response to Rescigno et al. Int J Radiat Oncol Biol Phys 31:203
78. Keidan RD, Hoffman JP, Weese JL et al (1990) Delayed breast abscesses after lumpectomy and radiation therapy. Am Surg 56:440–444
79. Parry BR (1992) Radiation recall induced by tamoxifen. Lancet 340:49
80. Rostom AY, El-Sayed ME (1987) Fat necrosis of the breast: an unusual complication of lumpectomy and radiotherapy in breast cancer. Clin Radiol 38:31
81. Styring E, Fernebro J, Jönsson PE et al (2010) Changing clinical presentation of angiosarcomas after breast cancer: from late tumors in edematous arm to earlier tumors on the thoracic wall. Breast Cancer Res Treat 122:883–887
82. Hodgson NC, Bowen-Wells C, Moffat F, Franceschi D, Avisar E (2007) Angiosarcomas of the breast: a review of 70 cases. Am J Clin Oncol 30:570–573
83. Bertelli G, Dini D, Forno GG, Gozza A (1994) Preventing cellulitis after axillary lymph node dissection. Am J Med 97:202–203
84. Dixon JM (1994) Breast infection. Br Med J 309:946–949
85. Finegold SM (1995) Anaerobic bacteria: general concepts. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, douglas and bennett's principles and practice of infectious diseases, 4th edn. Churchill Livingstone, New York, pp 2156–2173
86. Klein RS, Recco RA, Catalano MT, Edberg SC, Casey JI, Steigbigel NH (1977) Association of *Streptococcus bovis* with carcinoma of the colon. N Engl J Med 297:800–802
87. Klein RS, Catalano MT, Edberg SC, Casey JI, Steigbigel NH (1979) *Streptococcus bovis* septicemia and carcinoma of the colon. Ann Intern Med 91:560–562
88. Grinberg M, Mansur AJ, Ferreira DO, Bellotti G, Pileggi F (1990) Endocarditis caused by *Streptococcus bovis* and colorectal neoplasms. Arc Bras Cardiol 54:265–269
89. Fass R, Alim A, Kaunitz JD (1995) Adenocarcinoma of the colon presenting as *Streptococcus sanguis* bacteremia. Am J Gastroenterol 90:1343–1345
90. Wiseman A, Rene P, Crelinsten GL (1985) *Streptococcus agalactiae* endocarditis: an association with villous adenomas of the large intestine. Ann Intern Med 103:893–894
91. Gelfand MS, Hughey JR, Sloas DD (1994) Group B streptococcal bacteremia associated with adenocarcinoma of the stomach. Clin Infect Dis 39:364
92. Gorbach SL, Thadepalli H (1975) Isolation of *Clostridium* in human infections: evaluation of 114 cases. J Infect 131:S81–S85
93. Kornbluth AA, Danzig JB, Bernstein LH (1989) *Clostridium septicum* infection and associated malignancy: report of 2 cases and review of the literature. Medicine 68:30–37
94. Katlic MR, Derkac WM, Coleman WS (1981) *Clostridium septicum* infection and malignancy. Ann Surg 193:361–364
95. Koransky JR, Stargel MD, Dowell VR (1979) *Clostridium septicurn* bacteremia: its clinical significance. Am J Med 66:63–66
96. Kaiser CW, Milgrom ML, Lynch JA (1986) Distant nontraumatic clostridial myonecrosis and malignancy. Cancer 57:885–889
97. Hovenden JL, Murdoch GE, Evans AT (1992) Non-traumatic *Clostridium septicum* arthritis in a patient with caecal carcinoma. Br J Rheumatol 31:571–572
98. Fallon SM, Guzik HJ, Kramer JE (1986) *Clostridium septicum* arthritis associated with colonic carcinoma. J Rheumatol 13:662–663
99. Alpern RJ, Dowell VR (1969) *Clostridium septicum* infections and malignancy. JAMA 209:385–388
100. Rucker CM, Menias CO, Bhalla S, Geraghty P, Heiken JP (2004) *Clostridium septicum* infrarenal aortitis secondary to occult cecal adenocarcinoma. AJR Am J Roentgenol 183:1316–1318
101. Gorse GJ, Slater LM, Sobol E et al (1984) Infection and bacteremia due to *Clostridium septicum*. Arch Neurol 41:882–884
102. Kahn SP, Lindenauer SM, Wojtalik RS et al (1972) Clostridia hepatic abscess: an unusual manifestation of metastatic colon carcinoma. Arch Surg 104:209–212

103. Kudsk KA (1992) Occult gastrointestinal malignancies producing metastatic *Clostridium septicum* infections in diabetic patients. Surgery 112:765–772
104. Abella BS, Kuchinic P, Hiraoka T, Howes DS (2003) Atraumatic clostridial myonecrosis: case report and literature review. J Emerg Med 24:401–405
105. Jendrzejewski JW, Jones SR, Newcombe RL, Gilbert DN (1978) Nontraumatic clostridial myonecrosis. Am J Med 65:542–546
106. Cohen JL, Martin M, Rossi RL, Schoetz DJ (1989) Liver abscess: the need for complete gastrointestinal evaluation. Arch Surg 124:561–564
107. Marcus SG, Walsh TJ, Pizzo PA, Danforth DN (1993) Hepatic abscess in cancer patients: characterization and management. Arch Surg 128:1358–1364
108. Harnik IG (2007) Pyogenic liver abscess presenting after malignant polypectomy. Dig Dis Sci 52:3524–3525
109. Okada S, Aoki K, Okazaki N et al (1993) Liver abscess after percutaneous ethanol injection (PEI) therapy for hepatocellular carcinoma. A case report. Hepato-gastroenterology 40:496–498
110. Isobe H, Sakamoto S, Nawata H (1992) Splenic abscess as a complication of percutaneous ethanol injection therapy for hepatocellular carcinoma. J Clin Gastroenterol 15:167–169
111. Teitz S, Guidetti-Sharon A, Manor H, Halevy A (1995) Pyogenic liver abscess: warning indication of silent colonic cancer: report of a case and review of the literature. Dis Colon Rectum 38:1220–1223
112. Lonardo A, Grisendi A, Pulvirenti M et al (1992) Right colon adenocarcinoma presenting as *Bacteroides fragilis* liver abscesses. J Clin Gastroenterol 14:335–338
113. Brooker DC, Savage JE, Twiggs LB et al (1987) Infectious morbidity in gynecologic cancer. Am J Obstet Gynecol 156:513–520
114. WeIton JA (1965) Significance of infection in carcinonia of the cervix. Obstet Gynecol 26:441–446
115. Rose PG, Wilson G (1994) Advanced cervical carcinoma presenting with toxic shock syndrome. Gynecol Oncol 52:264–266
116. Barton DPJ, Fiorica JV, Hoffman MS et al (1993) Cervical cancer and tuboovarian abscesses: A report of three cases. J Reprod Med 38:561–564
117. Imachi M, Tanaka S, Ishikawa S, Matsuo K (1993) Spontaneous perforation of pyometra presenting as generalized peritonitis in a patient with cervical cancer. Gynecol Oncol 50:384–388
118. Douvier S, Nabholtz J-M, Friedman S et al (1989) Infectious pneumoperitoneum as an uncommon presentation of endometrial carcinoma: report of two cases. Gynecol Oncol 33:392–394
119. Andriessen MPHM, Mulder JG, Sleijfer DT (1991) *Lactobacillus* septicemia, an unusual complication during the treatment of metastatic choriocarcinoma. Gynecol Oncol 40:87–89
120. Connor JP, Buller RE (1994) Lactobacillus sepsis with pelvic abscess. Gynecol Oncol 54:99–100
121. Van Nagell JR, Parker JC, Maruyama Y et al (1977) The effect of pelvic inflammatory disease on enteric complications following radiation therapy for cervical cancer. Am J Obstet Gynecol 128:767–771
122. Graham JE (1990) Infectious morbidity in gynecologic oncology. J Reprod Med 35:348–352
123. Lamm DL, van der Meijden PM, Morales A et al (1992) Incidence and treatment of complications of Bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. J Urol 147:596–600
124. Proctor DD, Chopra S, Rubenstein SC et al (1993) *Mycobacteremia* and granulomatous hepatitis following initial intravesical Bacillus Calmette-Guérin installation for bladder carcinoma. Am J Gastroenterol S8:1112–1115
125. Hakim S, Heaney JA, Heinz T, Zwolak RW (1993) Psoas abscess following intravesical Bacillus Calmette-Guérin for bladder cancer: a case report. J Urol I50:188–189

126. Katz DS, Wogalter H, D'Esposito RF, Cunha BA (1992) *Mycobacterium bovis* vertebral osteomyelitis and psoas abscess after intravesical BCG therapy for bladder carcinoma. Urology 40:63–66
127. Chazerain P, Desplaces N, Mamoudy P et al (1993) Prosthetic total knee infection with a Bacillus Calmette Guérin (BCG) strain after BCG therapy for bladder cancer. J Rheumatol 20:2171–2172
128. Van Thiel RJ, Nossent GD, Tjonpiangi NP (1992) Articular complications of intravesical BCG treatment for bladder carcinoma. Br J Urol 70:446–447
129. Alvarez-Mugica M, Gomez JMF, Vazquez VB et al (2009) Pancreatic and psoas abscesses as a late complication of intravesical administration of Bacillus Calmette-Guérin for bladder cancer: a case report and review of the literature. J Med Case Reports 3:7323
130. Colebatch AN, Mounce KE (2010) *Mycobacterium bovis* discitis as a complication of intravesical Bacillus Calmette-Guérin therapy. J Clin Rheumatol 16:74–75
131. Seelig M, Oldenburg W, Klingler P et al (1999) Mycotic vascular infections of large arteries with Mycobacterium bovis after intravesical bacillus Calmette-Guérin therapy case report. J Vasc Surg 29:377–381
132. Kristjansson M, Green P, Manning HL et al (1993) Molecular confirmation of bacillus Calmette-Guérin as the cause of pulmonary infection following urinary tract installation. Clin Infect Dis 17:228–230
133. Jawad ASM, Kahn L, Copland RFP et al (1993) Reactive arthritis associated with bacillus Calmette-Guérin immunotherapy for carcinoma of the bladder: a report of two cases. Br J Rheumatol 32:1018–1020
134. Tinazzi E, Vincenzo F, Simeoni S et al (2006) Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. Rheurmatol Int 26:481–488
135. Pancaldi P, Van Linthoudt D, Alborino D et al (1993) Reiter's syndrome after intravesical bacillus Calmette-Guérin treatment for superficial bladder carcinoma. Br J Rheumatol 199332:1096–1098
136. Bonner JA, Harari PM, Giralt J et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567–578
137. Burtness B, Goldwasser MA, Flood W et al (2005) Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 23:8646–8654
138. Haddad RI, Shin DM (2008) Recent Advances in Head and Neck Cancer. N Engl J Med 359(11):1143–1154
139. Chambers MS, Garden AS, Kies MS, Martin JW (2004) Radiation-induced xerostomia in patients with head and neck cancer: pathogenesis, impact on quality of life, and management. Head Neck 26:796–807
140. Ariyan S (1979) Infections following surgery for head and neck cancer. Clin Plast Surg 6:523–535
141. Curtis TA, Griffith MR, Firtell DN (1976) Complete denture prosthodontics for the radiation patient. J Prosthet Dent 36:66–76
142. Brown LR, Dreizen S, Handler S, Johnston DA (1975) Effect of radiation-induced xerostomia on human oral microflora. J Dent Res 54:740–750
143. Dreizen S, Brown LR, Handler S, Levy BM (1976) Radiation-induced xerostomia in cancer patients: effect on salivary and serum electrolytes. Cancer 38:273–278
144. Martin MV, Al-Tikriti U, Bramley PA (1981) Yeast flora of the mouth and skin during and after irradiation for oral and laryngeal cancer. J Med Microbiol 14:457–467
145. Bartlett JG, Gorbach SL (1976) Anaerobic infections of the head and neck. Otolarygol Clin North 9:655–678
146. Sawyer R (1988) Clinical implications of metronidazole antianaerobic prophylaxis in major head and neck surgical procedures. Ear Nose Throat J 67:655–662

147. Robbins KT, Byers RM, Cole R, Fainstein V, Guillamondegui OM, Schantz SP, Weber RS, Wolf P, Goepfert H (1988) Wound prophylaxis with metronidazole in head and neck surgical oncology. Laryngoscope 98:803–806
148. Brook I, Hirokawa R (1989) Microbiology of wound infection after head and neck cancer surgery. Ann Otol Rhino1 Laryngol 98:323–325
149. Coleman JJ (1986) Complications in head and neck surgery. Surg Clin North Am 66:149–167
150. Tandon DA, Bahadur S, Laldina HC, Sundaram KR (1992) Role of prophylactic antibiotics in surgery for advanced head and neck cancer. J Laryngol Otol 106:621–624
151. Robbins KT, Favrot S, Hanna D, Cole R (1990) Risk of wound infection in patients with head and neck cancer. Head Neck 12:143–148
152. Brown BM, Johnson JT, Wagner RL (1987) Etiologic factors in head and neck wound infections. Laryngoscope 97:587–590
153. Hussain M, Kish JA, Crane L et al (1991) The role of infection in the morbidity and mortality of patients with head and neck cancer undergoing multimodal therapy. Cancer 67:716–721
154. Papac RJ (1985) Medical aspects of head and neck cancer. Cancer Invest 3:435–444
155. Weber RS, Hankins P, Kosenbaum B, Rand I (1993) Nonwound infections following head and neck oncologic surgery. Laryngoscope 103:22–27
156. Jansma J, Vissink A, Spijkervet FKL et al (1992) Protocol for the prevention and treatment of oral sequelae resulting from head and neck radiation therapy. Cancer 70:2171–2180

# Antimicrobial Agents, Drug Adverse Reactions and Interactions, and Cancer

Ximena Millan, Victoria Muggia and Belinda Ostrowsky

**Abstract**

The intent of this chapter is to review the types of adverse drug reactions and interactions associated with antimicrobial agents, specifically in the setting of patients with malignancies. The initial sections will discuss categorizing and describing the mechanisms of adverse reactions and interactions. The later sections include a detailed discussion about adverse reactions and drug interactions associated with commonly used antibacterial, antiviral, and antifungal agents in this subpopulation. Where relevant, the clinical use and indication for the drugs will be reviewed. The antibacterial section will specifically address the emergence of antimicrobial resistance and drugs of last resort (newer agents, such as linezolid and daptomycin and novel uses of older previously retired agents, such as polymyxin B). The antifungal section will address the ramification of pharmacokinetic interactions and the need to measure drug levels. The chapter is not meant to be exhaustive and as such will not extensively address all antimicrobials or all interactions for each of these agents.

**Keywords**

Antimicrobials · Interactions · Adverse reactions

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## Contents



## 1 Introduction

As cancer therapies have advanced, many patients with malignancies will receive life-saving interventions such as surgery, chemo- and other immunomodulatory therapies, radiation, and hematopoietic stem cell transplantation (HSCT). These interventions assault host immunodefenses and increase risk for an array of infections requiring prophylactic, preemptive, empiric or pathogen-directed antimicrobial therapy.

At any given time, large populations of hospitalized patients receive antimicrobial agents, and patients on specialty services such as the hematology and oncology and intensive care units are over represented. In some of these units, up to 70 % of the patients receive courses of antimicrobials [1, 2]. Adverse events to

medication likely occur in only a small proportion of medication regimens; however, effects can be great since antimicrobials are so common. Most events are mild, but serious side effects do occur. A meta-analysis published in 1998 estimated that 6–7 % of hospitalized patients had a serious reaction and that approximately 5 % of these types of reaction were fatal [3].

The terminology relating to the effects of drugs in the clinical setting is confusing and sometimes overlaps. An adverse drug reaction is a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function [4]." Adverse reactions associated with drugs can include allergies, toxicities, and side effects [4, 5].

A drug interaction occurs when the pharmacodynamics or pharmacokinetics of a drug in the body is altered by the presence of one or more interacting substances [6]. Pharmacodynamics explores what "a drug does to the body." With regard to antimicrobials, pharmacodynamics also relates to the actions of the drug on the pathogen. Pharmacokinetics explores what "the body does to the drug" [6]. The intent of this chapter is to review the adverse drug reactions and interactions associated with antimicrobial agents, specifically in the setting of patients with malignancies.

## 2 Drug Reactions and Pharmacologic Considerations

Drug reactions encompass all adverse events related to drug administration, regardless of etiology. This includes immunologic and non-immunologic reactions, toxicities, side effects, and drug interactions. The majority (75–80 %) of adverse drug reactions are caused by predictable, non-immunologic effects [5, 7]. The remaining 20–25 % of adverse drug events are caused by unpredictable effects that may or may not be immune-mediated [5, 7]. Immune-mediated reactions account for 5–10 % of all drug reactions and constitute true drug hypersensitivity, with IgE-mediated drug allergies falling into this category [5, 7–9].

Toxicity is generally due to either excessive dosing or impaired drug metabolism; thus, the drug is in quantities that cannot be physiologically managed by the host [10]. Examples include neurological toxicity from excessive dosing of penicillin and nephrotoxicity from aminoglycosides. If nephrotoxicity from an aminoglycoside impairs drug metabolism and excretion, this can potentiate nephrotoxicity and neurotoxicity to other drugs. Side effects include adverse events that are neither immunologically mediated nor related to toxic levels of the drug.

Drug interactions most commonly occur between two drugs [6]. However, given the complexities of the hematology–oncology population, multiple drug interactions are possible. Other than drug–drug interactions, drugs may interact with foods, drink, vitamins, minerals, herbal and homeopathic remedies, drug formulations, cytokines, or environmental factors [6].

Antimicrobial pharmacodynamics is an evolving science that focuses on the relationship between drug concentration and pharmacologic effect. The pharmacologic action of antimicrobials is commonly described as concentration-dependent or concentration-independent, although such classifications are highly reliant on the specific drug and pathogen being studied. It is important not just to choose the correct antimicrobial, but also to choose the correct dose, route, and interval and understand how that drug may adversely affect the patient or interact with other drugs.

The primary measure of antimicrobial activity is the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of an antimicrobial that completely inhibits the growth of a microorganism in vitro. While the MIC is a good indicator of the potency of an antimicrobial, it does not inform about the time course of antimicrobial activity.

The three pharmacokinetic parameters that are most important for evaluating antimicrobial efficacy are the peak serum level (Cmax), the trough level (Cmin), and the area under the serum concentration–time curve (AUC). While these parameters quantify the serum-level time course, they do not describe the killing activity of an antimicrobial [11, 12].

Integrating the pharmacokinetic parameters with the MIC gives us three pharmacokinetic/pharmacodynamic (PK/PD) parameters that quantify the activity of an antimicrobial: the Peak/MIC ratio, the time above MIC ($T > \text{MIC}$), and the 24-h AUC/MIC ratio. The Peak/MIC ratio is simply the Cmax divided by the MIC. The $T > \text{MIC}$ is the percentage of a dosage interval in which the serum level exceeds the MIC. The 24-h AUC/MIC ratio is determined by dividing the 24-h AUC by the MIC [11, 12].

The rate of killing of an antimicrobial is determined by either the length of time necessary to kill (time-dependent) or the effect of increasing concentrations (concentration-dependent). Persistent effects include the post-antibiotic effect (PAE) or the persistent suppression of bacterial growth following antimicrobial exposure [11, 12].

Antimicrobials have been categorized into classic "types" that use the above principles to aid in understanding dosing and characteristics of the drug. These are summarized in Table 1. For Type I antimicrobials, the ideal dosing regimen would maximize concentration, because the higher the concentration, the more extensive and faster the killing. Therefore, the 24-h AUC/MIC ratio, and the Peak/MIC ratio are important predictors of antimicrobial efficacy [11, 12]. An example of the practical use of this information would relate to quinolone drugs and dosing, such as use of ciprofloxacin in a patient with renal failure. In this situation, instead of decreasing the dosing to 1/2 every 12 h, it would be better to give the full dose once a day [13].

Type II antimicrobials demonstrate opposite properties. The ideal dosing regimen for these antimicrobials maximizes the duration of drug exposure. The $T > \text{MIC}$ is the parameter that best correlates with efficacy. This explains why $\beta$-lactam antimicrobials such as the penicillins need to be dosed frequently [11, 12, 14].

**Table 1** Pharmacodynamic properties of antimicrobials

| Pattern of activity | Antimicrobial class or drug | Goal of therapy | Parameters to measure |
|---|---|---|---|
| *Type I* | Fluoroquinolones | Maximize concentration | 24-h AUC/MIC Ratio<br>Peak/MIC Ratio |
| Concentration-dependent killing | Aminoglycosides | | |
| | Daptomycin[a] | | |
| *Type II* | $\beta$-Lactams | Maximize duration of exposure | T > MIC |
| Time-dependent killing | Penicillins | | |
| | Cephalosporins | | |
| | Carbapenems | | |
| | Vancomycin[a] | | |
| *Type III* | Daptomycin[a] | Maximize amount of drug | 24-h AUC/MIC Ratio |
| Mixed properties | Linezolid | | |
| | Azithromycin | | |
| | Vancomycin[a] | | |
| | Tigecycline | | |

[a]Some antimicrobials behave as >1 pattern of activity. For additional details, refer to text
*AUC* area under curve, *MIC* minimum inhibitory concentration, *T* time. (Adapted from Refs. [12–17])

Type III antimicrobials have mixed properties. Some drugs, such as vancomycin, daptomycin, and tigecycline, may behave differently depending on the host, organism, and condition being treated [11, 12, 15–17].

Pharmacodynamic interactions are an alteration in the pharmacological response of a drug. They may be caused by direct competition at certain sites of action or by indirectly involving altered physiological mechanisms. Pharmacodynamic interactions can be beneficial in that an improved therapeutic response may occur or detrimental in that toxicity may be heightened. Examples of beneficial antimicrobial interactions are fixed combination antimicrobials that work synergistically such as trimethoprim–sulfamethoxazole (inhibits bacterial folic acid synthesis at different steps), piperacillin–tazobactam and ampicillin–sulbactam (use of a $\beta$-lactamase inhibitor to broaden antibacterial activity against $\beta$-lactamase-producing organisms) and imipenem (marketed in combination with cilastatin to inhibit the dehydropeptidase in the proximal tubule that converts imipenem into metabolites that are nephrotoxic) [6, 10]. Examples of detrimental effects include concomitant use of antimicrobials such as aminoglycosides, amphotericin, or pentamidine with other agents such as radiocontrast, nonsteroidal anti-inflammatory agents, cyclosporine, or cisplatinum, which may result in an increased risk of nephrotoxicity [6, 10].

## 3 Antimicrobial Agents by Drug Class

The following sections include a detailed discussion about adverse drug reactions, clinical pearls for dosing, and interactions associated with commonly used antibacterial, antiviral, and antifungal agents in the cancer population. Tables 2, 3 and 4 supplement this discussion.

### 3.1 Antibacterial Agents

A discussion regarding antimicrobials in the cancer population must occur in the context of increasingly antimicrobial-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE) and penicillin-resistant *Streptococcus pneumoniae* (PRSP). The emergence of these resistant gram-positive pathogens has brought vancomycin to the forefront as a first-line antimicrobial. In addition, a more prominent role now exists for newer agents, such as linezolid and daptomycin. $\beta$-Lactam agents are the cornerstone of anti-infective therapy for the cancer population. However, the emergence of extended-spectrum $\beta$-lactamase (ESBL)-producing and other multidrug-resistant (MDR) gram-negative pathogens, including *Klebsiella pneumoniae* with carbapenemase (KPC), has limited the efficacy of the B-lactam drug class and highlighted the lack of new options for problematic gram-negative pathogens. The use of older drugs, such as polymyxin, and more attention to dosing and delivery strategies have taken on an important role. Table 2 summarizes several antibacterial agents relevant to the care of patients with malignancies.

### 3.2 $\beta$-Lactam Agents

The $\beta$-lactam antimicrobials are a large diverse class of compounds used in oral and parenteral form for an array of indications. The $\beta$-lactam class includes four families of antimicrobials: penicillins, cephalosporins, carbapenems, and monobactams and are grouped together based upon a shared structural feature, the $\beta$-lactam ring. $\beta$-lactam antimicrobials inhibit the growth of sensitive bacteria by inactivating enzymes that are involved in the third stage of cell wall synthesis. $\beta$-lactam antimicrobials are generally bactericidal [17, 18]. $\beta$-lactams are generally well tolerated with minimal toxicity when used in moderate dosing. These agents are commonly used for the empiric treatment for neutropenic fever and for the directed treatment for infections in cancer patients [1], and so it is relevant to highlight a few adverse reactions common to the whole family.

Allergy to penicillin is self-reported in up to 10 % of patients. Anaphylaxis is a severe form of acute hypersensitivity that can result in urticaria, laryngospasm, bronchospasm, hypotension, and death. $\beta$-lactams and specifically penicillins are the antimicrobials most associated with these types of reaction [19]. However, older data probably over-estimates the reactions related to penicillins. In large-scale

**Table 2** Characteristics of antibacterial agents by class

| Antibacterial | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Penicillins [14, 18–23, 36] | Inhibit cell wall synthesis by inactivating bacterial cell membrane enzymes | Broad-spectrum agents<br>Commonly used in treatment for neutropenic fever<br>Directed therapy—for methicillin susceptible *S. aureus* (oxacillin, nafcillin) | IgE-mediated allergic reactions, anaphylaxis<br>Nephrotoxicity (glomerulonephritis, interstitial nephritis, may be agent—rather than class-specific)<br>Hematological reactions<br>Serum sickness<br>Dermatological reactions<br>Neurological reactions, seizures<br>Pulmonary reactions<br>Gastrointestinal/*C. difficile*<br>Hepatobiliary | Vitamin K deficiency Warfarin<br>Probenecid<br>Oral contraceptives<br>Methotrexate<br>Aminoglycoside inactivation (in vitro)<br>Cyclosporine (nafcillin) |
| Higher-generation cephalosporins [29–33, 36] | Inhibit cell wall synthesis by inactivating bacterial cell membrane enzymes | Broad-spectrum agents<br>Commonly used as monotherapy for neutropenic fever (ceftazidime, cefepime) | As above<br>Biliary sludging (ceftriaxone) | As above<br>Acid suppression drugs |
| Monobactams (Aztreonam) [36] | Inhibit cell wall synthesis by inactivating bacterial cell membrane enzymes | Alternative drug for patients with severe penicillin allergy<br>Only has gram-negative aerobic antibacterial activity | | |
| Carbapenems [14, 34–37, 190] | Inhibit cell wall synthesis by inactivating bacterial cell membrane enzymes | Commonly used in treatment for neutropenic fever<br>Broad coverage, including ESBL-producing and ESBL-inducing gram-negative pathogens | As above | As above<br>Valproic acid<br>Cyclosporine, Theophylline, Ganciclovir |

(continued)

**Table 2** (continued)

| Antibacterial | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Fluoroquinolones [38–43] | Bind to and inhibits DNA gyrase and topoisomerase IV | Used for low-risk/short duration neutropenic fever<br>Antibacterial prophylaxis<br>Directed therapy | Central nervous system toxicity<br>Prolonged Q-T interval<br>Achilles tendon rupture<br>*C. difficile* diarrhea | Antacids<br>Minerals<br>NSAIDS<br>Warfarin<br>Alkalyzing agents, Theophylline<br>Caffeine |
| Aminoglycosides [40, 44–53] | Bind to the aminoacyl site of 16S ribosomal RNA within the 30S ribosomal subunit, leading to misreading of the genetic code and inhibition of translocation | Neutropenic fever in combination with antipseudomonal $\beta$-lactam<br>Directed therapy | Nephrotoxicity<br>Ototoxicity<br>Neuromuscular blockade | Neuromuscular blocking agents<br>Increased nephrotoxicity with amphotericin B, cyclosporins, cisplastin, loop diuretics, vancomycin |
| Vancomycin [16, 54, 55, 57, 58, 60, 61, 191] | Inhibits bacterial cell wall synthesis by blocking peptidoglycan synthesis | Neutropenic fever in the following settings: sepsis, suspected catheter or skin infection, pneumonia, mucositis, MRSA colonization<br>Treatment for gram-positive pathogens, including first line for MRSA infections | Infusion-related toxicity ("red man syndrome")<br>Anaphylaxis<br>Cutaneous reactions<br>Ototoxicity | |
| Linezolid [59, 62, 63, 65, 66, 192] | Inhibits ribosomal translation by binding the 23S ribosomal RNA of the 50S subunit, preventing initiation complex formation with the 70S ribosomal subunit | Wide spectrum of activity against gram-positive pathogens, including MRSA and VRE<br>May have an advantage over vancomycin for MRSA pneumonia | Myelosuppression<br>Thrombocytopenia<br>Lactic acidosis<br>Serotonin syndrome<br>Seizures<br>Optic neuropathy/visual disturbances<br>Peripheral neuropathy | Serotonin reuptake inhibitors (SSRI)<br>MAO inhibitors<br>Rifampin |

(continued)

**Table 2** (continued)

| Antibacterial | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Daptomycin [67–70] | Not completely understood<br>Action involves calcium dependent insertion of the lipophilic daptomycin tail into the bacterial cell membrane causing rapid depolarization and potassium ion efflux | Good activity against gram-positive pathogens, including MRSA and VRE<br>Cannot be used for treatment for pneumonia due to inactivation by surfactant | Myopathy | |
| Tigecycline [71–74] | Inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit | Wide spectrum of activity, including MRSA, VRE, MDR *Klebsiella* spp.<br>Does not provide antipseudomonal activity | Pancreatitis | |
| Polymyxins [75–77] | Detergent-like action, resulting in bactericidal activity | MDR gram-negative pathogens, including *Pseudomonas Acinetobacter* and *Klebiella* spp. (KPC)<br>No gram-positive or anaerobic coverage | Nephrotoxicity<br>Neurotoxicity | |
| Televancin [78–81] | Inhibits cell wall synthesis | Gram-positive pathogens, including MRSA and penicillin-resistant *S. pneumoniae* (PRSP) | Taste disturbances<br>Nausea and vomiting<br>Nephrotoxicity<br>Prolonged QT interval<br>Tetratogenic | |
| Clindamycin [82–84] | Binds to the 50S ribosomal subunit, inhibits chain elongation | Gram-positive coverage, including skin and soft tissue infections with community-acquired MRSA<br>Additive to the treatment for complex skin/soft tissue infections (i.e., necrotizing fasciitis) by binding toxin | Gastrointestinal intolerance<br>*C. difficile*-associated colitis<br>Allergic reactions<br>Local reactions | Neuromuscular blocking agents |

(continued)

**Table 2** (continued)

| Antibacterial | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Trimethoprim–sulfamethoxazole [82, 83] | Inhibits successive steps in folic acid synthesis | Wide range of uses: including skin and soft tissue infections with community-acquired MRSA<br>Prophylaxis and treatment for *Pneumocystis* infections | Dermatological reactions, including Steven-Johnson syndrome<br>Hypersensitivity reactions<br>Hepatitis<br>Hyperkalemia<br>Hypoglycemia | Oral anticoagulants<br>Cyclosporine<br>Oral hypoglycemic agents |
| Tetracycline [82, 83] | Inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit | Skin and soft tissue infections with community-acquired MRSA | Photosensitivity<br>Diarrhea<br>Liver toxicity | Heavy metals<br>Digoxin<br>Oral contraceptives<br>Anticonvulsants<br>Warfarin |

*MSSA* methicillin susceptible *S. aureus*, *MRSA* methicillin-resistant *S. aureus*, *MDR* multidrug resistant, *ESBL* extended-spectrum-$\beta$-lactamase, *KPC Klebiella pneumoniae* with carbapenamase, *VRE* vancomycin-resistant *Enterococcus*, *PRSP* penicillin-resistant *S. pneumoniae*, *MAO* monoamine oxidase inhibitors

studies, approximately 85–90 % of patients with reported penicillin allergy are found not to be allergic and are able to tolerate penicillins. In addition, the prevalence of IgE-mediated penicillin allergy has declined over the last 2 decades [19–22].

Varying degrees of cross-reactivity between cephalosporins and penicillins have been documented. Since the 1980s, the rate of cross-reactions between penicillin and second- or third-generation cephalosporins has been found to be 5 % or less. The degree of cross-reactivity appears to be greater for first-generation cephalosporins. The explanation, at least in part, is that the antimicrobials used in older studies probably were not as purified as compounds are today. Also the higher-generation cephalosporins are less similar to the chemical composition of penicillin. Additional studies suggest that the cross-reactivity of upper generation cephalosporins to those with penicillin allergies is lower than older studies would suggest and that it is reasonable to prescribe these agents when the allergic reaction in question is not severe. The incidence of carbapenem cross-reaction with penicillins is unclear. Administration of aztreonam is safe in patients with a history of anaphylaxis to all $\beta$-lactams except ceftazidime [19–22].

These data are clinically relevant because of emerging resistance to aztreonam and fluoroquinolones [19], both of which are heavily used in patients who report penicillin allergies. For example, the antibiogram of Montefiore Medical Center indicates that a large portion of *Escherichia coli* are not susceptible to ciprofloxacin or aztreonam; however, the higher-generation cephalosporins cover a larger percentage of gram-negative organisms in this institution. Thus, obtaining a careful allergy history is important since those with simply rash caused by prior penicillin use will likely tolerate a cephalosporin or carbapenem and will also get more appropriate empiric coverage for the pathogens in this facility.

When it is critical to utilize $\beta$-lactam antimicrobials in a patient with prior IgE-mediated hypersensitivity to a member of this drug class, desensitization procedures may be required. Desensitization is typically achieved by gradual reintroduction of small doses of drug antigens to which an individual is allergic at fixed time intervals. It is aimed at providing increased safety and protection from side effects, including anaphylaxis [23]. Desensitization procedures are high-risk interventions. Inhibition of cellular activation mechanisms occurs during drug desensitization, allowing for the protective clinical outcomes and lack of side effects in the majority of cases, but the cellular and molecular inhibitory mechanisms are incompletely understood. The indication for desensitization protocols should be done in collaboration with trained allergists and should be implemented in a controlled setting such as an intensive care unit [23].

The $\beta$-lactam antimicrobials have been associated with nephrotoxicity from interstitial nephritis [1]. Methicillin was the first antimicrobial shown to be associated with fevers, chills, rash, and arthralgias. However, the presentation of antimicrobial-induced interstitial nephritis can be variable, and it should be suspected in any patient on a potentially offending agent who develops renal dysfunction. Urinary eosinophilia supports the diagnosis, but conclusive documentation of the disease requires renal biopsy. Discontinuation of the offending agent generally reverses the

process, and permanent sequelae are unusual. These are usually related to the specific drug and do not limit use of the entire class of antimicrobials in the future.

The β-lactam antimicrobials have been associated with some hematological adverse events [14], including immune-mediated destruction of polymorphonuclear leukocytes, hemolytic anemia, or acute immune thrombocytopenia. The first syndrome presents as abrupt onset neutropenia with fever, rash, and eosinophilia. The second syndrome can be with or without associated positive Coomb's test and is usually associated with prolonged, high-dose therapy, and signs of hypersensitivity are often absent. With acute immune thrombocytopenia, the platelet count generally normalizes within a few weeks of the antimicrobial discontinuation. Platelet dysfunction has been associated with the older β-lactam-β-lactamase agent, ticarcillin-clavulanate, but pipercillin–tazobactam has less effect on platelets. There is little data on the cross-reactivity of these types of reactions; however, such reactions usually develop several days into therapy and as long as monitoring is present, likely do not prohibit use of other agents within the β-lactam family [10, 14].

β-Lactam agents, as well as other broad-spectrum antimicrobials, can suppress gut flora and may contribute to vitamin K deficiency. In the past, some cephalosporins, especially cefaperazone and cefotetan, were associated with hypoprothrombinemia due to their chemical structure, namely the *N*-methythiotetrazole-containing side chain.

Although rare, β-lactam antimicrobials are associated with other reactions including serum sickness, dermatological reactions, neurological reactions (especially penicillins), pulmonary reactions, gastrointestinal, and hepatobiliary reactions [10, 14].

### 3.3 β-Lactam–β-Lactamase Inhibitor Combination Drugs

The β-lactam–β-lactamase combination pipercillin–tazobactam may be used for neutropenic fever or other infections during non-neutropenic periods, when broad-spectrum coverage, including *Pseudomonas* species is desired. Particular care is needed to assure that the compound is given in sufficient dosing to cover *Pseudomonas* spp. [24, 25]. In vitro and animal studies of piperacillin have demonstrated the time above the MIC is the best predictor of bacterial killing. Pharmacokinetic models have shown difficulty achieving adequate killing parameters at higher MICs with standard infusion regimens. For a creatinine clearance of >40 ml/min, a dose of 4.5 g every 6 h should be used. To increase the possibility of exceeding the MIC, there is data to support either continuous or extended infusions of these antimicrobials for those with normal renal function. This includes extending the infusion over 4 h [24, 25].

An interesting issue with the use of pipercillin/tazobactam in cancer patients is the interference with newer testing for *Aspergillus* spp. [26, 27]. Among 218 patients surveyed from June 2002 through June 2003, 42 (19.3 %) had ≥1 serum sample positive for galactomannan (optical density index >1.5). Of these patients, 38 had no additional evidence of invasive aspergillosis, and therefore, their test

results were considered false-positives. Case-control analysis showed that treatment with piperacillin–tazobactam was the only risk factor significantly associated with false-positive test results. When tested for galactomannan antigen, 3 of 4 piperacillin–tazobactam batches had positive results. Although penicillins and cephalosporins, with the exception of the cephamycins, are of fungal origin, the exact reasons for cross-reactivity between piperacillin–tazobactam and galactomannan remain unclear. Physicians should be aware of the possible interference of treatment with piperacillin–tazobactam when interpreting the results of the galactomannan assay. Some authorities suggest that collecting the galactomannan test prior to the administration of a piperacillin–tazobactam dose or timing the collection at the trough concentrations of the drug may decrease false-positive results [28].

Cefepime, a fourth-generation cephalosporin with antipseudomonal coverage, is widely used as a single agent for neutropenic fever and as part of the regimen for non-neutropenic conditions such as hospital-acquired pneumonia and meningitis/shunt-related infections. There have been concerns about an increase in mortality in patients treated with cefepime [29–31]. Data are inconclusive regarding an association between cefepime and all-cause mortality [29–33]. Two meta-analyses demonstrated an association between cefepime and all-cause mortality [30, 31]; however, one meta-analysis and one retrospective cohort study, specific to the pediatric population, did not find an association [32, 33]. The FDA has determined that cefepime remains safe for approved indications [33].

### 3.4 Cetibiprole

Ceftobiprole medocaril is a newer extended-spectrum cephalosporin. It has been described in some places as a fifth-generation cephalosporin. It has an established stability against hydrolysis by many gram-positive $\beta$-lactamases and a higher affinity for various PBPs, such as PBP2a of MRSA or PBP2x of *S. pneumoniae*, which leads to a wider spectrum of activity compared with older $\beta$-lactams against methicillin-resistant *Staphylococcus* spp., vancomycin-resistant *S. aureus*, PRSP, VRE, and Enterobacteriaceae, Ceftobiprole activity does not cover ESBL-producing Enterobacteriaceae and some other pathogens, including *Enterococcus faecium, P. aeruginosa,* and *Acinetobacter baumannii* [34, 35].

The activity of ceftobiprole and limited clinical data suggest that it may be useful as empiric monotherapy for complex skin and skin structure infections and in combination with other antimicrobials in lower respiratory tract infections. It is generally well tolerated, with nausea and taste disturbance being the most common adverse events [34, 35].

### 3.5 Aztreonam

Aztreonam is the only monobactam antimicrobial marketed in the United States. Its antibacterial spectrum includes the majority of gram-negative aerobic and facultative bacteria, including the Enterobacteriaceae and *P. aeruginosa*, but has

virtually no activity against gram-positive organisms or anaerobes. Many strains of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* are resistant, and resistance to *P. aeruginosa* can emerge while on aztreonam. The spectrum is similar to aminoglycosides, but is less reliable for the above organisms [36].

Data support the absence of cross-allergenicity between aztreonam and the other $\beta$-lactam antimicrobials. The side chains of aztreonam and ceftazidime have elements in common; thus, there is theoretical data that aztreonam should not be used in a patient with ceftazidime allergy [36]. It may be used as part of the empiric regimen for neutropenic fever for a patient with severe penicillin allergy, but due to its limited spectrum should not be used as monotherapy.

## 3.6 Carbapenems

The carbapenems are generally resistant to most beta-lactamases (plasmid- and chromosomally mediated) and have broad-spectrum antimicrobial activity. These drugs are not active against *S. maltophila, Burkholderia cepacia, E. faecium,* oxacillin-resistant staphylococci, or JK diphtheroids [34]. Although initial isolates of *P. aeruginosa* are usually susceptible to the carbapenems, resistance can emerge on therapy when used as a single agent. The mechanism is usually related to altered permeability to these drugs relating to changes in their outer membrane proteins. Comparing the four carbapenems aids in the understanding of the uses and benefits of each agent.

Imipenem is inactivated in the proximal tubule by human enzyme dehydrogenase I with low urinary levels of active drug and necrosis of the proximal tubule in animal models. This cleavage of imipenem is prevented by co-administration of cilastatin. Imipenem, meropenem, and doripenem have a very similar microbiological spectrum. Meropenem is specifically FDA-approved for treatment for bacterial meningitis, although studies also support use of imipenem for meningitis. Doripenem appears in in vitro studies to be more potent against *P. aeruginosa,* but less potent against *Acinetobacter* spp. [34, 35]. Doripenem, in some markets, is less expensive and can be given in extended infusions. Ertapenem has a narrower spectrum of activity. It is active against most Enterobacteriaceae and anaerobes, but less active than other carbapenems against *P. aeruginosa*, *Acinetobacter* spp., and gram-positive bacteria, particularly enterococci and resistant pneumococci. The major benefit of ertapenem over the other carbapenems is that it has a long half-life and can be administered once daily.

The carbapenems are generally safe. The most commonly reported adverse effects include local irritation at injection site, diarrhea, rash, nausea, vomiting, and pruritis. The carbapenems have been associated with central nervous system toxicity, including change in mental state, myoclonus, and, particularly, seizures. Clinical controversy exists around the seizure profile. In post-marketing surveillance, the incidence of imipenem/cilastatin-associated seizures was 1.5–2 %. Patients who developed this adverse effect had impaired renal function, known central nervous system disease or infection, history of seizures or stroke and were

receiving aggressive dosing of the drug. This adverse effect has since been re-evaluated, and a complex dosing strategy has been included in the package insert for imipenem/cilastatin [29, 37]. Some believe that meropenem may have lower risk of seizures, but the studies excluded those with history of seizure disorder; thus, the conclusion may not be valid.

Carbapenems retain activity against the extended-spectrum beta-lactamases and chromosomal cephalosporinases found in many gram-negative pathogens. Infection with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae is emerging as an important challenge in healthcare settings. Currently, *K. pneumoniae* with carbapenamase (KPC) is the species most commonly encountered in the United States. KPCs are resistant to almost all available antimicrobial agents, and infections with KPCs have been associated with high rates of morbidity and mortality, particularly among persons with prolonged hospitalization and those who are critically ill and exposed to invasive devices such as ventilators and central venous catheters [37]. Attention has been placed on appropriate microbiological screening and confirmation testing for these pathogens and exploring use of older drugs (colistin, rifampin) or newer broader-spectrum drugs (tigecycline), usually in combination.

## 3.7 Fluoroquinolones

Fluoroquinolones are broad-spectrum antimicrobials with concentration-dependent bactericidal activity. The mechanism by which they exert this effect is by binding to and inhibiting topoisomerase II (DNA gyrase) and topoisomerase IV [38]. There are basically two groups within the fluoroquinolones: the first are older agents with primarily gram-negative coverage used for UTIs. Norfloxacin, lomefloxacin, ofloxacin, and ciprofloxacin are included in this group. Ciprofloxacin is most notably used for its coverage against *P. aeruginosa*, and it figures prominently in the 2010 Clinical Practice Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer due to its spectrum of activity, excellent bioavailability, and suitability for outpatient management of low-risk neutropenia/neutropenic fever [1].

The later generation fluoroquinolones, including levofloxacin and moxifloxacin, have an extended half-life, less CNS toxicity, and broader-spectrum of activity including gram-positive bacteria and some anaerobes [39]. These agents often are used for respiratory tract infections. Importantly, moxifloxacin has limited renal excretion, so no dose reduction is needed for renal failure, but it should not be used for urinary tract infections.

Fluoroquinolones are often administered orally; thus, absorption interactions may compromise the efficacy of antimicrobial therapy [13]. Important drug–drug interactions, which can be specific to the specific agent, include antacids/minerals (aluminum, magnesium, calcium, iron, and zinc severely impair absorption of quinolones), NSAIDS (increase central nervous system effects), theophyllines (change in metabolism), warfarin (elevate PT/INR), and alkalyzing agents (cause crystallization in urine).

Fluoroquinolones have been associated with reversible central nervous system adverse events, including seizures, headaches, hallucinations, and slurred speech, in as many as 1–2 % of recipients. Previous underlying neurological conditions may predispose to these side effects, and fluoroquinolones may lower the seizure threshold in patients with seizure disorders [16, 40].

Fluoroquinolones can prolong the QT interval, usually only clinically significant in patients with baseline QTc interval elongation. Some experts recommend avoidance of fluoroquinolones in patients with baseline QTc of >500 ms or switching to an alternative agent if the interval increases by 30–60 ms with a quinolone [13, 39].

Both the older and newer fluoroquinolones have been associated with arthropathy in weight bearing joints. Studies have shown erosion and permanent lesions of the cartilage due to quinolone use in animals. Although Achilles tendon rupture has been the most common injury with over 200 cases reported, other joints may also be affected. Injury has been reported up to 90 days after completion of therapy. For such reasons, quinolones are not front-line antimicrobials in children, pregnant women, or nursing mothers [13, 39].

Resistance develops to fluoroquinolones due to three possible mechanisms: alterations in topoisomerase enzymes, decreased permeability, and drug efflux [41]. Resistance is clinically relevant at many facilities where oral quinolones are highly used [42].

Finally, although many antimicrobials have been associated with *C. difficile*-associated diarrhea, the quinolones have especially been implicated as a factor associated with the toxigenic B1/NAP1 strain causing recent outbreaks throughout the United States and Canada [43]. The recent increase in drug resistance and emergence of this *C. difficile* strain has made the quinolones a target for antimicrobial stewardship.

## 3.8 Aminoglycosides

The aminoglycosides primarily act by binding to the aminoacyl site of 16S ribosomal RNA within the 30S ribosomal subunit, leading to misreading of the genetic code and inhibition of translocation. Nine aminoglycosides, gentamicin, tobramycin, amikacin, streptomycin, neomycin, kanamycin, paromomycin, netilmicin, and spectinomycin, are approved by the FDA for use in the United States [44]. Their most common clinical application, either alone or as part of combination therapy, is in the treatment for serious infections caused by aerobic gram-negative bacilli. Less commonly, aminoglycosides, in combination with cell wall active agent, are used for the treatment for serious staphylococcal and enterococcal infections. In some instances, aminoglycosides are used in combination with an antipseudomonal $\beta$-lactam for neutropenic fever. The primary toxicities of aminoglycosides are nephrotoxicity, ototoxicity, and, rarely, neuromuscular blockade [40, 44–48].

A few important pharmacodynamic properties are important with aminoglycosides, including PAE and concentration-dependent killing [11, 12, 46]. For

concentration-dependent killing, achievement of optimal peak concentrations of aminoglycosides is limited by the nephrotoxicity associated with sustained high trough concentrations of these agents. Importantly, for obese patients, dosing should be based on adjusted body weight and not actual body weight.

Acute kidney injury due to acute tubular necrosis is a common complication of aminoglycoside therapy, occurring in 10–20 % of patients. Major risk factors for nephrotoxicity include prolonged length of therapy, advanced age, comorbid diseases such as diabetes and leukemia, reduced effective arterial volume, sepsis, co-administration of other nephrotoxic medications, high plasma drug concentrations, type of aminoglycoside (higher with gentamicin vs. tobramycin or amikacin), and frequency of dosing [40, 49, 50]. Clinical strategies to minimize the potential for nephrotoxicity include selection of the least toxic aminoglycoside when possible, correction of hypokalemia and hypomagnesemia prior to aminoglycoside administration, avoidance of these agents in patients with reduced effective arterial volume, adjustment of the dose for renal function, limiting the duration of therapy to 7–10 days, and minimizing concomitant nephrotoxic medications [40, 49, 50]. Once-daily aminoglycoside therapy, employing a larger loading dose of the agent every 24–48 h, exploits the concentration-dependent activity and PAE but leads to less nephrotoxicity than conventional dosing methods [50–52]. It is beyond the scope of this review, but a good guide to dosing and monitoring aminoglycosides may be found in the reference section [49].

Aminoglycoside-induced ototoxicity may result in either vestibular or cochlear damage. Manifestations of vestibular toxicity include vertigo, disequilibrium, lightheadedness, nausea, vomiting, and ataxia, while the usual symptoms of cochlear toxicity are tinnitus and hearing loss. There appears to be a genetic predisposition to the development of ototoxicity with aminoglycosides. To prevent the development of ototoxicity due to aminoglycosides, strategies include once-daily dosing and careful monitoring of serum drug concentrations. *N*-acetylcysteine can also be given to patients with end-stage renal disease receiving an aminoglycoside. Another approach to prevention is to use audiometric testing among patients receiving aminoglycoside therapy. However, hearing loss may occur even after the termination of antimicrobial therapy [15, 53].

Neuromuscular blockade is a rare but serious adverse effect induced by aminoglycoside therapy. Most patients experiencing such reactions have disease states and/or concomitant drug therapies that interfere with neuromuscular transmission. Myasthenia gravis is an absolute contraindication to aminoglycoside use [15, 44].

## 3.9 Vancomycin

Vancomycin is a glycopeptide that is widely used for treatment for serious gram-positive infections. It inhibits bacterial cell wall synthesis by binding tightly to the D-alanyl-D-alanine portion of peptidoglycan precursors, preventing polymerization of these cell wall units [16].

Early use of vancomycin was associated with a number of adverse effects, including infusion-related toxicity, nephrotoxicity, and possibly ototoxicity [16, 54–56]. However, it appears that early formulations contained impurities that may have accounted for these events.

Additionally, vancomycin causes several different types of hypersensitivity reactions, ranging from localized skin reactions to generalized cardiovascular collapse [54, 57, 58]. However, the most frequent adverse reaction, the "red man syndrome" (RMS), is a rate-dependent infusion reaction and not a true allergic reaction. RMS is characterized by flushing, erythema, and pruritus that usually affect the upper body, neck, and face more than the lower body. Pains and muscle spasms in the back and chest, dyspnea, and hypotension may also occur. It is rarely life threatening, although severe cardiovascular toxicity and even cardiac arrest have been reported. It is best classified as an idiopathic infusion reaction that resembles IgE-mediated anaphylaxis, but does not involve drug-specific IgE. RMS is a rate-related infusion reaction in most instances. To avoid this type of reaction, vancomycin should be infused over a minimum of 100 min or at a rate no higher than 10 mg/min, whichever results in a slower infusion. This is especially important when infusing larger doses (>1 g) such as in obese patients [54, 57].

Vancomycin is associated less commonly with anaphylaxis, but in these cases, desensitization procedures can be performed if vancomycin is essential. Other adverse events are drug rash, cytopenias, eosinophilia with systemic symptoms and other cutaneous reactions (e.g., linear IgA bullous dermatosis), and renal disorders. In these cases, desensitization is not effective and may be dangerous, and thus, the drug must be discontinued.

In recent years, *S. aureus* with reduced or intermediate susceptibility to vancomycin (or glycopeptides) (VISA or GISA) and vancomycin-resistant *S. aureus* (VRSA) have emerged, raising important questions about the overall and future utility of this antimicrobial [16, 56]. In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered the susceptibility and resistance MIC breakpoints of vancomycin from ≤4 to ≤2 mg/L for "susceptible," from 8–16 to 4–8 mg/L for "intermediate," and from ≥32 to ≥16 mg/L for "resistant." This decision was primarily based on clinical data indicating that successful treatment for *S. aureus* infections was less likely if the vancomycin MIC exceeded 4 mg/L [59]. Despite this change in breakpoints, two reports have suggested that patients with *S. aureus* isolates having vancomycin [60, 61] MICs of 1–2 mg/L are less likely to be successfully treated with vancomycin compared to patients with *S. aureus* isolates with greater susceptibility. This raises the question whether the MIC breakpoints should be lowered even further and providers should consider treatment with an alternate agent for infections with isolates of *S. aureus* with vancomycin MICs > 2 [56, 60, 61]. Updated guidelines for dosing and therapeutic monitoring of vancomycin address the optimal treatment for infections, avoidance of toxicity, and the prevention of antimicrobial resistance [16].

## 3.10 Drugs of "Last Resort"

The emergence and spread of antimicrobial-resistant gram-positive pathogens such as community-associated MRSA (CA-MRSA), VISA, and VRSA have become frontline public health issues. In response, a handful of novel antimicrobials to treat infections with these pathogens have been developed and approved, including linezolid, daptomycin, tigecycline and, most recently, telavancin. In addition, trimethoprim–sulfamethoxazole, clindamycin, and doxycycline have found a new niche in the treatment for CA-MRSA. The emergence of gram-negative resistance has been more problematic and some older, previously retired drugs such as polymyxin B are now back in use. The following sections highlight use of some of these antibacterial drugs of "last resort." It is important to underscore that no antimicrobial can cover every pathogen. In some complex MDR infections, drainage or surgical intervention is necessary. Lastly, becoming comfortable with the niche for some of these drugs, in many circumstances, can best be accomplished in consultation with an infectious diseases specialist.

### 3.10.1 Linezolid

Linezolid is an oxazolidinone antimicrobial that inhibits the bacterial ribosomal translation process by selectively binding to a site on the 23S ribosomal RNA of the 50S subunit, thereby preventing initiation complex formation with the 70S ribosomal subunit [61]. It has good activity against gram-positive pathogens, including MDR pathogens, MRSA, and VRE. Since its approval in the United States in 2000, it has been heavily marketed to treat skin and soft tissue infections, lower respiratory tract infections, and VRE infections, including cases with concurrent bacteremia [59, 62, 63].

Randomized multicenter trials in patients with serious gram-positive infections show clinical cure rates with linezolid were similar to those with vancomycin and related drugs [59, 62, 64]. In subgroup analyses, which must be interpreted with a degree of caution, clinical advantages were noted for linezolid over vancomycin, such as in confirmed MRSA nosocomial pneumonia and complicated skin and soft tissue infections [59, 65, 66].

Linezolid is generally well tolerated. Although more expensive than vancomycin, linezolid does not require testing for adequate serum drug concentrations or dosing adjustment for renal or hepatic insufficiency [62]. In addition, the oral bioavailability is 100 % thus allowing sequential intravenous to oral administration without changing drug or dosage [62].

Serious side effects of linezolid include myelosuppression and thrombocytopenia. For some patients who stay on therapy for four or more weeks, the risk of these hematological side effects is more concerning and should be monitored weekly. There have been reports of linezolid-associated lactic acidosis and serotonin syndrome. Linezolid should not be used in individuals receiving monoamine oxidase inhibitors (MAO inhibitors). Neurological side effects, including seizures and optic and peripheral neuropathy, have been reported. Monitoring is recommended for extended linezolid use (3 months or greater) and in patients reporting new visual

symptoms. As a practical issue, linezolid is largely hepatically excreted; thus, it is not a good agent for treatment for urinary tract infections [59, 64].

Most reports of linezolid resistance have been individual cases or small case series; however [63], the Tennessee Department of Health reported a hospital-wide outbreak of linezolid-resistant enterococcal infections associated with increase linezolid use [63]. In summary although there are some attractive qualities to linezolid, the cost, toxicity, and potential resistance limit its use. It should be reserved for those who do not respond or cannot tolerate an older agent.

### 3.10.2 Daptomycin

Daptomycin is a novel bactericidal antimicrobial with excellent activity against gram-positive organisms. The exact mechanism of action is not completely understood. It is believed to have a unique mechanism of action that involves calcium-dependent insertion of the lipophilic daptomycin tail into the bacteria's cell membrane causing rapid depolarization and potassium ion efflux [66].

Daptomycin has broad activity against gram-positive aerobes and anaerobes, including resistant strains of MRSA, VRE, coagulase-negative staphylococci, and PRSP. Daptomycin is currently approved for the treatment for complicated skin and soft tissue infections, bacteremia-associated intravascular line infection, and bacteremia due to *S. aureus*, including right-sided infective endocarditis. It also has shown activity in models for peritonitis, septic arthritis, and central nervous system infections [67, 68].

Daptomycin has predominately renal clearance, requiring dose adjustments in those with impaired renal function [67, 68]. Daptomycin has been shown to have a PAE on *S. aureus* and *S. pneumoniae* allowing for once-daily dosing in patients with normal renal function. Daptomycin should not be used to treat pneumonia since it is inhibited by surfactant [67, 68]. There appears to be a low rate of spontaneous resistance to daptomycin. However, there have been multiple case reports of gram-positive organisms with daptomycin resistance including MRSA, *E. faecium*, and *E. faecalis* [68, 69]. Dosing depends on indication with 4 mg/kg daily for soft tissue infections but higher dosing from 6 mg/kg up to 10 mg/kg for bacteremia and infective endocarditis to achieve clinical success and prevent resistance development [69].

In early clinical trials, daptomycin was associated with skeletal muscle effects including myopathy and elevated creatine phosphokinase. Additional animal studies revealed that changing the dosing to once daily from every 12 h could overcome the problem [70]. There are no significant drug–drug interactions with daptomycin, but the manufacturers recommended temporarily discontinuing use of HMG CoA reductase inhibitors while patients receive daptomycin [67, 68].

### 3.10.3 Tigecycline

The US FDA approved tigecycline in 2005 for the treatment for complicated skin and soft tissue infections, intra-abdominal infections, and community-acquired pneumonia, although it has been used for other conditions [71, 72].

Its spectrum of activity is fairly wide, including MRSA, VRE, and MDR *Klebsiella*. Tigecycline does not have activity against *Pseudomonas* spp. [71].

Tigecycline is the first in a new generation of tetracyclines known as the glycylcyclines. Tigecycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. It blocks entry of the amino-acyl tRNA molecules into the A site of the ribosome, preventing incorporation of amino acid residues into elongating peptide chains. Tigecycline is generally considered to be a bacteriostatic drug. However, it has bactericidal activity against isolates of *S. pneumoniae* and *Legionella pneumophila* [72].

Tigecycline is fairly well tolerated. In post-marketing evaluations, it has been associated with the development of acute pancreatitis, including fatal cases. Some reports have been in patients without known risk factors. Drug discontinuation should be considered in patients who develop signs or symptoms of pancreatitis during therapy [72, 73].

Tigecycline received attention in September 2010 when it was linked to an increased risk of death in patients with certain severe infections [74]. The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, but was also seen in patients with complicated skin and skin structure infections, complicated intra-abdominal infection, and diabetic foot infections. The increased mortality was determined using pooled analysis of 13 clinical trials with patients given tigecycline for both approved and unapproved indications [74]. The cause of the excessive deaths in these trials is uncertain, but has given pause to some prescribers.

In practical terms, tigecycline is primarily hepatically metabolized and has little renal excretion. Thus, it is of lesser utility in treatment for urinary tract infections, except in larger doses. Because the drug is largely bacteriostatic, it should not be used in bacteremic or septic patients. The lack of *Pseudomonas* spp. coverage is also a disadvantage in the hematology–oncology population.

### 3.10.4 Polymyxins

Polymyxin B and colistin (polymyxin E) are the two polymyxins used clinically. These are lipopeptide antimicrobials isolated from *Bacillus polymyxa* and are bactericidal agents with a detergent-like action. There is only one amino acid difference between polymyxin B and colistin. The former is administered parenterally as the sulfate salt and the latter is administered as the sodium salt of colistin methane sulfonate, an inactive prodrug that undergoes hydrolysis in vivo and in vitro to form the active entity colistin [75].

Polymyxin B has no activity against gram-positive bacteria and anaerobes, but is active against a variety of gram-negative bacilli, including Enterobacteriaceae and non-fermentative species. This specifically includes MDR strains of *P. aeruginosa, A. baumannii,* and *K. pneumoniae*. Of interest, *Proteus* spp., *Providencia* spp., *Morganella* spp, and *Serratia* spp. are resistant to this agent [75]. Knowledge of the pharmacokinetics and pharmacodynamics of polymyxin B is limited given its lack of use in the last 50 years [75, 76]. In addition, since these drugs are old, the

procedures for standardization of susceptibility testing, establishment of break points and quality of control strains were less rigorous [75, 76]. Acquired resistance to polymyxins in MDR gram-negatives is not common due to infrequent usage. There is cross-resistance between polymyxin B and colistin.

Nephrotoxicity and neurotoxicity are the most common toxicities associated with parenteral administration of polymyxins [75]. Newer literature suggests that nephrotoxicity may have been over estimated in older studies and is likely in the range of 0–37 % [77]. Clinicians should be alert to the potential for nephrotoxicity by adjusting dosage for renal function, avoiding concomitant administration of other potential nephrotoxic drugs where possible, and monitoring for deteriorating renal function.

Neurotoxicities are less frequent than nephrotoxicities and are usually mild and resolve when medication is discontinued. Neurotoxicities include dizziness, generalized weakness, facial and peripheral paresthesias, partial deafness, visual disturbances, vertigo, confusion, hallucinations, seizures, and ataxia and occur more commonly with colistin than polymyxin B [75].

### 3.10.5 Televancin

Televancin is a lipoglycopeptide derivative of vancomycin. Similar to vancomycin, it demonstrates activity in vitro against a variety of gram-positive pathogens, including but not limited to MRSA and PRSP. Televancin binds to the D-alanyl-D-alanine terminus in gram-positive organisms, resulting in inhibition of bacterial cell wall synthesis. In addition, televancin activity in vitro causes depolarization of the bacterial cell membrane and increased membrane permeability. The resulting activity in vitro is rapidly bactericidal and concentration-dependent, with the ratio of AUC/MIC as the best predictor of activity in animal models [77, 78].

Modification to the structure of vancomycin expanded the spectrum of televancin activity to include organisms such as GISA, VRSA, and VRE [78]. It can be dosed once daily. Since televancin is extensively cleared renally, dosage adjustments are required in patients with moderate to severe renal impairment.

Approval of televancin was based on data from two double-blind, randomized phase 3 studies (ATLAS I and II) of 1,867 patients showing that its use was statistically non-inferior to vancomycin for curing skin and skin structure infections caused by gram-positive organisms [79, 80]. The exact niche of this drug is evolving and likely will be as directed therapy for those with resistance or intolerance to other first-line agents.

In these studies, adverse effects were mild and reversible including taste disturbances, nausea, vomiting, and foamy urine. Renal toxicity was more common than with vancomycin (3 vs. 1 %), and QTc interval was elongated but without clinical significance. Limb malformations occurred in animal studies; thus, the agent is considered a teratogen [78, 81].

## 3.11 A New Role for Clindamycin, Trimethoprim–Sulfamethoxazole, and Tetracycline

Facilities are attempting to integrate previously retired drugs of last resort into their armamentarium. The discussion would not be complete without discussing the roles of the narrower, older drugs clindamycin, trimethoprim–sulfamethoxazole (TMP-SMX), and doxycycline for skin and soft tissue infections with CA-MRSA. Incision and drainage is often required and may be the only treatment needed; however, these drugs can be used adjunctively. All are inexpensive, fairly well tolerated, and administered orally [82, 83].

Clindamycin has good activity against MRSA and also inhibits bacterial production of toxins such as Panton-Valentine leukocidin and other virulence factors. Clindamycin, however, is only bacteriostatic and should not be used for intravascular infections. Careful testing and monitoring for local clindamycin resistance is important. Isolates that may appear susceptible to clindamycin by standard testing techniques may be capable of inducing resistance. Clinicians should confer with their microbiology laboratory to request evaluation for this inducible resistance prior to treatment with clindamycin [84]. The major side effect is gastrointestinal intolerance.

TMP-SMX has been used for treatment for skin and soft tissue infections with MRSA [83, 84]. The data for efficacy are largely from observational and retrospective reports. This is reasonable in the setting of MRSA with known susceptibility, although it should be used with caution in the empiric management of soft tissue infection when group A streptococci are an etiologic consideration. It should also be noted that the dosing for these types of infections is much higher than that used for prophylaxis for pneumocystosis. TMP-SMX may be more difficult to use in those with renal dysfunction or cytopenias.

Longer-acting tetracyclines, such as doxycycline or minocycline, can also be used for MRSA soft tissue infections with known susceptibility. As with TMP-SMX, this is not an advisable empiric choice if group A streptococci may be a pathogen. This drug is well tolerated, but prescribers must be aware of interactions such as poor absorption if taken with common agents such as antacids and iron.

## 3.12 Antiviral Agents

The development of antivirals has transformed the care of oncology patients and transplant recipients. Antivirals active against the herpesviruses have led to a reduction in viral-associated morbidity and mortality in these patients [85].

Much of the toxicity of antiviral agents in patients undergoing chemotherapy for cancer treatment or conditioning for HSCT is from cumulative side effects of medications rather than direct drug interactions. However, a severe drug interaction of a novel antiviral, sorivudine, with the cancer agent 5-flouro-uracil (5FU) led to FDA rejection and complete halt to studies in the US despite demonstrated efficacy and safety in HIV-infected individuals [86].

One sees diverse clinical practices in the approach to treatment and prophylaxis of viral infections; therefore, the following section will address the more commonly used antivirals in cancer and HSCT recipients [1, 85]. Knowledge of the pharmacokinetics and pharmacodynamics of a medication can help predict drug interactions, thereby reducing toxicity, and improving outcomes. Table 3 summarizes several antiviral agents relevant to the care of patients with malignancies.

## 3.13 Acyclovir

Acyclovir is an analogue of 2′-deoxyguanosine. In order for acyclovir to be effective, it requires phosphorylation to acyclovir triphosphate. The first phosphorylation step is catalyzed by the viral thymidine kinase, which is found in herpes simplex viruses (HSV) types 1 and 2, and varicella zoster virus (VZV). Once acyclovir monophosphate has been formed, cellular enzymes catalyze the production of di- and tri-phosphate forms. Acyclovir triphosphate then competes with 2′-deoxyguanosine triphosphate as a substrate for viral DNA polymerase. DNA synthesis is interrupted when acyclovir triphosphate is intercalated into viral DNA, resulting in chain termination. Acyclovir triphosphate can also directly inhibit herpesvirus DNA polymerase [87]. Acyclovir has higher affinity for herpes simplex viral DNA than human cellular alpha-DNA polymerase, leading to less cytotoxicity and few side effects.

Both oral and intravenous formulations are available for acyclovir, and they are generally well tolerated. The major side effects are inflammation at the infusion site and increase in serum creatinine in 5–10 % of patients, which results from crystallization of drug in renal tubules [88]. The nephrotoxic effects of acyclovir are usually related to the intravenous formulation and may be due to rapid infusion [89]. Adequate dose reductions must be made in patients with reduced renal function, and caution should be taken if used concomitantly with probenecid, which may increase the AUC as much as 40–46 %. Hydration of the patient is paramount to reduce these effects. Patients receiving chemotherapeutic agents with strong emetic potential or mucositis need adequate hydration to reduce the risk of acyclovir-related nephrotoxicity. The bioavailability of the oral formulation requires frequent dosing, up to five times daily, for VZV infection, thereby making adherence more difficult, but the cost is significantly less.

The antiviral spectrum of acyclovir is well established against alpha herpesviruses, including HSV, VZV, and the zoonotic herpesvirus B. Acyclovir has poor activity against cytomegalovirus (CMV), but in high doses (10 mg/kg per dose) has been used in HSCT recipients for antiviral prophylaxis, with reduction in CMV replication when compared with placebo. Acyclovir has activity against Epstein–Barr virus (EBV) and decreases viral shedding in infectious mononucleosis, although its role in treating post-transplant lymphoproliferative disorder remains uncertain [87, 88].

**Table 3** Characteristics of antiviral agents by class

| Agent | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Acyclovir [87–89] | Metabolized to acyclovir triphosphate<br>Inhibits viral DNA polymerase | HSV<br>VZV<br>Antiviral prophylaxis in HSCT, leukemia, and lymphoma patients | Nephrotoxicity<br>Rash<br>Encephalopathy | Potential cumulative effects with nephrotoxic agents |
| Valacyclovir [87–89] | Same as acyclovir | HSV<br>VZV<br>Antiviral prophylaxis in HSCT, leukemia, and lymphoma patients<br>CMV prophylaxis (in high doses) | Similar to acyclovir | |
| Famciclovir [87–89] | Same as acyclovir | HSV<br>VZV | Gastrointestinal upset<br>Headache | Raloxifene (theoretical) |
| Ganciclovir [87, 91, 94] | Metabolized to ganciclovir triphosphate<br>Inhibits viral DNA polymerase | Well studied in immunocompromised hosts. CMV active agent, but also activity against HSV, VZV, EBV, & HHV-6, HHV-8 | Bone marrow suppression<br>Nephrotoxicity<br>Encephalopathy<br>Rash | Encephalopathy, can be potentiated by imipenem/cilastatin or cefepime |
| Valganciclovir [87, 95] | Same as ganciclovir | Accumulating data of efficacy and safety in stem cell recipients for treatment for CMV and preemptive approach | Similar toxicities to Ganciclovir | |
| Foscarnet [97] | Inhibits viral polymerase and reverse transcriptase at the pyrophosphate-binding site | CMV<br>HSV<br>VZV | Nephrotoxicity<br>Electrolyte abnormalities<br>Mucosal irritation and ulceration | |

(continued)

**Table 3** (continued)

| Agent | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Cidofovir [99–101] | Nucleotide analogue<br>Selective inhibition of CMV DNA polymerase | Herpesviruses, including CMV<br>Adenovirus<br>BK virus activity | Irreversible nephrotoxicity | Methotrexate if administered with probenecid |
| Zanamivir [103–105] | Inhibits neuraminidase | Influenza A & B | Bronchospasm | |
| Oseltamivir [106–108, 110] | Inhibits neuraminidase | Influenza A & B | Delirium and self-injury (children) | |

*HSV* Herpes simplex virus, *VZV* Varicella zoster virus, *CMV* Cytomegalovirus, *EBV* Epstein–Barr Virus, *HHV*-6 Human herpesvirus 6, *HHV*-8 Human herpesvirus 8

### 3.14 Valacyclovir and Famciclovir

Valacyclovir is the l-valyl ester of acyclovir [87] and is converted to the active drug by acetylases in the gastrointestinal tract and liver. The bioavailability is 3–5 times that of acyclovir, allowing for once-daily dosing for prophylaxis [90].

Famciclovir is the diacetyl-6 deoxy analogue of penciclovir. It is well absorbed orally and rapidly metabolized in the gastrointestinal tract, blood, and liver, after which it is metabolized in the liver. Since the intracellular half-life of the active drug, penciclovir triphosphate, is very long, it is can be used for once-daily dosing. It is effective against genital HSV and herpes zoster infections. There is some data supporting its use in the prevention of hepatitis B virus (HBV) reactivation after chemotherapy and HSCT, although this is of limited practical use given the availability of better anti-HBV agents [87].

### 3.15 Ganciclovir

Ganciclovir is a nucleoside analogue active against herpesviruses and was one of the first agents with demonstrable efficacy in the treatment for CMV disease [91]. The development of ganciclovir has led to reductions in morbidity and mortality associated with CMV disease in both HIV-infected individuals and transplant recipients [92, 93]. Ganciclovir is converted to the monophosphate form by the protein kinase product of the UL97 gene, and cellular enzymes then continue with phosphorylation to form ganciclovir triphosphate, which inhibits viral DNA polymerases by competitive inhibition of 2′-deoxyguanosine intercalation. Because it does not result in absolute chain termination, it is considered virustatic. Ganciclovir triphosphate has a long intracellular half-life in CMV-infected cells and reaches concentrations ten times that of acyclovir triphosphate, and, for these reasons, ganciclovir is a superior antiviral for CMV compared to acyclovir [87, 91].

The major limiting side effect of ganciclovir is bone marrow suppression. Hematological effects include severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow depression, and aplastic anemia [87, 91]. Oncology patients and HSCT recipients are often on other medications that cause suppression of the major cell lines, which can make some practitioners uneasy in using ganciclovir; however, in many centers, it is considered the first-line treatment for CMV disease.

Ganciclovir should be used with caution in patients with renal impairment or hemodialysis, including dose adjustment or interruption. Animal studies have demonstrated carcinogenic and teratogenic effects and inhibition of spermatogenesis [94].

### 3.16 Valganciclovir

Valganciclovir is the L-valyl ester of ganciclovir. Valganciclovir is converted to ganciclovir by intestinal and hepatic esterases and has replaced the oral formulation

of ganciclovir. Data are accumulating regarding the safety and efficacy of valganciclovir in cancer and HSCT transplant patients [95, 96]. The FDA approved valganciclovir for the treatment for CMV retinitis in HIV-infected individuals and prevention of CMV disease in solid organ transplant recipients. It has a similar side effect profile to ganciclovir but has the advantage of oral administration, making it an ideal drug for treatment, preemptive therapy, and prophylaxis in the transplant recipient. Providers must exercise caution when using this drug in patients with mucositis, diarrhea, and graft-versus-host disease with gastrointestinal involvement, as absorption could be impaired leading to sub-optimal dosing and the potential for development of drug resistance.

## 3.17 Foscarnet

Foscarnet, also known as trisodium phosphonoformate, is a direct inhibitor of viral DNA polymerase. In contrast to antiviral agents like acyclovir, ganciclovir, and their analogues, foscarnet does not require thymidine kinase for activation and therefore has activity against acyclovir- and ganciclovir-resistant strains of HSV and CMV [87, 97]. Renal toxicity and electrolyte abnormalities are the major limitations in its use. Foscarnet is eliminated essentially unchanged in the urine, and dose reduction is critical in patients with renal impairment. Drug interactions tend to be few, but concomitant use of other nephrotoxic medications can complicate the use of foscarnet. In order to reduce toxicity, patients need adequate hydration prior to drug administration [87]. Foscarnet has excellent antiviral activity against VZV, HSV, and CMV. Uses in cancer patients have ranged from preemptive approach to treatment for CMV disease in HSCT recipients [98]. Often considered an alternate agent for treating CMV viremia and disease in cancer patients, some centers use foscarnet as a first-line agent because of fewer bone marrow-related toxicities than ganciclovir, although anemia is still a significant concern [87, 98].

## 3.18 Cidofovir

Cidofovir is a nucleotide analogue approved for use in HIV-infected individuals with CMV retinitis. This drug has broad-spectrum activity against viruses such as CMV, other herpesviruses, adenovirus, and polyomaviruses [87, 99]. Nephrotoxicity is the major limiting side effect of this agent, and the FDA has issued a black box warning regarding its use in patients with preexisting renal insufficiency [99]. Additionally, cidofovir can cause proximal renal tubular damage leading to glucosuria, proteinuria, and electrolyte imbalances, in particular hypophosphatemia [99–101]. Patients receiving cidofovir require monitoring of renal function and screening for proteinuria 2 days prior to each infusion. Probenecid and hydration are administered prior to, during, and after infusion to mitigate the nephrotoxic effects of cidofovir. Its use in HSCT recipients should be with caution given

cumulative effects of nephrotoxic agents, especially since prior chemotherapy and foscarnet may predispose to nephrotoxicity [87, 99, 101]. However, in very ill HSCT recipients, benefits of antiviral activity may outweigh the risks of worsening renal disease.

## 3.19 Antiretroviral Agents and Chemotherapy

Human immunodeficiency virus (HIV) deserves a special mention, as it is associated with increased rates of both solid and hematological malignancies. Although there is an extensive body of literature on drug interactions, limited data exists on antineoplastic agents and antiretroviral therapy. Data support the continued use of antiretroviral agents during and after treatment for malignancies. In lymphoma, the majority of the data is derived from retrospective analyses. An Italian cohort found that highly active antiretroviral therapy (HAART) duration $\geq$24 months was independently associated with a longer progression-free survival [102]. First-line treatment for Kaposi sarcoma includes initiation of HAART. In HIV-infected patients undergoing cancer chemotherapy, concerns exist for drugs known to cause bone marrow suppression (zidovudine and ganciclovir) and mitochondrial toxicity (didanosine and stavudine). The emphasis should be on viral suppression, optimal prophylaxis and, if possible, limiting antiretrovirals that produce additive gastrointestinal and bone marrow toxicities. Due to the complexities of interactions between agents such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors and hepatically metabolized chemotherapeutic agents, the authors recommend consultation with pharmacy and infectious diseases experts for optimizing antiretroviral therapy during cancer chemotherapy.

## 3.20 Antivirals Agents for Influenza

The 2009 H1N1 influenza A pandemic raised interest in the use of antivirals directed against influenza. Although acutely debilitating, influenza is usually a self-limited infection. However, it can be associated with increased morbidity and mortality in high-risk populations, including those with malignancies.

When initiated promptly, antiviral therapy can shorten the duration of influenza symptoms by 1–3 days; the greatest benefit occurs in those who receive treatment within the first 24–30 h and in patients with fever at presentation. Little to no benefit has been demonstrated when treatment is initiated 2 days or more after the onset of uncomplicated influenza [103–105]. The use of antiviral agents in HSCT recipients has not been studied in randomized trials. A retrospective review of laboratory-confirmed influenza cases in HSCT recipients found that 62 of 4,797 patients were diagnosed with influenza within 120 days of the HSCT. Of the 51 patients who were initially diagnosed with upper respiratory tract involvement and no signs or symptoms of pneumonia, 6 of 34 untreated patients developed pneumonia, whereas none of the nine patients treated with oseltamivir and one of the eight patients

treated with rimantadine developed pneumonia [106]. Individuals with severe disease or at high risk for complications should receive antiviral therapy. Antiviral therapy, when indicated, should be initiated promptly [107, 108].

Two classes of antiviral drugs are available for the treatment and prevention of influenza. The neuraminidase inhibitors, zanamivir and oseltamivir, are active against both influenza A and B. The adamantanes, amantadine and rimantadine, are only active against influenza A. Due to a marked increase in resistant isolates, the Advisory Community on Immunization Practices (ACIP) recommends that the adamantanes not be used in the United States for the treatment for influenza, except in selected circumstances [107, 108].

Oseltamivir is orally administered and is available as a capsule or powder for liquid suspension. Zanamivir is administered by oral inhalation. An intravenous formulation of zanamivir is under investigation [107].

Adverse effects of neuraminidase inhibitors are typically mild, although more serious side effects have been described. Inhaled zanamivir can cause bronchospasm and respiratory decompensation in patients with asthma and chronic respiratory disorders and thus is contraindicated in this population [109]. In November 2006, manufacturers of oseltamivir notified healthcare professionals and the FDA of post-marketing reports of self-injury and delirium in patients (primarily children) receiving the drug. Most of the reports were in Japan and subsequent study has not found a causal association between the neuraminidase inhibitors and abnormal behavior [110]. A dose reduction is required for those patients with a creatinine clearance <30 mL/min.

## 3.21 Antifungal Agents

Invasive fungal infections are an important cause of morbidity and mortality in patients with malignant diseases. The risk factors are well established and include AML, allogeneic HSCT, persistent, profound neutropenia resulting from chemotherapy or myeloablative therapy, and use of corticosteroids [111–115]. Older age, breakdown of physical barriers, prior fungal infections and use of broad-spectrum antimicrobials are also important risk factors [116].

Several new antifungal agents are now available. The newer antifungal class of echinocandins, such as caspofungin, micafungin, and anidulafungin, and new triazole derivatives, including posaconazole, and voriconazole, are currently part of the armamentarium for treatment and prophylaxis of fungal infections. The antifungal agents, in particular, have interactions that are clinically significant in the hematology–oncology population. Table 4 summarizes several antifungal agents relevant to the care of patients with malignancies.

**Table 4** Characteristics of antifungal agents by class (includes relevant adverse reactions and interactions)

| Antifungal (References) | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Amphotericin B (Traditional and Lipid Preparations) [117–121, 125–127, 141, 193, 194] | Binds to the ergosterol present in the fungal cell membranes. The interaction with these sterols results in the formation of pores, which in turn increase the permeability of the membrane and cell death | Wide spectrum of activity against fungi—however, no longer first line for cancer/neutropenic patients due to adverse effects<br>Treatment for *Cryptococcus* and mucormycosis | Infusion-related reactions<br>Nephrotoxicity (less in lipid formulations)<br>Electrolyte abnormalities<br>Bone marrow suppression<br>Hepatoxicity | Concomitant use with calcineurin inhibitors, ganciclovir, foscarnet, aminoglycosides or cisplatin increases nephrotoxicity |

(continued)

**Table 4** (continued)

| Antifungal (References) | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Azoles [128, 131, 144–146, 150, 153, 157, 161, 163, 167, 169, 195, 196] | Inhibition of the CYP-450 dependent lanosterol 14-α demethylase which inhibits the growth of the fungi | *Fluconazole*<br>• First-line antifungal prophylaxis<br>• Empiric treatment for prolonged neutropenic fever<br>• Treatment for infections caused by susceptible *Candida* species<br>*Voriconazole*<br>First-line therapy for aspergillosis<br>• Alternate agent for empiric treatment for prolonged neutropenic fever<br>• Antifungal prophylaxis<br>*Itraconazole*<br>• First line for histoplasmosis<br>• Antifungal prophylaxis in BMT/HSCT (limited to difficulty with absorption issues)<br>*Posaconazole*<br>• Salvage therapy for refractory aspergillosis and mucormycosis<br>• Antifungal prophylaxis for molds for refractory leukemia and HSCT with GVHD | *Azole group*<br>• Hepatotoxicity<br>• Prolonged QT interval<br>*Voriconazole*<br>• Visual disturbances<br>• Cutaneous phototoxicity<br>*Itraconazole*<br>• Congestive heart failure<br>*Posaconazole*<br>• Gastrointestinal upset | Co-administration with CYP 450 inducers like H2 blockers, isoniazid, carbamazepine, phenytoin, rifampin and rifabutin may result in decreased levels of azole antifungal<br>Vinca alkaloids (increased plasma concentrations of these agents)<br>Calcineurin inhibitors (increased plasma concentrations)<br>mTOR inhibitors (increased plasma concentrations)<br>Proton pump inhibitors (hinder absorption of itraconazole capsules and posaconazole) |

(continued)

**Table 4** (continued)

| Antifungal (References) | Mechanism of action | Major indications | Adverse reactions | Interactions |
|---|---|---|---|---|
| Echinocandins [183, 185, 187–189] | Inhibit the production of 1,3-ß-D glucan, one of the fibrillar proteins that form the fungal cell wall, which leads to reduced cell wall integrity, rupture and death | Empiric treatment for prolonged neutropenic fever<br>Directed therapy for infections caused by azole-resistant *Candida* | Histamine-mediated infusion-related reaction<br>Hepatotoxicity | |

*BMT* bone marrow transplant, *HSCT* hematopoietic stem cell transplant, *GVHD* graft-versus-host disease

## 3.22 Conventional and Lipid Formulations of Amphotericin B

Amphotericin B deoxycholate has a broad spectrum of activity and is the best antifungal available against the majority of systemic fungal infections; however, it is far from being an ideal agent. Despite its use, systemic fungal infections are associated with significant mortality in immunocompromised patients. Amphotericin B deoxycholate is associated with infusion-related toxicity and severe renal toxicity in up to 50 % of cases [117]. For these reasons, it has fallen out of favor and is no longer the drug of choice for fungemia in the cancer population. It still has a role in the treatment for *Cryptococcus neoformans* and Mucor infections.

Amphotericin B binds to ergosterol present in the fungal cell membrane. The interaction with ergosterol results in the formation of pores, which in turn increases the permeability of the cell membrane and leads to the leakage and loss of intracellular molecules resulting in fungal cell death [118].

Amphotericin has a relatively wide spectrum of activity against fungi. It is useful in treating infections with most *Candida* spp., *C. neoformans, Aspergillus fumigatus,* Mucoraceae, *Histoplasma capsulatum, Coccidiodes immitis, Blastomyces dermatitidis, Paracoccidiodes brasiliensis, Sporothrix schenckii,* and *Penicillium marneffei* [118, 119].

Lipid formulations were developed to improve the side effect profile and decrease nephrotoxicity of the parent drug and thus to provide a better therapeutic index. Three such formulations are currently available in the United States: amphotericin B colloidal dispersion (ABCD, Amphotec®), amphotericin B lipid complex (ABLC, Abelcet®), and liposomal amphotericin B (AmBi, AmBisome®). The lipid-based amphotericin preparations differ somewhat in their chemical structure, clinical pharmacokinetics, and incidence of side effects, but all have excellent antifungal activity [119, 120].

Amphotericin B deoxycholate has an established clinical efficacy for treatment for invasive fungal infections. The lipid formulations have also demonstrated efficacy in the treatment for invasive aspergillosis, zygomycosis, and invasive candidiasis [121, 122]. Lipid formulations are also options for the treatment for severe and refractory invasive fungal infections including endemic mycoses, as published in treatment guidelines [118, 123, 124].

All lipid-based amphotericin B formulations have negligible absorption in the gastrointestinal tract and require parenteral administration. Once in the bloodstream, amphotericin is released from its complex and remains in plasma heavily protein-bound (90 %). The distribution of amphotericin B is multicompartmental with high concentrations found in the liver and lung and only low concentrations reached in peritoneal, pleural, pericardial, and synovial fluids. Only minimal amounts penetrate into the CSF, amniotic fluid, and vitreous humor. Most amphotericin B is removed from the blood in the liver, and it undergoes excretion with the bile (40 %) and in feces. In adult patients with normal renal function, the plasma half-life is 24–48 h; however, its elimination half-life can be as prolonged as 15 days due to extensive tissue binding [125–130].

Despite its clinical use for over 3 decades, resistance to amphotericin B remains very unusual. Some *Candida* spp. including *C. lusitaniae, C. guilliermondii* and *C. glabrata* can express resistance to amphotericin B [131, 132]. Resistance is attributed to a decrease in the amount of ergosterol production or a change in the target lipid. The proposed mechanisms include mutations in the ergosterol biosynthesis pathways with production of ergosterol-like compounds, changes in the orientation of ergosterol within the membrane, and changes in ergosterol content that decrease the affinity for amphotericin B [133, 134].

Dimorphic molds are susceptible to amphotericin B. However, resistance has been reported in cases of infection with *Aspergillus flavus,* and *A. fumigatus,* and *Aspergillus terreus* which seems to be more resistant than all other *Aspergillus* species [135].

Infusion-related adverse events (IRAE) often accompany the administration of amphotericin B deoxycholate. Most frequently, the symptoms include fever, chills, and rigors. More severe cases may present with tachypnea and stridor. This type of toxicity is associated with the release of IL-1 and IL-6 as well as tumor necrosis factor from monocytes and macrophages [136]. This is the major dose-limiting toxicity of amphotericin B deoxycholate and at least one IRAE was observed within the first 7 days of its administration in 71 % of adult patients [136]. Corticosteroids, acetaminophen, meperidine, and antihistamines are part of the armamentarium used in attempts to decrease the frequency of IRAE. However, data are limited in demonstrating benefit of any of the pretreatment regimens in decreasing the incidence of IRAE [137].

Comparative trials have shown that liposomal amphotericin B is the formulation least likely to cause IRAE, whereas similar rates of IRAE occurred with conventional amphotericin B and the lipid complex and colloidal dispersion formulations [138].

Nephrotoxicity occurs in at least one-third of patients receiving amphotericin B deoxycholate. It is multifactorial with events such as an early arteriolar vasoconstriction that decreases both the renal blood flow and glomerular filtration rate. The manifestations range between azotemia and renal failure requiring hemodialysis [117]. Later in the course of therapy, amphotericin B exerts a direct toxic effect on epithelial cell membranes, causing acute tubular necrosis and renal tubular acidosis with subsequent potassium and magnesium wasting [139, 140]. Several meta-analyses have reported that lipid formulations are less nephrotoxic than amphotericin B deoxycholate, with the incidence of nephrotoxicity reduced by 49–75 % with these agents [141, 142].

Other side effects of amphotericin B deoxycholate are normocytic hypochromic anemia attributed to decreased production of erythropoietin, bone marrow suppression with leukopenia and thrombocytopenia, which are reversible upon discontinuation of the antifungal [141].

Drug interactions are relevant as the risk of severe nephrotoxicity is increased by the concomitant use of nephrotoxic agents. In oncologic and HSCT patients, the concurrent administration of amphotericin B with cyclosporine, tacrolimus, ganciclovir, foscarnet, aminoglycosides, and cisplatin deserves special attention [139, 143].

Any increase in serum creatinine is considered important and should trigger review of further parameters and consideration to start alternative antifungal therapy.

Amphotericin B-associated hypokalemia can be exacerbated when used with other potassium-depleting agents like corticosteroids and diuretics. There especially can be exacerbated hypokalemia if the patient on both amphotericin and digoxin.

## 3.23 Azoles

This group of antifungals includes two classes, imidazoles and triazoles, that share the same mechanism of action. Antifungal agents such as ketoconazole, clotrimazole, miconazole are early imidazoles; their characteristics like poor bioavailability and interactions with commonly used medications have limited their use in cancer patients.

Fluconazole and itraconazole are triazoles. Their slower metabolism and lesser effects on human sterol synthesis prompted further research into this class, and these and newer agents such as voriconazole and posaconazole are now important options in the treatment and prophylaxis of invasive fungal infections.

The major effect of azoles in fungi is the inhibition of the cytochrome P450 (CYP450)-dependent lanosterol 14-α-demethylase. This effect impairs the synthesis of ergosterol. Accumulated 14-α-methylsterols disrupt several membrane-bound systems such as ATPase and enzymes of the electron transport chain, which inhibits the growth of the fungi [143].

As a group, azoles have activity against most *Candida* spp., *C. neoformans, B. dermatitidis, H. capsulatum,* and *Coccidiodes* spp. The second-generation triazoles have additional activity; voriconazole has an antifungal spectrum that includes most *Aspergillus* spp. and *Fusarium* and posaconazole has the broadest spectrum in the class with activity against zygomycetes and *Scedosporium apiospermum* [144].

All azole agents can cause mild to moderate abnormalities in liver function, and cases of fatal hepatotoxicity have been reported with itraconazole, voriconazole, and posaconazole. Therefore, close monitoring of hepatic function is recommended in patients at high risk [145, 146].

Due to the mechanism of action, all the azole antifungals inhibit CYP450 enzymes to some extent. However, the potential for drug–drug interactions is higher for voriconazole and itraconazole because they are metabolized to a greater extent by CYP isoenzymes than posaconazole and fluconazole. When adding or discontinuing azole agents to a drug regimen, the list of concurrent medications should be reviewed carefully and dosage adjustments should be made accordingly. Co-administration with CYP450 inducers like isoniazid, carbamazepine, phenytoin, rifampin, and rifabutin may result in decreased levels of azole antifungal with reduced efficacy [147, 148]. For example, administration of rifampin is contraindicated with itraconazole and voriconazole and avoided with fluconazole. Also,

rifampin may reduce posaconazole levels by induction of glucuronidation, and therefore, co-administration is contraindicated [149].

Medications that may prolong the QT interval such as cisapride, terfenadine, and astemizole are contraindicated when using azole antifungals. Cautious use should be exercised when co-administering other medications that may prolong the QT interval including quinolones and antipsychotics [150]. Doses of tacrolimus, sirolimus, and cyclosporine need to be reduced by 50–75 % and levels monitored when administered concurrently with azole antifungals.

Itraconazole, voriconazole, and posaconazole may increase the plasma concentrations of vinca alkaloids such as vinblastine and vincristine, with subsequent neurotoxicity. To avoid this complication, dose reductions of the chemotherapeutic agent versus switch to a non-azole antifungal agent can be considered. Additionally, azole agents may increase plasma concentrations of the calcineurin inhibitors, and calcineurin dose adjustments are recommended when these antifungal agents are used concomitantly.

## 3.24 Fluconazole

Fluconazole can reach the same plasma concentrations whether given orally or intravenously. Fluconazole is almost completely absorbed from the gastrointestinal tract and its bioavailability is unchanged by food or gastric acidity. Fluconazole is only 12 % protein-bound in plasma and has widespread dissemination to tissues and body fluids including breast milk, saliva, and sputum. It also distributes well into the CSF and reaches concentrations that are between 50 and 90 % that of the plasma. Renal excretion is the main path of elimination (90 %), with an elimination half-time of approximately 30 h in patients with normal renal function [151].

In terms of pharmacodynamic data, there is a strong relationship between MIC, fluconazole dose, and outcome. Since the AUC is almost identical to the administered dose, it allows quick determination of whether a dosage will achieve the target AUC/MIC ratio. In the case of *Candida* spp., an AUC/MIC ratio $\geq$25 is required to ensure a high probability of successful treatment [152]. Patients who are infected with *Candida* isolates with higher MICs and receive lower doses of fluconazole have poorer outcomes, including increased mortality [153, 154].

In the past, a favorable safety profile and high oral bioavailability positioned this antifungal agent as one of the initial choices for treatment for candidiasis in several patient populations, including oncology patients. A change in the distribution of *Candida* spp. has occurred in the past 10 years, with an increase in the incidence of infections with non-*albicans Candida* spp. such as *C. krusei* and *C. glabrata* [155]. This trend prompted reconsideration of fluconazole as the most appropriate initial therapy for invasive candidiasis in high-risk populations, including patients with hematological malignancies or HSCT. The use of fluconazole still is favored for the initial treatment for candidemia in non-neutropenic patients who are less critically ill and do not have recent azole exposure [123].

Fluconazole is extremely well tolerated and adverse effects are uncommon. Headache, reversible alopecia, and nausea are the most common side effects. In allogeneic HSCT recipients receiving tacrolimus, caution should be used in changing dose or discontinuing fluconazole. Similar drug-level issues exist for the new mTOR inhibitors such as sirolimus.

## 3.25 Itraconazole

Itraconazole is available both for oral and intravenous administration. The pure compound is highly protein-bound and has poor solubility at physiological pH. In practical terms, patients are often asked to take itraconazole with a cola beverage [156]. The parenteral formulation has an incorporated cyclodextrin derivative, which precludes its use in patients with GFR $< 30$ ml/min. The use of the intravenous formulation achieves target concentrations within 48 h of initiation of therapy [157].

Itraconazole is metabolized by the liver, where it is a substrate and inhibitor of CYP3A4, and undergoes extensive oxidative metabolism to its active metabolite, hydroxyitraconazole [158]. Its terminal half-life is 24 h and the steady state is reached by day 13 [159], warranting the use of loading doses with the oral formulation when treating deep mycoses. It is not excreted in the urine or CSF, and plasma levels are not affected by an impaired renal function or hemodialysis.

Oral itraconazole absorption exhibits extensive inter-subject variability. This has been documented among HSCT recipients and suggests that the presence of concurrent mucosal disorders such as mucositis or GVHD limits its absorption [160]. This characteristic, along with an exposure-effect relationship, warrants therapeutic drug monitoring to optimize dosing and improve clinical outcome [161, 162]. An itraconazole trough level of 0.5 mg/L is considered a reasonable target [161–163].

Oral itraconazole solution is most commonly associated with nausea and diarrhea [164], which are more frequent with the solution than capsules and caused by the presence of the excipient, cyclodextrin. It has also been associated with congestive heart failure due to negative inotropic effect [165] and as the cause of a unique triad of hypertension, edema, and hypokalemia [166]. Itraconazole is first-line therapy for histoplasmosis. Some data exist for prophylaxis in HSCT recipients, but its use for this or other indications is limited due mainly to the difficulty with the gastrointestinal absorption.

## 3.26 Voriconazole

In healthy volunteers, voriconazole reaches maximum plasma concentration in 1.4–1.8 h after oral administration. The bioavailability is approximately 85 % [167]. Since the bioavailablitiy is affected by fat content of meals, voriconazole should be administered by mouth either 1 h before or 1 h after meals [168].

The metabolism of voriconazole varies widely among individuals [169], with serum concentrations that can be highly variable due to nonlinear pharmacokinetics; it is 58 % protein-bound and has a large volume of distribution. Less than 5 % of the drug is excreted unchanged in the urine. Voriconazole metabolism is primarily hepatic via the CYP450, with CYP2C19 as the major pathway. Once CYP2C19 is saturated, voriconazole exposure increases disproportionately. Also, polymorphisms of CYP2C19 occur in up to 5 % of Caucasians and up to 20 % of Asian populations and are associated with slow voriconazole metabolism, which may lead to higher drug exposure [170]. It is necessary to halve the maintenance dose for patients with mild to moderate liver dysfunction. Like itraconazole, the intravenous formulation of voriconazole contains cyclodextrin and, therefore, it should be avoided in patients with creatinine clearance <50 mL/min [163].

Voriconazole has been associated with two unique adverse events: visual disturbances and cutaneous phototoxicity. Up to 45 % of patients develop photophobia or abnormal vision [171]; however, these effects are transient and tend to disappear within the first week of therapy [172]. Phototoxicity-related rash occurs infrequently; however, it is a significant problem for ambulatory patients and is only reversible with the discontinuation of therapy [173].

Due to its more favorable toxicity profile over amphotericin and superior efficacy, voriconazole has become a first-line therapy for *Aspergillus*. It is also an alternate agent for patients failing fluconazole prophylaxis.

## 3.27 Posaconazole

Posaconazole is administered orally as a suspension. Its bioavailability improves when taken with a low-fat or high-fat diet or nutritional supplement [174], and its absorption is not affected by gastric acidity [175]. The maximum daily dose is 800 mg, and to achieve higher drug levels in plasma, it should be divided into two doses, or into four doses, when given on empty stomach. This drug has a large volume of distribution despite being highly protein-bound (98 %), and steady-state concentration can be achieved in 7–10 days with a half-life of 35 h [176]. Peak serum concentrations have considerable inter-patient variability [177] for reasons that have not been completely elucidated; however, this provides a rationale for monitoring of posaconazole levels in blood. Unlike itraconazole and voriconazole, up to 30 % of posaconazole is metabolized by uridine diphosphate glucuronosyltransferase (UGT) and the remainder is excreted unchanged in the feces and as glucuronidated metabolites in the urine [178]; dose adjustments are not required with concurrent hepatic or renal insufficiency. Posaconazole is well tolerated, with gastrointestinal complaints such as nausea, vomiting, and diarrhea reported in up to 10 % of patients [179].

### 3.28 Echinocandins

This is the newest class of antifungals. Caspofungin was released in 2001 followed by micafungin in 2005, and anidulafungin a year later. The echinocandins inhibit the production of 1,3-ß-D glucan, one of the fibrillar proteins that form the fungal cell wall [180], which leads to reduced cell wall integrity, rupture, and death. Echinocandins are active against *Aspergillus* spp. and most *Candida* spp. while *C. neoformans* [181], *Fusarium* spp., *Scedosporium* spp., the Mucorales, and *Trichosporon* spp. [182] are intrinsically resistant to the echinocardins. Echinocandins are recommended as initial therapy for most adult non-neutropenic patients, favoring those with moderately severe to severe illness and history of azole exposure [123].

The echinocandins have poor oral absorption due to large molecular weights; therefore, all three agents require intravenous administration. They follow linear kinetics after a single IV dose and have a terminal half-life of 8–13 h, making single daily dosing possible [183]. Protein binding varies from 85 to 99 %.

Of the available echinocandins, two undergo metabolism to produce two distinctive inactive metabolites. Caspofungin undergoes hepatic hydrolysis and *N*-acetylation [184], and micafungin undergoes non-oxidative metabolism [185]. Of interest, anidulafungin is not metabolized by the liver but, rather, undergoes nonenzymatic degradation [186].

Echinocandins are safe agents with few associated toxicities. Although uncommon, this antifungal class may be associated with a histamine-mediated infusion-related reaction similar to that of vancomycin and, this too, can be relieved by slowing the rate of infusion or with antihistamine premedication.

Overall, there are few interaction issues when compared to azoles because echinocandins are poor substrates of the CYP450 enzyme system. Caspofungin concentrations can be lowered by CYP450 inducers like rifampin [187] and increasing the maintenance dose to 70 mg IV daily should be considered. Levels of cyclosporine and tacrolimus need to be monitored when co-administered with micafungin and caspofungin as the latter two have weak inhibitory properties against CYP3A4 [188, 189]. Anidulafungin does not appear to have these interactions [186].

## 4 Conclusions

Medical technology has advanced the treatment for patients with malignancies. Invasive procedures and immunosuppressive drugs have become lifesaving, but also place patients are increasing risk for routine and opportunistic pathogens. Treatment for infections has become much more complex in the last few years, especially given the emergence of antimicrobial-resistant pathogens, including bacterial species that are resistant to most, if not all, first-line agents. Although some new agents, especially antifungals, have been developed recently, the pipeline for new antimicrobials, especially novel antibacterial agents has slowed to

a trickle in the recent decade and likely for the foreseeable future. Thus, it is vital that clinicians who care for these complex patients maintain a working knowledge of the principles of antimicrobial selection and stewardship to minimize risk and optimize outcomes.

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## References

1. Freifeld A et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 52:e56–e93. On-line at: http://www.idsociety.org/Antimicrobial_Agents/#Neutropenic%20Patients%20with%20Cancer. Last accessed on 12 Mar 2013
2. Roder BL, Nielsen SL, Magnussen P, Engquist A, Frimodt-Moller N (1993) Antibiotic usage in an intensive care unit in a Danish university hospital. J Antimicrob Chemother 32:633–642
3. Lazarou J et al (1998) Incidence of adverse drug reactions in hospitalized patients: a meta analysis of prospective studies. JAMA 279:1200–1205
4. Nebeker JR, Barach P, Samore M (2004) Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 140:795–801
5. Riedl M, Casillas A (2003) Adverse drug reactions: types and treatment options. Am Fam Physician 68(9):1781–1791
6. Gallicano K, Drusano G (2005) Introduction to drug interactions. In: Piscitelli S, Rodvold K (eds) Drug interactions in infectious diseases, 2nd edn. Humana Press, Totowa, pp 1–11
7. Executive summary of disease management of drug hypersensitivity: a practice parameter. Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology (1999). Ann Allergy Asthma Immunol 83:665–700
8. deShazo RD, Kemp SF (1997) Allergic reactions to drugs and biologic agents. JAMA 278:1895–1906
9. Anderson JA, Adkinson NF Jr (1987) Allergic reactions to drugs and biologic agents. JAMA 258:2891–2899
10. Granowitz E, Brown R (2008) Antibiotic adverse reactions and drug reactions. Crit Care Clin 24:421–442
11. Gunderson BW et al (2001) What do we really know about antibiotic pharmacodynamics? Pharmacotherapy 21(11s):302s–318s
12. Rodvold KA (2001) Pharmacodynamics of antiinfective therapy: taking what we know to the patient's bedside. Pharmacotherapy 21(11 Pt 2):319S–330S
13. Guay D (2005) Quinlones. In: Piscitelli S, Rodvold K (eds) Drug interactions in infectious diseases, 2nd edn. Humana Press, Totowa, pp 215–244
14. Neuhauser M, Danziger L (2005) $\beta$-lactam antibiotics. In: Piscitelli S, Rodvold K (eds) Drug interactions in infectious diseases, 2nd edn. Humana Press, Totowa, pp 255–288
15. Susla G (2005) Miscellaneous antibiotics. In: Piscitelli S, Rodvold K (eds) Drug interactions in infectious diseases, 2nd edn. Humana Press, Totowa, pp 332–389
16. Rybak M, Rotschafer J, Moellering R et al (2009) Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm 66(1):82–98
17. Shoemaker M, Simou J, Roland W (2006) A review of daptomycin for injection (Cubicin) in the treatment of complicated skin and skin structure infections. Ther Clin Risk Manag 2(2):169–174

18. Spratt BG, Cromie KD (1988) Penicillin-binding proteins of gram negative bacteria. Rev Infect Di s 10:699–711
19. Pichichero ME (2007) Use of selected cephalosporins in pencillin-allergic patients—a paradigm shift. Diag Microbiol Infect Dis 57:13S–18S
20. Saxon A et al (1984) Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin in penicillin-allergic subjects. J Infect Dis 149(1):16–22
21. Lee CE, Zembower TR, Fotis MA et al (2000) The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med 160:2819
22. Park M, Markus P, Matesic D, Li JT (2006) Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. Ann Allergy Asthma Immunol 97:681
23. Castells M (2009) Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am 29(3):585–606
24. Kim A, Sutherland CA, Kuti JL, Nicolau DP (2007) Optimal dosing of piperacillin-tazobactam for the treatment of *Pseudomonas aeruginosa* infections: prolonged or continuous infusion? Pharmacotherapy 27(11):1490–1497
25. Lodise TP Jr, Lomaestro B, Drusano GL (2007) Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 44(3):357–363
26. Adam O, Auperin A, Wilquin F, Bourhis JH, Gachot B, Chachaty E (2004) Treatment with piperacillin-tazobactam and false-positive *Aspergillus* galactomannan antigen test results for patients with hematological malignancies. Clin Infect Dis 38:917–920
27. Ansorg R, van den Boom R, Rath P (1997) Detection of *Aspergillus* galactomannan antigen in foods and antibiotics. Mycoses 40:353–357
28. Singh N et al. (2004) Reactivity of platelia *Aspergillus* galactomannan antigen with piperacillin-tazobactam: clinical implications based on achievable concentrations in serum. AAC 48:1989–1992. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC415629/
29. Yahav D, Paul M, Fraser A et al (2007) Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis 7:338–348
30. Leibovici L, Yahav D, Paul M (2010) Meta-analysis of a possible signal of increased mortality associated with cefepime use. Clin Infect Dis 51:1350–1351
31. Kim PW et al (2010) Meta-analysis of a possible signal of increased mortality associated with cefepime use. Clin Infect Dis 51(4):381–389
32. Fisher BT, Aplenc R, Localio R, Leckerman KH, Zaoutis TE (2009) Cefepime and mortality in pediatric acute myelogenous leukemia: a retrospective cohort study. Pediatr Infect Dis J 28(11):971–975
33. FDA (2007) Cefepime (marketed as Maxipime). Update of ongoing safety review. Updated May 2008
34. Zhanel GG et al (2007) Comparative review of the carbapenems. Drugs 67(7):1027–1052
35. Paterson DL, Depestel DD (2009) Doripenem. Clin Infect Dis 49(2):291–298
36. Asbel LE, Levison ME (200) Caphalosporins, carbapenems and monbactams. Infect Dis Clin North Am 14:435–447
37. CDC (2009) Guidance for control of infections with carbapenem-resistant or carbepenemase—producing Enterobacteriacea in acute care facilities. MMWR 58 (10):256–260
38. Wolfson JS, Hooper DC (1989) Fluoroquinolone antimicrobial agents. Clin Microbiol Rev 2(4):378–442
39. Lipsky BA, Baker CA (1999) Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis 28(2):352
40. Meyer RD (1986) Risk factors and comparisons of clinical nephrotoxicity of aminoglycosides. Am J Med 80:119
41. Hooper DC (1999) Mechanisms of fluoroquinolone resistance. Drug Resist Updat 2(1):38

42. Neuhauser MM (2003) Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA 289(7):885
43. Mcdonald CL et al (2005) An epidemic, toxin gene–variant strain of *Clostridium difficile*. N Engl J Med 353:2433–2441
44. Kumana CR, Yuen KY (1994) Parenteral aminoglycoside therapy. Selection, administration and monitoring. Drugs 47:902–913
45. Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM (1999) Aminoglycosides: activity and resistance. Antimicrob Agents Chemother 43:727–737
46. Fantin B, Ebert S, Leggett J et al (1991) Factors affecting duration of in vivo postantibiotic effect for aminoglycosides against gram-negative bacilli. J Antimicrob Chemother 27:829–836
47. Humes HD (1988) Aminoglycoside nephrotoxicity. Kidney Int 33:900
48. Moore RD, Smith CR, Lipsky JJ et al (1984) Risk factors for nephrotoxicity in patients treated with aminoglycosides. Ann Intern Med 100:352
49. Aronson JK, Reynolds DJ (1992) ABC of monitoring drug therapy. Aminoglycoside antibiotics. BMJ 305(6866):1421
50. Freeman CD, Nicolau DP, Belliveau PP, Nightingale CH (1997) Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. J Antimicrob Chemother 39(6):677
51. Munckhof WJ, Grayson ML, Turnidge JD (1996) A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. J Antimicrob Chemother 37:645
52. Ferriols-Lisart R, Alós-Almiñana M (1996) Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. Am J Health Syst Pharm 53:1141
53. Dobie RA, Black FO, Pezsnecker SC, Stallings VL (2006) Hearing loss in patients with vestibulotoxic reactions to gentamicin therapy. Arch Otolaryngol Head Neck Surg 132(3):253
54. Polk RE, Healy DP, Schwartz LB et al (1988) Vancomycin and the red-man syndrome: pharmacodynamics of histamine release. J Infect Dis 157:502
55. Bailie GR, Neal D (1988) Vancomycin ototoxicity and nephrotoxicity. A review. Med Toxicol Adverse Drug Exp 3:376
56. Moellering RC (2006) Vancomycin: a 50 year reassessment. Clin Infect Dis 42(suppl 1):S3–S4
57. Healy DP, Sahai JV, Fuller SH, Polk RE (1990) Vancomycin-induced histamine release and "red man syndrome": comparison of 1- and 2-hour infusions. Antimicrob Agents Chemother 34:550
58. Anne S, Middleton E Jr, Reisman RE (1994) Vancomycin anaphylaxis and successful desensitization. Ann Allergy 73:402
59. Moellering R (2003) Linezolid: the first oxazolidinone antimicrobial. Ann Intern Med 138:135–142
60. Sakoulas G, Moise-Broder PA, Schentag J et al (2004) Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol 42:2398–2402
61. Hidayat LK, Hsu DI, Quist R et al (2006) High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 166:2138–2144
62. Plosker G, Figgitt D (2005) Linezolid: a pharmcoeconomic review of its use in serious gram positive infections. Pharmcoeconomics 23(9):945–964
63. Kainer M et al (2007) Response to emerging infection leading to outbreak of linezolid-resistant enterococci. EID 13(7):1024–1030
64. Perry CM, Jarvis B (2001) Linezolid: a review if its use in the management of serious gram—positive infections. Drugs 61(4):525–531

65. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH (2003) Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 124:1789–1797
66. ATS/IDSA (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416
67. Shoemaker D, Simou J, Roland W (2006) A review of daptomycin for injection (Cubicin) in the treatment of complicated skin and skin structure. Ther Clin Risk Manag 2(2):169–174
68. Cubicin package insert (2008) Cubist Pharmaceuticals Inc, Lexington
69. Rose W, Rybak W, Kaatz G (2007) Evaluation of daptomycin treatment of *Staphylococcus aureus* bacterial endocarditis: an in vitro and in vivo simulation using historical and current dosing strategies. Antimicrob Chemother 60(2):334–340
70. Oleson FB, Berman CL, Kirkpatrick JB et al (2000) Once-daily dosing in dogs optimizes daptomycin safety. Antimicrob Agents Chemother 44:2948–2953
71. Wenzel R, Bate G, Kirkpatrick P (2005) Fresh from the pipeline: tigecycline. Nat Rev Drug Discov 4:809–810
72. Greer N (2006) Tigecycline (Tygacil): the first in the glycylcycline class of antibiotics. Proc (Bayl Univ Med Cent) 19(2):155–161
73. Hung WY et al (2009) Tigecycline-induced acute pancreatitis: case report and literature review. Int J Antimicrob Agents 34(5):486–489
74. U.S. Food and Drug Administration (2010) FDA drug safety communication: increased risk of death with tygacil (tigecycline) compared to other antibiotics used to treat similar infections, Safety announcement [09-01-2010] http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm. Last Accessed 12 Mar 2013
75. Zavascki A, Goldani L, Nation R (2007) Polymyxin B for the treatment of multidrug-resistant pathogens: a critical review. J Antimicrob Chemother 60(6):1206–1215
76. Evans ME, Feola DJ, Rapp RP (1999) Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant gram-negative bacteria. Ann Pharmacother 33:960–967
77. Falagas ME, Kasiakou SK (2006) Toxicity of polymyxins: a systematic review of the evidence fromold and recent studies. Crit Care 10:R27
78. Higgins DL et al (2005) Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 49(3):1127–1134
79. Stryjewski ME, Graham DR, Wilson SE et al (2008) Assessment of telavancin in complicated skin and skin-structure infections study. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis 46(11):1683–1693
80. Wilson SE, O'Riordan W, Hopkins A (2009) Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections associated with surgical procedures. Am J Surg 197(6):791–796 (Epub 2008 Dec 18)
81. Dunbar L, Tang D, Manausa M (2008) A review of telavancin in the treatment of complicated skin and skin structure infections (cSSSI). Ther Clin Risk Manag 4(1):235–244
82. Daum RS (2008) Clinical practice. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. N Engl J Med 359:1063–1067
83. Moellering R (2008) Current treatment options for community-acquired methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis 46:1032–1037
84. Siberry G, Tekle T, Carroll K et al (2003) Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. Clin Infect Dis 37(9):1257–1260
85. Centers for Disease Control and Prevention (2000) Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow

Transplantation. MMWR Recomm Rep 49(RR-10):1–112. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm. Last accessed on 12 Mar 2013
86. Diasio R (1998) Sorivudine and 5-fluorouracil; a clinically significant drug–drug interaction due to inhibition of dihydropyrimidine dehydrogenase. Br J Clin Pharmacol 46(1):1–4
87. Balfour H (1999) Antiviral drugs. N Engl J Med 340(16):1255–1268
88. Acyclovir for injection USP, package insert. Bedford laboratories (2013) http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Ben+Venue_Bedford+Labs/55390-612-10+ACY500MG/5539061210. Last accessed on 12 Mar 2013
89. Mason J, Nickols H (2008) Crystalluria from acyclovir use. N Engl J Med 358(13):e14
90. Trifilio S, Verma A, Mehta J (2004) Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: heterogeneity of current clinical practice. Bone Marrow Transplant 33:735–739
91. Crumpaker C (1996) Ganciclovir. N Engl J Med 335(10):721–729
92. Gooley T et al (2010) Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 363:2091–2101
93. Holland GN (2008) AIDS and ophthalmology: the first quarter century. Am J Ophthalmol 145(3):397
94. Ganciclovir for infusion package insert (Cytovene). Roche Labs (2006, January) http://www.gene.com/gene/products/information/cytovene/pdf/pi.pdf. Last accessed on 12 Mar 2012
95. Pescovitz MD, Rabkin J, Merion RM et al (2000) Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. Antimicrob Agents Chemother 44(10):2811–2815
96. Ljungman P, de La Camara R, Milpied N et al (2002) Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood 99(8):3050–3056
97. Wagstaff A, Bryson H (1994) Foscarnet. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. Drugs 48:199
98. Avery RK et al (2000) A survey of allogeneic bone marrow transplant programs in the United States regarding cytomegalovirus prophylaxis and pre-emptive therapy. Bone Marrow Transplant 26:763–767
99. Cidofovir (Vistide®) package insert Gilead Sciences. http://www.gilead.com/pdf/vistide.pdf. Last accessed on 12 Mar 2013
100. Vandercam B, Moreau M, Goffin E et al (1999) Cidofovir-induced end-stage renal failure. Clin Infect Dis 29:948
101. Meier P, Dautheville-Guibal S, Ronco PM, Rossert J (2002) Cidofovir-induced end-stage renal failure. Nephrol Dial Transplant 17:148
102. Vaccher E et al (2003) Improvement of systemic human immunodeficiency virus-related non hodgkin lymphoma in the era of highly active antiretrovial therapy. Clin Infect Dis 37:1556–1564
103. Jefferson T, Demicheli V, Rivetti D et al (2006) Antivirals for influenza in healthy adults: systematic review. Lancet 367:303
104. Cooper NJ, Sutton AJ, Abrams KR et al (2003) Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ 326:1235
105. Hayden FG, Osterhaus AD, Treanor JJ et al (1997) Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med 337:874
106. Nichols WG, Guthrie KA, Corey L, Boeckh M (2004) Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 39:1300

107. Fiore AE, Fry A, Shay D et al (2011) Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Surveill Summ 60:1
108. Harper SA, Bradley JS, Englund JA et al (2009) Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 48:1003
109. Kiatboonsri S, Kiatboonsri C, Theerawit P (2010) Fatal respiratory events caused by zanamivir nebulization. Clin Infect Dis 50:620
110. Dominick L. Tamiflu (oseltamivir phosphate) Important Prescribing Information. Roche Pharmaceuticals. Revised 13 Nov 2006. http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153422.pdf. Last accessed on 12 Mar 2013
111. Marr KA, Patterson T, Denning D (2002) Aspergillosis: pathogenesis, clinical manifestations and therapy. Infect Dis Clin North Am 16:875–894
112. Marr KA, Carter RA, Boeckh M, Martin P, Corey L (2002) Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 100:4358–4366
113. Pfaller MA, Diekema DJ (2007) Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 20:133–163
114. Chamilos G, Luna M, Lewis RE et al (2006) Invasive fungal infections in patients with hematologic malignancies in a tertiary care center: an autopsy study over a 15-year period (1989–2003). Haematologica 91:986–989
115. Roden MM, Zaoutis TE, Buchanan WL et al (2005) Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 41:634–653
116. Nucci M, Silveira MI, Spector N et al (1998) Risk factors for death among cancer patients with fungemia. Clin Infect Dis 27:107–111
117. Carlson MA, Condon RE (1994) Nephrotoxicity of amphotericin B. J Am Coll Surg 179:361–381
118. Walsh TJ et al (2008) Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46(3):327–360
119. Ellis D (2002) Amphotericin B: spectrum and resistance. J Antimicrob Chemother 49:7–10
120. Dupont B (2002) Overview of the lipid formulations of amphotericin B. J Antimicrob Chemother 49:31–36
121. Larkin J, Montero J (2003) Efficacy and safety of amphotericin B lipid complex for zygomycosis. Infect Med 20:201–206
122. Kuse ER, Chetchotisakd P, da Cunha CA et al (2007) Micafungin versus liposomal amphotericin B for candidemia and invasive candidosis: a phase III randomized double-blind trial. Lancet 369:1519–1527
123. Pappas PG, Kauffman CA, Andes D et al (2009) Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 48:503–535
124. Wheat LJ, Freifeld AG, Kleiman MB et al (2007) Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 45:807–825
125. Fielding RM, Smith PC, Wang LH et al (1991) Comparative pharmacokinetics of amphotericin B after administration of a novel colloidal delivery system, ABCD, and a conventional formulation to rats. Antimicrob Agents Chemother 35:1208–1213
126. Boswell GW, Buell D, Bekersky I (1998) AmBisome (liposomal amphotericin B): a comparative review. J Clin Pharmacol 38:583–592
127. Bekersky I, Fielding RM, Dressler DE et al (2002) Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. Antimicrob Agents Chemother 46:828–833

128. Daneshmend TK, Warnock DW (1983) Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet 8:17–42
129. Olsen SJ, Swedel MR, Blue B, Clark JM et al (1991) Tissue distribution of amphotericin B lipid complex in laboratory animals. J Pharmacol 43:831–835
130. Atkinson A, Bennett J (1978) Amphotericin B pharmacokinetics in humans. Antimicrob Agents Chemother 13(2):271–276
131. Nguyen MH, Peacock JE Jr, Morris AJ et al (1996) The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am J Med 100:617–623
132. Martins MD, Rex JH (1996) Resistance to antifungal agents in the critical care setting: problems and perspectives. New Horiz 4:338–344
133. Yoon SA, Vazquez JA, Steffan PE et al (1999) High-frequency, in vitro reversible switching of Candida lusitaniae clinical isolates from amphotericin B susceptibility to resistance. Antimicrob Agents Chemother 43:836–845
134. Dick JD, Merz WG, Saral R (1980) Incidence of polyene-resistant yeasts recovered from clinical specimens. Antimicrob Agents Chemother 18:158–163
135. Steinbach WJ, Perfect JR, Schell WA et al (2004) In vitro analyses, animal models, and 60 clinical cases of invasive *Aspergillus terreus* infection. Antimicrob Agents Chemother 48:3217–3225
136. Wingard JR, White MH, Anaissie E, Raffalli J et al (2000) A randomized double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. Clin Infect Dis 31:1155–1163
137. Goodwin SD, Cleary JD, Walawander CA et al (1995) Pretreatment regimens for adverse events related to infusion of amphotericin B. Clin Infect Dis 20:755–761
138. Girois SB, Chapuis F, Decullier E et al (2006) Adverse effects of antifungal therapies in invasive fungal infections; review and meta-analysis. Eur J Clin Microbiol Infect Dis 25:138–149
139. Luber AD, Maa L, Lam M et al (1999) Risk factors for amphotercin B-induced nephrotoxicity. J Antimicrob Chemother 43:267–271
140. Deray G (2002) Amphotericin B nephrotoxicity. J Antimicrob Chemoter 49(Suppl 1):37–41
141. Girois SB, Chapuis F, Decullier E et al (2006) Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. Eur J Clin Microbiol Infect Dis 25:138–149
142. Barrett JP, Vardulaki KA, Conlon C et al (2003) A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. Clin Ther 23:1295–1320
143. Walsh TJ, Finberg RW, Arndt C et al (1999) Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med 340:764–771
144. Gubbins P, McConnell S, Amsden J (2005) Antifungal agents. In: Piscitelli S, Rodvold K (eds) Drug interactions in infectious diseases, 2nd edn. Humana Press, Totowa, pp 289–337
145. Sporanox package insert (2004) Janssen Pharmaceutica, Titusville
146. Vfend package insert (2004) Roeirg, New York
147. Purkins L, Wood N, Ghahramani P et al (2003) Coadministration of voriconazole and phenytoin: pharmacokinetic interaction, safety and toleration. Br J Clini Pharmacol 56(Suppl 1):37–44
148. Krishna G, Parsons A, Kantesaria B et al (2007) Evaluation of pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. Curr Med Res Opin 23:545–552
149. Karthaus M, Cornely OA (2006) Second-line treatment in invasive mould infections. Mycoses 49(Suppl 1):23–26
150. Owens RC Jr, Nolin TD (2006) Antimicrobial-associated QT interval prolongation: pointes of interest. Clin Infect Dis 43:1603–1611

151. McLachlan AJ, Tett ES (1996) Pharmacokinetics of fluconazole in people with HIV infection: a population analysis. Br J Clin Pharmacol 41:291–298
152. Pfaller MA, Diekema DJ, Sheehan DJ (2006) Interpretive breakpoints for fluconazole and Candida revisited: a blueprint for the future of antifungal susceptibility testing. Clin Microbiol Rev 19:435–447
153. Pai MP, Turpin RS, Garey KW et al (2007) Association of fluconazole area under concentration-time curve/MIC and dose/MIC ratios with mortality in nonneutropenic patients with candidemia. Antimicrob Agents Chemother 51:35–39
154. Baddley JW, Patel M, Bhavnani SM et al (2008) Association of fluconazole pharmacodynamics with mortality in patients with candidemia. Antimicrob Agents Chemother 52:3022–3028
155. Pfaller MA, Diekema DJ, Gibbs DL et al (2007) Results from the ARTEMIS DISK global antifungal surveillance study, 1997 to 2005: an 8.5-year analysis of susceptibilities of *Candida* species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J Clin Microbiol 45(6):1735–1745
156. Diaz M, Negroni R, Montero-Gei F et al (1992) A Pan-American 5-year study of fluconazole therapy for deep mycosis in the immunocompetent host. Pan-American Study Group. Clin Infect Dis 14(Suppl 1):S68–S76
157. Barone JA, Koh JG, Bierman RH et al (1993) Food interaction and steady-state pharmacokinetics of itraconazole capsules in healthy male volunteers. Antimicrob Agents Chemother 37:778–784
158. Prentince AG, Glasmacher A (2005) Making sense of itraconazole pharmacokinetics. J Antimicrob Chemother 56:17–22
159. Hardin TC, Graybill JR, Fetchick R et al (1988) Pharmacokinetics of intraconazole following oral administration to normal volunteers. Antimicrob Agents Chemother 32:1310–1313
160. Persat F, Marzllo C, Guyotat D et al (1992) Plasma itraconazole concentrations in neutropenic patients after repeated high-dose treatment. Eur J Cancer 45:838–841
161. Cartledge JD, Midgely J, Gazzard BG (1997) Itraconazole solution: higher drug concentrations and better clinical response rates than the capsule formulation in acquired immunodeficiency syndrome patients with candidosis. J Clin Pathol 50:477–480
162. Boogaerts MA, Verhoef GE, Zachee P et al (1989) Antifungal prophylaxis with itraconazole in prolonged neutropenia: correlation with plasma levels. Mycoses 32(Suppl 1):103–108
163. Potter M (2005) Strategies for managing systemic fungal infection and the place of itraconazole. J Antimicrob Chemoter 56 (Suppl 1): 149–154
164. Tucker RM, Haq Y, Denning DW et al (1990) Adverse events associated with itraconazole in 189 patients on chronic therapy. J Antimicrob Chemother 26:561–566
165. Ahmad SR, Singer SJ, Leissa BG (2001) Congestive heart failure associated with itraconazole. Lancet 357:1766–1767
166. Sharkey PK, Rinaldi MG, Dunn JF et al (1991) High-dose itraconazole in the treatment of severe mycoses. Antimicrob Agents Chemother 35:707–713
167. Purkins L, Wood N, Ghahramani P et al (2002) Pharmacokinetics and safety of voriconazole following intravenous-to oral-dose escalation regimens. Antimicrob Agents Chemother 46:2546–2553
168. Purkins L, Wood N, Kleinermans D, Greenhalgh K et al (2003) Effect of food on the pharmacokinetics of multiple-dose oral voriconazole. Br J Clin Pharmacol 56(Suppl 1):17–23
169. Dening DW, Ribaud P, Milpied N et al (2002) Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 34:563–571
170. Shimizu T, Ochiai H, Asell F, Shimizu H et al (2003) Bioinformatics research on inter-racial difference in drug metabolism I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CPY2C19. Drug Metab Pharmacokinet 18:48–70
171. Herbrecht R, Denning DW, Metry D (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415
172. Johnson LB, Kauffman CA (2003) Voriconazole: a new triazole antifungal agent. Clin Infect Dis 36:630–637

173. Denning DW, Griffiths CEM (2001) Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. Clin Exp Dermatol 26:648–653
174. Ezzet F, Wexler D, Courtney R et al (2005) Oral bioavailability of posaconazole in fasted healthy subjects comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 44:211–220
175. Courtney R, Radwanski E, Lim J et al (2004) Pharmacokinetics of posaconazole co-administered with antacid in fasting and nonfasting healthy men. Antimicrob Agents Chemother 48:804–808
176. Ezzet F, Wexler D, Courtney R et al (2005) Oral bioavailability of posaconazole in fasted healthy subjects comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 44:211–220
177. Krishna G, Sansone-Parsons A, Martinho M et al (2007) Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. Antimicrob Agents Chemother 51:812–818
178. Krieter P, Flannery B, Musick T et al (2004) Disposition of posaconazole following single-dose oral administration in healthy subjects. Antimicrob Agents Chemother 48:3543–3551
179. Raad II, Graybill JR, Bustamante AB et al (2006) Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis 42:1726–1734
180. Kurtz MB, Rex JH (2001) Glucan synthase inhibitors as antifungal agents. Adv Protein Chem 56:463–475
181. Feldmesser M, Kress Y, Mednick A et al (2000) The effect of the echinocandin analogue caspofungin on cell wall glucan synthesis by *Cryptococcus neoformans*. J Infect Dis 182:1791–1795
182. Espinel-Ingroff A (1998) Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 36:2950–2956
183. Denning DW (2002) Echinocandins: a new class of antifungals. J Antimicrob Chemother 49:889–891
184. Balani SK, Xu X, Arison BH et al (2000) Metabolites of caspofungin acetate, a potent antifungal agent in human plasma and urine. Drug Metab Dispos 28:1274–1278
185. Hebert MF, Smith HE, Marbury TC et al (2005) Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. J Clin Pharmacol 45:1145–1152
186. Stogniew M, Pu F, Henkel T et al (2003) Anidulafungin biotransformation in humans is by degradation not metabolism. Clin Microbiol Infect 9:291
187. Stone JA, Migoya EM, Hickey L et al (2004) Potential for interactions between caspofungin and nelfinavir or rifampin. Antimicrob Agents Chemother 48:4306–4314
188. Sanz-Rodriguez C, Lopez-Duarte M, Jurado M et al (2004) Safety of the concomitant use of caspofungin and cyclosporin A in patients with invasive fungal infections. Bone Marrow Transplant 34:13–20
189. Hebert MF, Townsend RW, Austin S et al (2005) Concomitant cyclosporine and micafungin pharmacokinetics in healthy volunteers. J Clin Pharmacol 45:954–960
190. Greer N (2008) Doripenem (Doribax): the newest addition to the carbapenems. Proc (Bayl Univ Med Cent). 21(3):337–341
191. Tenover FC, Moellering RC Jr (2007) The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. Clin Infect Dis 44:1208–1215
192. Rubinstein E, Cammarata S, Oliphant T, Wunderink R, Linezolid Nosocomial Pneumonia Study Group (2001) Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double blind, multicenter study. Clin Infect Dis 32:402–412
193. Bellmann R, Egger P, Wiedemann CJ et al (2003) Differences in pharmacokinetics of amphotericin B lipid formulations despite clinical equivalence. Clin Infect Dis 36:1500–1501

194. Cornely OA, Maertens J, Bresnik M et al (2007) Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (Ambiload trial). Clin Infect Dis 44:1289–1297
195. Thomas LD, Miller GG, The AST Infectious Diseases Community of Practice (2009) Interactions between antiinfective agents and immunosuppressants. Am J Transplant 9(Suppl4):263–266
196. Boogaerts MA, Maertens J, Van Der Geest R et al. (2001) Pharmacokinetics and safety of a 7-day administration of intravenous itraconazole followed by a 14-day administration of itraconazole oral solution in patients with hematologic malignancy. Antimicrob Agents Chemoter 45:981–985

# Infection Control and Prevention Considerations

Titus L. Daniels and Thomas R. Talbot

**Abstract**

Due to the nature of their underlying illness and treatment regimens, cancer patients are at increased risk of infection. Though the advent and widespread use of anti-infective agents has allowed for the application of ever-greater immune-suppressing therapies with successful treatment of infectious complications, prevention of infection remains the primary goal. The evolutionary changes of microorganisms, whereby resistance to anti-infective therapy is increasingly common, have facilitated a paradigm shift in the field of healthcare epidemiology. No longer is the focus on "control" of infection once established in a healthcare environment. Rather, the emphasis is on prevention of infection before it occurs. The most basic tenet of infection prevention, and the cornerstone of all well-designed infection prevention and control programs, is hand hygiene. The hands of healthcare workers provide a common potential source for transmission of infectious agents, and effective decontamination of the hands reduces the risk of transmission of infectious material to other patients. Once infection is suspected or established; however, implementation of effective control strategies is important to limit the spread of infection within

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a healthcare environment. This chapter outlines the basic tenets of infection prevention, principles of isolation precautions and control measures, and elements for a successful infection control and prevention program.

**Keywords**

Infection control and prevention · Hand hygiene · Healthcare-associated infections (HAIs) · Transmission-based precautions · Contact precautions · Droplet precautions · Airborne precautions · Standard precautions · Protective environment · Multidrug-resistant organisms (MDROs) · *Clostridium difficile*

## Contents



## 1 Introduction

The area of infection control has undergone substantial changes in the past decade. The most substantive change has been a shift in emphasis from "control" of healthcare-associated infections (HAIs) to developing and implementing strategies for preventing HAIs. This effort has been led by the Centers for Disease Control and Prevention (CDC), who adopted the addition of "and Prevention" in 1992 to their name [1]. A variety of published reports support the notion that most HAIs are preventable. These data challenge the concept of HAIs as a simply the "cost of doing business" in an increasingly complex healthcare environment. Thus, developing effective strategies to prevent HAIs is the foundation of any infection "control" program.

Healthcare-associated infections not only impart substantial morbidity and mortality upon patients; they are associated with enormous costs to the healthcare system. As an effort to provide better safer care and to assist in containing costs associated with HAI, the Centers for Medicare and Medicaid Services (CMS) no longer provides reimbursement for many hospital-acquired conditions. Several of these conditions are related to infection including catheter-associated blood stream infections, catheter-associated urinary tract infections, and selected surgical site infections.

The increased interest in HAIs has highlighted many important challenges that institutions must overcome. These include the development of systematic processes to ensure hand hygiene compliance and provide acceptable rates of

healthcare-worker (HCW) influenza vaccination rates, develop methods for tracking and reporting infection rates, and designing and/or implementing evidence-based practice "bundles" associated with reductions in several HAIs (i.e., ventilator-associated pneumonia, catheter-associated blood stream infections, and surgical site infections). Developing effective infection prevention programs involves unique challenges under the best of circumstances. Many of these challenges are exemplified when considering the immune-compromised host. However, the majority of infection prevention and control initiatives apply to all patients equally regardless of the immune status of the host. Ensuring adherence to the basic tenets of infection prevention and control will serve all patient populations well, especially those already at increased risk of infectious complications.

## 2 Hand Hygiene

Ignaz Semmelweis demonstrated in 1847 that disinfecting the hands resulted in a marked reduction in puerperal fever. More than 150 years have passed since learning of the fundamental role that contaminated hands play in the transmission of HAIs [2]. Unfortunately, hand hygiene rates remain unacceptably low at around 40 % in most U.S. healthcare institutions. It is accepted by most experts that high rates of hand hygiene compliance are associated with reductions in HAIs. Emphasis thus is on improving the rate of hand hygiene compliance in healthcare institutions rather than continued study into the effectiveness of hand hygiene.

A comprehensive approach is necessary to sustain high rates of hand hygiene compliance. While education must be conducted and maintained, the majority of healthcare professionals accept the value and importance of hand hygiene. Therefore, directed efforts aimed at ensuring hand hygiene are performed and are the most beneficial. Such efforts are best focused on modeling of behavior by key institutional leaders [4, 5] and ensuring wide availability of hand hygiene products [3]. The selection of hand hygiene products often involves an extensive process that includes many representatives of the healthcare team (e.g., physicians, nurses, technicians, phlebotomists, etc.). The CDC recommends the use of alcohol-based hand-rubs preferentially over the use of soap and water in most situations. Reasons for such recommendations are severalfold. Because these products do not require the use of water, can be distributed in a variety of locations, are rubbed onto the hands until dry, and can be applied while walking to the location of the next task, hand hygiene is more likely to be performed appropriately and can be done quickly when using alcohol-based hand-rubs. On the contrary, use of soap and water requires remaining in a specified location, staying in this location while washing, and using soap and water for at least 15–20 s. Because of the frequent time-constraints placed on busy healthcare professionals, it is less likely that use of soap and water for hand hygiene is performed appropriately. Therefore, preference is given to the use of hand-rubs.

However, there are instances when the use of soap and water is preferred over that of an alcohol-based hand-rub. When hands are visibly soiled, hand-rubs are not effective in removing debris, and the use of soap and water is necessary to clean the hands. Another common situation where soap and water is preferred is when caring for patients infected or colonized with organisms that are not effectively killed or inactivated by hand-rubs. Organisms capable of forming spores are not inactivated with the use of hand-rubs. Therefore, use of a hand-rub does not eliminate the organisms from the hands allowing for possible transmission to another patient. *Clostridium difficile* is a commonly encountered pathogen that has the ability to form spores. While soap and water does not kill or inactivate the spores, the mechanical action of rubbing the hands under running water removes the spores from the hands. Soap is still necessary in order inactivate other organisms on the hands and to provide a surfactant for effective removal of spores from the hands [6].

## 3 Standard Precautions

Standard precautions encompass a set of infection prevention practices that are used for all patient encounters [5]. Standard precautions are based on the premise that all blood, body fluids, secretions, non-intact skin, and mucous membranes contain potentially infectious material. Therefore, handling of blood or body fluids demands the use of precautions to protect the HCW from exposure to a potentially infectious agent and to minimize the risk of transmission of such pathogens to others. Standard precautions include the practice of hand hygiene, the use of personal protective equipment (gowns, gloves, masks, and eye protection) depending on the anticipated procedure, and the performance of safe injection practices. Hand hygiene is a universal action practiced in all healthcare settings and with all patient interactions. The use of personal protective equipment (PPE), however, is designed only when exposure to potentially infectious material (blood and bodily fluids) may occur.

The 2007 CDC Guidelines for Isolation Precautions include *respiratory hygiene/cough etiquette*, a new practice recommendation incorporated as part of standard precautions [6]. Respiratory hygiene and cough etiquette refer to practices that minimize transmission of respiratory pathogens (i.e., influenza, common cold viruses, etc.) and includes covering of coughs/sneezes, use of a surgical mask for those with respiratory symptoms, and performing hand hygiene after coughing and/or sneezing. Further, use of signage to provide instruction on the performance of respiratory hygiene and cough etiquette is suggested. While these practices are congruent with the notion of standard precautions, they differ in that respiratory hygiene and cough etiquette applies to all individuals within the healthcare institution, including visitors and patients in addition to HCWs. Standard precautions, on the other hand, generally apply only to HCWs.

## 4 Transmission-Based Precautions

Transmission-based precautions are utilized to prevent the spread of specific pathogens and are based on the mode of transmission of the organism in question. Such precautions generally are of three types: airborne, droplet, and contact. Each of these sets of precautions has specific environmental components and recommendations for the use of PPE by HCWs. For all circumstances, the implementation of transmission-based precautions should occur whenever infection or colonization with a pathogen is suspected or confirmed to be present. Implementation of precautions early in the course when infection or colonization is suspected, even before being confirmed, minimizes the risk of disease transmission to other patients and HCWs. Minimizing the exposure risk is expected to minimize the risk of transmission to subsequent patients.

Airborne precautions are designed to minimize the transmission of infectious pathogens spread by the airborne route. Pathogens spread by the airborne route are highly infectious particles that have the ability to spread via air currents, thus allowing for easy spread over relatively long distances. These include tuberculosis, measles, and varicella zoster virus. The spread of novel respiratory viruses (i.e., avian influenza H5N1) is often unknown. Recommendations for control of these viruses includes using airborne precautions as a component of protection until further data demonstrating other precautions are sufficient for interruption of transmission [6, 7].

Use of an airborne infection isolation room (AIIR) is necessary for patients requiring airborne precautions. An AIIR is a room in which the pressure in the room (where the infected patient is located) is negative relative to the pressure in the areas adjacent to the room. This design allows for air outside of the room to flow into the room, pass through a high-efficiency filter, and then be exhausted. The other major component of caring for patients with suspected or confirmed pathogens requiring airborne precautions is that all HCWs entering into the room wear a respirator capable of filtering the potentially infectious material (i.e., fit-tested N-95 particulate respirator). The design to minimize the risk of transmission of infectious organisms to patients in adjacent areas and rooms poses unique challenges to patients with compromised immune systems where the general goal is to move environmental air from the patient's environment into adjacent areas, hence using positive pressure ventilation rather than negative pressure ventilation. However, positive pressure ventilation allows for the dispersion of airborne infectious material to potentially be spread to other, often immune-compromised, patients in adjacent areas or rooms. Because of the risk of disease transmission to others from patients with infections such as tuberculosis and measles, it is recommended that all patients requiring airborne precautions, regardless of immune status, be cared for in negative pressure rooms.

A not uncommon situation, though, occurs when immune-compromised patients present with cutaneous or disseminated varicella zoster virus (VZV) infections. Due to impaired immunity, these patients are likely to shed virus from

lesions for prolonged periods. Daily culturing of lesions from immune-compromised patients with cutaneous VZV demonstrated that virus may be viable and able to be cultured from lesions for up to 8 days (mean 4.7 days) [8]. Immune-compromised patients are also more likely to develop disseminated disease, and in this same series of patients, 61 % (11/18) developed disseminated disease after the third day of rash onset. Because airborne transmission of VZV has been demonstrated to occur in hospital settings [9], patients with either primary varicella or disseminated zoster infections are recommended to be cared for using airborne precautions. The propensity for dissemination, and therefore potential airborne transmission, after the first day of rash onset in immune-compromised patients suggests that the use of airborne isolation precautions early in the course of illness is a prudent strategy for mitigating the nosocomial spread of VZV infections. The CDC recommends the use of airborne precautions for patients with disseminated disease, regardless of immune status and any disease severity, including localized skin eruptions, due to VZV in immune-compromised patients. Discontinuing the use of airborne precautions is dependent primarily on the pathogen of concern. For VZV (shingles), for example, it is recommended that patients remain in an AIIR with airborne precaution use until all lesions have fully crusted.

The next type of transmission-based precautions is droplet precautions. Droplet transmission occurs when infectious material is expelled from the respiratory tract of an individual when the person coughs, sneezes, or talks [10]. The droplet particles are of larger size than particles associated with pathogens that are spread by the airborne route. The larger size of the droplet particles, therefore, does not allow the infectious material to be dispersed over long distances via air currents as occurs with airborne transmission. The specific distance for which droplet particles remain infectious is largely unknown. Limited data suggest that the risk of transmission is limited to a distance within three feet of the patient [11, 12]. Personal protective equipment for droplet precautions includes the use of a surgical mask by healthcare personnel. The masks should be donned when within about six feet of the patient, a distance considered to be safe and recommended as an additional modicum of caution [6]. Pathogens transmitted via respiratory droplets include influenza virus, adenovirus, rhinovirus, *Bordetella pertussis, Streptococcus pyogenes,* and *Neisseria meningitides*. Respiratory syncytial virus may be transmitted by the droplet route, though the primary mode of transmission is via direct contact with infected material.

Transmission of pathogens within the healthcare environment most commonly occurs by the contact route. Contact transmission is divided into direct and indirect contact transmissions. Direct contact transmission is that which occurs when pathogens are transmitted from one person to another without an intermediary, be it a person or object. Transmission of hepatitis B virus from an infected patient to an HCW from a contaminated needle stick and transmission of scabies from a patient to a HCW are two examples of direct transmission. More commonly, however, indirect contact transmission of pathogens occurs in the healthcare environment.

Indirect contact transmission occurs when a microorganism is transmitted from one person to another via a contaminated person or object. The contaminated hands of HCWs are the most important vector responsible for the indirect contact transmission of microorganisms. Other potential transmission sources include equipment used in the care of patients (i.e., thermometers, blood pressure measurement devices, stethoscopes, etc.). These objects have the opportunity to transmit infectious material if not appropriately disinfected between patients.

Equipment necessary for interrupting transmission of organisms spread by the contact route includes the use of gloves and gowns by HCWs. Ideally, patients should be cared for in a private room. Cohorting of patients colonized or infected with the same type of infectious agent is acceptable [6, 13]. Guidelines for discontinuation of contact precautions have not been well defined.

## 5 Environmental Issues

One aspect of infection control and prevention unique to the immune suppressed population is the use of the protective environment. The protective environment has been specifically designed for patients who have undergone hematopoietic stem cell transplantation (HSCT). A primary goal of the protective environment is to reduce fungal spore counts in the air and, therefore, the risk of invasive fungal disease. Though many types of fungal spores are likely affected by the environmental controls of the protective environment, control of *Aspergillus* spores and mitigation of invasive aspergillosis have been the primary goal.

High-efficiency particulate air (HEPA) filtration of incoming air, directed room airflow, positive room air pressure relative to the corridor, and well-sealed rooms to prevent flow of air from the outside are all part of the protective environment concept. The neutropenic diet is an additional component of the protective environment. The neutropenic diet consists of foods low in bacterial counts with the goal of limiting the introduction of bacteria into the gastrointestinal tract of patients and, thereby, potentially reducing infection by reducing the occurrence of colonization. Many institutions employ the use of the neutropenic diet in an effort to diminish the risk of infection in patients during periods of neutropenia (neutrophil counts $< 500 \times 10^9$/L). Prior to the introduction of the neutropenic diet, food was autoclaved and irradiated prior to serving to patients. This left the food unpalatable by many. The National Cancer Institute performed a randomized trial demonstrating little advantage to the sterile diet over a "cooked food" diet designed by the National Institutes of Health, Department of Dietary and Environmental Sanitation. The cooked food diet was more palatable than the sterile diet. However, it reportedly left patients dissatisfied after prolonged use [14]. Use of commercially available foods was desirable. Culturing of commercially available food [15] found that 66 % grew less than 500 colony-forming units of bacteria per gram of food. Therefore, this became the upper limit of bacterial counts determined to be acceptable for neutropenic patients. However, only 20 % of

processed meats and 30 % of fresh fruits and vegetables had colony counts of bacteria below this threshold. However, data evaluating the specific impact of the neutropenic diet are lacking. A systematic review and meta-analysis performed by Schlesinger et al. [16] evaluated the effect on the protective environment. Components of the protective environment varied across studies, though primarily included air quality control, barrier isolation, and the use of nonabsorbable antibiotics. The protective environment was associated with a 40 % reduction in all-cause mortality at 30 days (RR 0.6 [95 % CI: 0.50–0.72]). When evaluated for the longest period of follow-up (range, 100 days–3 years), mortality reduction was less substantial for patients when care was provided in a protective environment with a relative risk for mortality of 0.86 (95 % CI: 0.81–0.91). Examination of the individual components of the protective environment demonstrates that control of air quality alone was associated with a 19 % reduction in mortality at 100 days (RR 0.81 [95 % CI: 0.73–0.91]). Neither barrier isolation (RR 1.25 [95 % CI: 0.66–2.38]) nor suppression of endogenous flora alone (RR 0.88 [CI: 0.63–1.21]) resulted in a statistically significant effect on mortality. Significant reductions in mortality were also demonstrated among recipients of allogeneic hematopoietic stem cell transplantation (HSCT) (RR0.81, [95 % CI: 0.73–0.89]) and autologous HSCT (RR 0.72, [95 % CI: 0.58–0.88]) when cared for in a protective environment.

These data support the recommendation that patients undergoing HSCT should be cared for in a protective environment [17]. Because of the intensity of chemotherapy and associated prolonged periods of neutropenia associated with treatment for acute leukemia, it is reasonable to extend the use of a protective environment to this population, as well. The lack of available data coupled with dissatisfaction and potential for adverse events associated with isolation of the patient should temper the widespread use of the protective environment for all cancer patients. Strict adherence to routine infection prevention practices should be sufficient to protect non-HSCT patients.

## 6 Multidrug-Resistant Organisms

A number of bacterial pathogens have emerged demonstrating increased resistance to common, or more worrisome, many classes of antibiotics. The emergence of resistance complicates treatment of infections due to these pathogens, made all the more difficult in patients with underlying immune-compromising conditions. With the dwindling availability of effective antibiotic therapy, prevention of infection is paramount. Reducing the transmission of antibiotic-resistant bacteria is not necessarily different from that of other bacterial pathogens. Attention is focused on these antibiotic-resistant organisms because of their propensity to cause infection, their associated morbidity and mortality, and limited therapeutic options should infection be established.

Staphylococci remain the most common single bacterial cause of HAIs. The past two decades have seen an emergence of resistant staphylococci, namely methicillin-resistant *Staphylococcus aureus* (MRSA) [18–27]. A report by the CDC estimated that nearly 100,000 persons annually experience infections caused by MRSA. Infections due to MRSA vary from superficial carbuncles to life-threatening bloodstream infections, device-associated infections, and necrotizing pneumonia. Data have emerged demonstrating that infection with MRSA is associated with an increased mortality compared with an infection with a non-MRSA strain of *S. aureus*. Cosgrove et al. [28] conducted a meta-analysis demonstrating an increased odds of death (Odds Ratio OR 1.93, 95 % CI: 1.54–2.42) among patients with bloodstream infections from MRSA compared with patients with bloodstream infections due to methicillin-susceptible *S. aureus*.

Developing effective strategies to reduce transmission of MRSA remains a challenge. Much attention has focused on efforts to screen patients who may be harboring (i.e., colonized with) MRSA. This strategy, known as active surveillance culturing (ASC), has been reported to be beneficial in reducing infections from MRSA in selected populations [26]. However, other data have demonstrated that ASC is not useful in combination with several other infection control-based interventions in reducing infections due to MRSA or MRSA transmission [27].

Unless future data demonstrate conclusively that screening all patients for MRSA is associated with reduced transmission of and reduced infections due to MRSA, an approach targeted at a variety of pathogens seems most reasonable. For institutions that do well with other infection prevention and control activities (i.e., hand hygiene, adherence to isolation practices), yet still have high rates of infection due to MRSA, implementation of a screening program targeted at patient populations with the greatest risk and/or burden of infection may prove beneficial in assisting in the control of infections caused by MRSA.

*Enterococcus* species [29–38] are gram-positive bacteria related to the *Streptococcus* species. These bacteria have plagued healthcare institutions for years and have generated much interest among clinicians caring for immune-compromised patients due to the frequency of infections caused by these organisms as well as the associated morbidity and mortality. The basic tenets of infection prevention, an emphasis on hand hygiene, early isolation, and antimicrobial stewardship apply to this organism just as they do for other antibiotic-resistant pathogens.

Whereas MRSA is associated with increased mortality when compared with methicillin-susceptible *S. aureus* infection, data are less clear that VRE is associated with increased mortality when compared with vancomycin-susceptible enterococci. Risk factors for VRE [29, 34, 39–50] have been well described and most notably include an underlying hematologic malignancy, neutropenia, invasive device use, and prior antimicrobial therapy, of which vancomycin is the most consistently identified antibiotic associated with an independent risk for either colonization or infection.

Once either colonized or infected, however, whether VRE is an independent risk factor for death is less clear. Experience with VRE bloodstream infections (BSI) in an HSCT unit [51] found that 13 % of patients colonized with VRE

subsequently developed VRE BSI. The majority of these patients had acute leukemia. On multivariate analysis, the authors found that VRE BSI was not an independent risk factor for death and suggested the presence of VRE BSI is more a marker for severity of underlying illness. Similar findings were noted in another study of VRE BSI by Han et al. [52]. In contrast, a meta-analysis [53] demonstrated that vancomycin resistance is associated with increased mortality when compared with vancomycin-susceptible enterococci causing BSI (OR 2.52, 95 % CI: 1.9–3.4). In neutropenic patients, prolonged bacteremia may be a possible explanation [54].

Prevention of infection, then, becomes ever more important. Screening of patients is a strategy employed by many institutions to determine whether colonization is present. Patients with positive screening cultures are subsequently isolated in an effort to reduce transmission of bacteria to other patients. Culturing the perirectal region of patients for the presence of VRE is a strategy performed by many institutions. The goal of screening patients is twofold: first, to initiate isolation precautions to minimize the risk of transmission of bacteria to other patients and second, to identify carriage in the event, empirical antimicrobial therapy must be used for subsequent infection—a common occurrence among immune-suppressed patients. Weinstock et al. [55] followed 92 patients who were screened for VRE stool colonization at the time of admission for allogeneic HSCT (alloHSCT). Colonization with VRE was common (40.2 % of patients) and 34.2 % of patients with positive VRE screens on admission later developed BSI, whereas 1.8 % without initial VRE positive screens subsequently developed VRE BSI. Thus, for patients where stool culture is obtained for VRE and it is positive, subsequent empirical therapy for BSI should include adequate activity against VRE. Though screening for VRE in high-risk populations has also been associated with an overall decreased incidence of VRE-related infection in medical and surgical intensive care units [56], routinely screening all patients is not recommended [13]. If, however, standard infection prevention methods are not associated with control of healthcare-associated VRE infections, the addition of active screening programs targeted to the appropriate population should be considered. Such screening programs, though, must not supplant ongoing and more well-established infection prevention and control initiatives. Though much interest has been directed toward the gram-positive organisms, MRSA and VRE, many experts believe a more concerning situation exists with multidrug-resistant gram-negative pathogens. A variety of difficulty to treat gram-negative bacteria has emerged over the past decade. Currently, *Klebsiella pneumoniae, Eshershicia coli, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* appear to be the primary gram-negative organisms exhibiting the most troublesome resistance trends. These range from the previously known extended-spectrum beta-lactamase (ESBL)-producing pathogens to the newly emerged carbapenem-resistant *Enterobacteriacae* (CRE). Several recent reviews detail the changing epidemiology of these antibiotic-resistant bacteria [57–61]. Perhaps most disturbing is the emergence of CRE, which exhibit resistance to the carbapenem class of antibiotics, long considered the agents of choice for resistant gram-negative bacteria. More concerning is that these bacteria

are frequently accompanied by resistance to many, if not all, other classes of antibiotics.

Outcomes associated with infections due to the resistant gram-negative organisms are difficult to ascertain. Several studies have reported increased attributable mortality [62–68]. However, other studies have not been able to demonstrate a specific impact of the multidrug resistance on mortality [69–71]. The difficulty in ascertaining outcomes associated with gram-negative resistance is likely due to several factors. First, unlike the gram-positive organisms, where resistance is typically manifested against one class of antibiotic (e.g., methicillin or vancomycin for MRSA and VRE, respectively), the gram-negative organisms demonstrate complex and variable resistance profiles. Second, these pathogens appear to be more common among severely ill patients who are often hospitalized for prolonged periods of time and discerning the impact of one variable (resistance) from potentially hundreds of factors that may contribute to death is extraordinarily difficult. Next, related to the first, there is not an accepted standard definition for what comprises "multidrug resistance," and the heterogeneity of definitions has made interpretation and investigation of the effect of multidrug resistance elusive. Finally, it has been demonstrated that initial antimicrobial therapy ineffective against the causative pathogen is associated with poorer outcomes, even if appropriate therapy is initiated once susceptibilities are known [72–74]. With complex resistance patterns often demonstrated by these multidrug-resistant gram-negative pathogens, there is a greater risk of not choosing an effective empirical antimicrobial agent, and the poor outcomes observed in these patients may be more reflective of inappropriate antimicrobial choice rather than the a specific effect of resistance.

From an infection control and prevention perspective, there is no difference in the management of the patients infected or colonized with these pathogens. Patients harboring ESBL-producing organisms have long been recommended to have contact precautions used [6, 13]. The same principles apply to these pathogens as they do for others (i.e., MRSA, VRE). The use of active screening cultures to identify patients that may be colonized with multidrug-resistant gram-negative bacteria has not proven to be beneficial [75–77]. Emphasis on hand hygiene along with initiation of contact precautions for patients who are either colonized or infected is recommended. No specific guidance has been offered as to when patients can have contact precautions discontinued, though most experts suggest maintaining contact precautions at least until hospital discharge [13].

## 7 Other Organisms of Epidemiological Importance

*C. difficile* is a gram-positive, spore-forming organism that has been well described to be a common cause of intestinal infection among hospitalized patients [78, 79]. *C. difficile* is spread by direct or indirect contact with a patient or the environment of a patient who is either colonized or infected [80–89]. A variety of risk factors for disease have been described and include prior use of antibiotics, advanced age,

prolonged hospital stay, and severe underlying disease [90–92]. Persons with underlying malignancy may be especially at risk given their compromised immune status. Receipt of chemotherapy has been associated with an increased risk of developing diarrhea with a toxigenic *C. difficile* strain (OR 6, [95 % CI: 1.51–23.8] [93]. The use of interleukin-2, either during the index hospitalization or within 30 days of admission, has also been demonstrated to be associated with a greater risk of *C. difficile* infection [94]. The past decade has seen the emergence of a new strain of *C. difficile* [95–97]. When considering previously described strains of *C. difficile*, this newly described strain has increased virulence, increased toxin production, increased spore formation, and resistance to the fluoroquinolone antibiotics. While these factors may cause more severe clinical presentations, there are no data to suggest that control of infections due this new *C. difficile* strain requires an approach different from that of traditional control mechanisms for *C. difficile.*

Patients with suspected or confirmed infection with *C. difficile* should be placed in contact precautions. The use of gowns and gloves serves as a barrier to minimize the HCWs hands and clothing contamination. Empiric isolation of patients with diarrhea is a strategy that may help mitigate the transmission of *C. difficile* within an institution. A more targeted approach may be to empirically isolate those patients with a prior known history of *C. difficile* infection given that, as Boone et al. [98] described, 15 % of patients readmitted within 6 months of being diagnosed with *C. difficile* infection continued to test positive for toxigenic strains of *C. difficile.* The use of infection control measures (empiric isolation of patients with diarrhea, gowns, gloves, hand hygiene with soap/water) has been demonstrated to be effective in terminating transmission of *C. difficile* [64] infections, including among patients with leukemia [99, 100]. As described before, the spores of *C. difficile* are not inactivated by alcohol-based hand-rubs. Therefore, the use of soap and water is recommended for hand hygiene after contact in order to remove the spores from the hands, particularly in outbreak settings.

Aspergillosis is caused by a variety of *Aspergillus* species. The typical person inhales *Aspergillus* spores regularly, yet invasive aspergillosis is rare and typically seen only among those with severe immune suppression. Thus, control of *Aspergillus* is of primary concern among patients with severely impaired immune function, such as HSCT patients. Other patients, namely solid-organ transplant patients and those with acute leukemia undergoing induction chemotherapy, also appear to have increased risk for invasive aspergillosis. The control of *Aspergillus* spores begins with healthcare facility construction. To minimize the risk of mold exposure to patients, rooms with false ceilings should be avoided since these areas may serve as a reservoir for dust and various molds to accumulate. If false ceilings are present, ensuring a mechanism for routine cleaning and vacuuming is necessary to minimize the exposure risk. Rooms for patients undergoing HSCT should have HEPA filtration of the incoming air, and the air pressure in the room should be positive in relation to the corridor. The positive pressure allows air to be moved from within the room to outside the room, minimizing the risk of drawing in airborne infectious material, such as *Aspergillus* spores [6, 17, 101].

However, as healthcare facilities continue to experience construction and renovation, it becomes essential to ensure that before any construction begins, an infection control risk assessment (ICRA) is completed. The ICRA is designed to evaluate the type of construction that is planned and to determine whether there may be a potential risk for exposing patients to infectious agents, namely *Aspergillus* spores [17, 102]. While aspergillosis is commonly cited to be associated with hospital construction [103–105], one matched case–control study among renal transplant recipients found that an average daily dose of corticosteroid use equivalent to 1.25 mg/kg per day of prednisone was predictive of subsequent invasive aspergillosis [106]. Control of dust during construction or renovation generally involves erecting airtight barriers between the construction area(s) and patient care area(s). Ensuring a facility-wide systematic approach to evaluate construction projects, no matter how minor or trivial they may seem, is critically important to minimize the dissemination of *Aspergillus* spores, especially in areas where immune-suppressed patients are housed. Should a patient develop invasive aspergillosis while hospitalized full epidemiologic evaluation should be undertaken in an effort to evaluate for an environmental source.

Legionellosis, caused by *Legionella* species of bacteria, most commonly presents as pneumonia and has been well described to occur within healthcare institutions, including among immune-suppressed patients [107]. Outbreaks are typically associated with a contaminated water source such as a decorative fountain [107], common water supply [108–111], and cooling towers [112]. Therefore, the finding of even one healthcare-associated *Legionella* infection should prompt an investigation into a potentially contaminated water source [102]. Control measures for *Legionella* are many and varied and most have achieved inconsistent results [113]. For patients in protective environments or transplant units, the CDC recommends that heated water temperatures be maintained >123 °F (>50 °C) and cold water <68 °F (<20 °C). Alternately, heated water may be chlorinated to achieve 1–2 mg/L of free residual chlorine measured at the tap. Periodic culturing for *Legionellae* may also be performed though is not specifically recommended, as there is little guidance for the optimal culturing methodology. Showerheads in patient rooms or in inpatient care areas should be disinfected monthly using a chlorine-based cleaning solution. Use of humidifiers should be avoided as these may create aerosols increasing the risk of legionellosis. If the use of a humidifier is unavoidable, high-level disinfection should occur and only sterile water should be used.

Because of the epidemiologic importance of healthcare-associated legionellosis, an epidemiologic investigation should occur if even a single case of nosocomial *Legionella* is identified. Reporting to the local or state health department may be required in some jurisdictions. Investigation of healthcare-associated legionellosis will necessarily involve some form of environmental culturing. Sampling methods for obtaining reliable environmental cultures present unique challenges, and the resources, especially when attempting to identify fastidious pathogens such as *Legionella*, may not be readily available. Molecular typing of identified isolates

from suspected patients, and also the environment is useful to identify a water source responsible for patient infection.

Finally, various respiratory viral pathogens, such as respiratory syncytial virus (RSV) and influenza, can cause HAIs in the immune-compromised patient. While transmission of these pathogens may differ (i.e., RSV is spread primarily via direct contact, while influenza is spread mainly by respiratory droplets), control of febrile respiratory infections (FRI) due to these pathogens occurs through several core infection control practices. Patients with FRI should be identified upon entry to a healthcare facility. Such patients can then be cohorted from other noninfected patients and placed into appropriate isolation precautions. Strict adherence to hand hygiene, use of PPE, restriction of ill visitors and healthcare workers, and source control of the infected patient (such as having the patient wear a surgical mask when in public areas) are all important infection control measures [6].

For some respiratory pathogens, particularly influenza, vaccination remains a cornerstone of efforts to prevent nosocomial FRI. Healthcare workers are recommended as a target group for influenza vaccination due to their close contact with patients at high risk for complications of influenza [114]. Many healthy healthcare workers may become infected with influenza yet have no or minimal symptoms. These persons can still shed and spread influenza virus to their patients. In addition, in the 24 h prior to development of classic influenza symptoms (i.e., myalgias, high fevers, cough, fatigue), infected persons can shed virus. Studies have shown that influenza vaccination of healthcare workers reduces laboratory-confirmed influenza, sick days due to respiratory illness, and days lost from work [115]. Perhaps most striking are findings in several studies in long-term care facilities that demonstrate that vaccination of healthcare workers significantly reduced the mortality of their patients [116–119]. Despite the benefits of healthcare worker influenza vaccination, coverage rates of healthcare workers remain unacceptably low at approximately 65 %. Because of these low rates, several medical centers and hospitals have moved to requiring influenza vaccination as a condition of employment for healthcare workers [120]. Whatever the strategy utilized, increasing healthcare worker influenza vaccination rates is important to protect patients from healthcare-associated infections.

## 8 Essential Elements of a Successful Infection Control and Prevention Program

Essential for discovery of HAIs and developing processes to prevent infection is a strong infection prevention, control, and epidemiology program. Critical to the success of any program are highly trained nurses specially trained in infection prevention, control, and hospital epidemiology—infection preventionists (IP). The CDC recommends a staffing ratio of 1 full-time equivalent (FTE) IP for the first 100 beds of a hospital to 1 FTE IP for every additional 250 beds [121, 122]. The basis for this recommendation is the Study on the Efficacy of Nosocomial Infection

Control (SENIC) Project [123], sponsored by the CDC in the 1970s and the Delphi project [124] which recommended a staffing ratio 0.8–1 IP for every 100 occupied beds. The investigators of the SENIC Project, for the first time, provided evidence supporting the link between an established infection control and prevention program and fewer HAIs. The role of the IP has undergone substantial changes since the original SENIC Project, from initially gathering data and reporting infection rates to now requiring an understanding of process improvement, data analysis, transmission of infectious diseases, and epidemiology, to name a few. With the complexities of infection prevention and control along with the specialized knowledge necessary to implement and maintain a successful prevention program, formal certification in the specialty is available. All institutions, though especially those where care for severely immune-compromised patients is delivered, should have at least one certified IP leading the program of infection prevention.

Another important element of successful infection prevention and control programs is the use of standardized definitions, such as those provided by the CDC [125], for determining HAIs. The universal application of validated, standardized definitions for surveillance of HAIs provides several advantages. First, there is less variability in what is deemed an infection, and second, the use of standardized definitions allows for tracking trends over time. Institutional data on infection rates are most helpful for that specific institution in order to determine how successful a program is at reducing HAIs. Next, the use of standard definitions allows for data to be aggregated from multiple institutions to develop mean and median rates of specific types of infections. Only if definitions are applied in a consistent manner throughout multiple institutions is the development of such statistical "benchmarks" possible. Such benchmarks, then, allow institutions to develop an understanding of their specific HAIs and which types may be either significantly above or below that of other institutions, thus serving to direct resources where most appropriate. The CDC publishes aggregated infection rate data by infection type and care location annually [126]. These data are helpful to help understand how hospitals compare to one another and where there may be opportunities for improvement.

By directing appropriate resources to infection prevention programs and ensuring that these programs are staffed with specially trained infection preventionists and epidemiologists, healthcare institutions can substantially mitigate HAIs. Though achieving a rate of zero infections may not be possible, especially among severely immune-suppressed patients, the goal of having zero *preventable* infections is possible and is recommended to be the goal of all healthcare institutions. Focusing on effective prevention initiatives such as active surveillance for HAIs, minimizing exposure hazards (i.e., mold from construction, poorly maintained water sources), ensuring appropriate isolation of patients, and hand hygiene adherence will serve to provide a safe environment for the care of the immune-suppressed patient, as well as all other patients.

## References


1. CDC (1992) The nation's prevention agency. MMWR Morb Mortal Wkly Rep 41(44):833
2. Hugonnet S, Pittet D (2000) Hand hygiene-beliefs or science? Clin Microbiol Infect 6(7):350–356
3. Talbot TR et al (2013) Sustained improvement in hand hygiene adherence: utilizing shared accountability and financial incentives. Infect Control Hosp Epidemiol 34(11):1129–1136
4. Schneider J et al (2009) Hand hygiene adherence is influenced by the behavior of role models. Pediatr Crit Care Med 10(3):360–363
5. Lankford MG et al (2003) Influence of role models and hospital design on hand hygiene of healthcare workers. Emerg Infect Dis 9(2):217–223
6. Siegel JD et al (2007) Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 35(10(2)):S65–S164
7. Use of Surgical Masks and Respirators in Health Care Settings (2010) Oct 2006 (cited 26 Apr 2010). Available from www.pandemicflu.gov/professional/hospital/maskguidancehc.html
8. Bean B, Braun C, Balfour HH Jr (1982) Acyclovir therapy for acute herpes zoster. Lancet 2(8290):118–121
9. Leclair JM et al (1980) Airborne transmission of chickenpox in a hospital. N Engl J Med 302(8):450–453
10. Papineni RS, Rosenthal FS (1997) The size distribution of droplets in the exhaled breath of healthy human subjects. J Aerosol Med 10(2):105–116
11. Feigin RD et al (1982) Epidemic meningococcal disease in an elementary-school classroom. N Engl J Med 307(20):1255–1257
12. Dick EC et al (1987) Aerosol transmission of rhinovirus colds. J Infect Dis 156(3):442–448
13. Siegel JD et al (2007) Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control 35(10(2)):S165–S193
14. Moody K, Charlson ME, Finlay J (2002) The neutropenic diet: what's the evidence? J Pediatr Hematol Oncol 24(9):717–721
15. Pizzo PA, Purvis DS, Waters C (1982) Microbiological evaluation of food items. For patients undergoing gastrointestinal decontamination and protected isolation. J Am Diet Assoc 81(3):272–279
16. Schlesinger A et al (2009) Infection-control interventions for cancer patients after chemotherapy: a systematic review and meta-analysis. Lancet Infect Dis 9(2):97–107
17. Dykewicz CA, Jaffe HW, Kaplan JE (2000) Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 49(RR-10):1–125, CE 1–7
18. Supriya M et al (2009) Controlling MRSA in head and neck cancer patients: what works? Otolaryngol Head Neck Surg 140(2):224–227
19. Reitzel RA et al (2009) Efficacy of novel antimicrobial gloves impregnated with antiseptic dyes in preventing the adherence of multidrug-resistant nosocomial pathogens. Am J Infect Control 37(4):294–300 (Epub 19 Jan 2009)
20. Wenzel RP, Bearman G, Edmond MB (2008) Screening for MRSA: a flawed hospital infection control intervention. Infect Control Hosp Epidemiol 29(11):1012–1018
22. Wang FD et al (2008) Risk factors and mortality in patients with nosocomial *Staphylococcus aureus* bacteremia. Am J Infect Control 36(2):118–122
22. Rogers SN et al (2008) Which patients are most at risk of methicillin resistant *Staphylococcus aureus*: a review of admissions to a regional maxillofacial ward between 2001 and 2005. Br J Oral Maxillofac Surg 46(6):439–444
23. Hidron AI et al (2008) NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol 29(11):996–1011

24. Miyake M et al (2007) Risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) and use of a nasal mupirocin ointment in oral cancer inpatients. J Oral Maxillofac Surg 65(11):2159–2163
25. Scudeller L et al (2000) MRSA carriage: the relationship between community and healthcare setting. A study in an Italian hospital. J Hosp Infect 46(3):222–229
26. Robicsek A et al (2008) Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. Ann Intern Med 148(6):409–418
27. Harbarth S et al (2008) Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. JAMA 299(10):1149–1157
28. Cosgrove SE et al (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis 36(1):53–59
29. Worth LJ et al (2007) Vancomycin-resistant Enterococcus faecium infection in patients with hematologic malignancy: patients with acute myeloid leukemia are at high-risk. Eur J Haematol 79(3):226–233
30. Huang SS et al (2007) Improving the assessment of vancomycin-resistant enterococci by routine screening. J Infect Dis 195(3):339–346
31. Matar MJ et al (2006) Colonization and infection with vancomycin-resistant Enterococcus among patients with cancer. Am J Infect Control 34(8):534–536
32. Knoll M et al (2005) Outbreak of vancomycin-resistant enterococci (VRE) in a hematological oncology ward and hygienic preventive measures. A long-term study. Onkologie 28(4):187–192
33. Oh HS et al (2004) Outbreak of vancomycin resistant Enterococcus in a hematology/oncology unit in a Korean University Hospital, and risk factors related to patients, staff, hospital care and facilities. Scand J Infect Dis 36(11–12):790–794
34. Husni R et al (2002) Risk factors for vancomycin-resistant *Enterococcus* (VRE) infection in colonized patients with cancer. Infect Control Hosp Epidemiol 23(2):102–103
35. Hanna H et al (2001) Management of an outbreak of vancomycin-resistant *Enterococci* in the medical intensive care unit of a cancer center. Infect Control Hosp Epidemiol 22(4):217–219
36. McCarthy KM et al (2000) Control of an outbreak of vancomycin-resistant *Enterococcus faecium* in an oncology ward in South Africa: effective use of limited resources. J Hosp Infect 44(4):294–300
37. Kuehnert MJ et al (1999) Association between mucositis severity and vancomycin-resistant enterococcal bloodstream infection in hospitalized cancer patients. Infect Control Hosp Epidemiol 20(10):660–663
38. Roord JJ et al (1986) Infection prevention during induction of remission in children with newly diagnosed acute leukemia. Ann Ist Super Sanita 22(3):973–977
39. Olivier CN et al (2008) Risk of vancomycin-resistant *Enterococcus* (VRE) bloodstream infection among patients colonized with VRE. Infect Control Hosp Epidemiol 29(5):404–409
40. Fuller RE et al (1998) Vancomycin-resistant enterococci: risk related to the use of intravenous vancomycin in a university hospital. Infect Control Hosp Epidemiol 19(11):821–823
41. Sakka V et al (2008) Risk-factors and predictors of mortality in patients colonised with vancomycin-resistant enterococci. Clin Microbiol Infect 14(1):14–21
42. Dan M et al (1999) Rectal colonization with vancomycin-resistant enterococci among high-risk patients in an Israeli hospital. J Hosp Infect 43(3):231–238
43. Beltrami EM et al (2000) Risk factors for acquisition of vancomycin-resistant enterococci among patients on a renal ward during a community hospital outbreak. Am J Infect Control 28(4):282–285

44. MacIntyre CR et al (2001) Risk factors for colonization with vancomycin-resistant enterococci in a Melbourne hospital. Infect Control Hosp Epidemiol 22(10):624–629
45. Zaas AK et al (2002) Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. Clin Infect Dis 35(10):1139–1146
46. Martinez JA et al (2003) Role of environmental contamination as a risk factor for acquisition of vancomycin-resistant enterococci in patients treated in a medical intensive care unit. Arch Intern Med 163(16):1905–1912
47. Padiglione AA et al (2003) Risk factors for new detection of vancomycin-resistant enterococci in acute-care hospitals that employ strict infection control procedures. Antimicrob Agents Chemother 47(8):2492–2498
48. McEvoy SP et al (2006) Risk factors for the acquisition of vancomycin-resistant enterococci during a single-strain outbreak at a major Australian teaching hospital. J Hosp Infect 62(2):256–258
49. Assadian O et al (2007) Prevalence of vancomycin-resistant enterococci colonization and its risk factors in chronic hemodialysis patients in Shiraz. Iran BMC Infect Dis 7:52
50. Askarian M et al (2008) Risk factors for rectal colonization with vancomycin-resistant enterococci in Shiraz. Iran Int J Infect Dis 12(2):171–175
51. Dubberke ER et al (2006) Vancomycin-resistant enterococcal bloodstream infections on a hematopoietic stem cell transplant unit: are the sick getting sicker? Bone Marrow Transplant 38(12):813–819
52. Han SH et al (2009) Vancomycin-resistant enterococci bacteremia: risk factors for mortality and influence of antimicrobial therapy on clinical outcome. J Infect 58(3):182–190
53. DiazGranados CA et al (2005) Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. Clin Infect Dis 41(3):327–333
54. DiazGranados CA, Jernigan JA (2005) Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis 191(4):588–595
55. Weinstock DM et al (2007) Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. Biol Blood Marrow Transplant 13(5):615–621
56. Siddiqui AH et al (2002) The effect of active surveillance for vancomycin-resistant enterococci in high-risk units on vancomycin-resistant enterococci incidence hospital-wide. Am J Infect Control 30(1):40–43
57. Livermore DM (2009) Has the era of untreatable infections arrived? J Antimicrob Chemother 64(1):i29–i36
58. Hawkey PM, Jones AM (2009) The changing epidemiology of resistance. J Antimicrob Chemother 64(1):i3–i10
59. Gould IM (2008) The epidemiology of antibiotic resistance. Int J Antimicrob Agents 32(1):S2–S9
60. Septimus EJ, Kuper KM (2009) Clinical challenges in addressing resistance to antimicrobial drugs in the twenty-first century. Clin Pharmacol Ther 86(3):336–339
61. Walsh TR (2008) Clinically significant carbapenemases: an update. Curr Opin Infect Dis 21(4):367–371
62. Falagas ME, Bliziotis IA (2006) Attributable mortality of *Acinetobacter baumannii* infections in critically ill patients: a systematic review of matched cohort and case-control studies. Crit Care 10(2):R48
63. Falagas ME et al (2009) Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. Future Microbiol 4:1103–1109
64. Falagas ME, Kopterides P, Siempos II (2006) Attributable mortality of *Acinetobacter baumannii* infection among critically ill patients. Clin Infect Dis 43(3):389; author reply 389–390

65. Furtado GH et al (2009) Imipenem-resistant *Pseudomonas aeruginosa* infection at a medical-surgical intensive care unit: Risk factors and mortality. J Crit Care 24(4):625 (epub 9 Jul 2009, e9–e14)
66. Hakki M et al (2007) Invasive *Pseudomonas aeruginosa* infections: high rate of recurrence and mortality after hematopoietic cell transplantation. Bone Marrow Transplant 39(11):687–693
67. Krcmery V Jr et al (1998) Bacteremia due to multiresistant gram-negative bacilli in neutropenic cancer patients: a case controlled study. J Chemother 10(4):320–325
68. Zavascki AP et al (2006) The influence of metallo-beta-lactamase production on mortality in nosocomial *Pseudomonas aeruginosa* infections. J Antimicrob Chemother 58(2):387–392
69. Zavascki AP et al (2006) Reappraisal of *Pseudomonas aeruginosa* hospital-acquired pneumonia mortality in the era of metallo-beta-lactamase-mediated multidrug resistance: a prospective observational study. Crit Care 10(4):R114
70. Daniels TL et al (2008) Mortality rates associated with multidrug-resistant *Acinetobacter baumannii* infection in surgical intensive care units. Infect Control Hosp Epidemiol 29(11):1080–1083
71. Sunenshine RH et al (2007) Multidrug-resistant Acinetobacter infection mortality rate and length of hospitalization. Emerg Infect Dis 13(1):97–103
72. Morrell M, Fraser VJ, Kollef MH (2005) Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 49(9):3640–3645
73. Lodise TP Jr et al (2007) Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother 51(10):3510–3515
74. Kollef MH et al (1999) Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 115(2):462–474
75. Reddy P et al (2007) Screening for extended-spectrum beta-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. Clin Infect Dis 45(7):846–852
76. Santos RP, Mayo TW, Siegel JD (2008) Healthcare epidemiology: active surveillance cultures and contact precautions for control of multidrug-resistant organisms: ethical considerations. Clin Infect Dis 47(1):110–116
77. Maragakis LL et al (2008) Incidence and prevalence of multidrug-resistant acinetobacter using targeted active surveillance cultures. JAMA 299(21):2513–2514
78. Bartlett JG et al (1978) Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med 298(10):531–534
79. Johnson S et al (1990) Nosocomial *Clostridium difficile* colonisation and disease. Lancet 336(8707):97–100
80. Kuijper EJ et al (2001) Nosocomial outbreak of *Clostridium difficile*-associated diarrhoea due to a clindamycin-resistant enterotoxin A-negative strain. Eur J Clin Microbiol Infect Dis 20(8):528–534
81. Muto CA et al (2005) A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 26(3):273–280
82. Mekonen ET et al (2002) Predominance of a single restriction endonuclease analysis group with intrahospital subgroup diversity among *Clostridium difficile* isolates at two Chicago hospitals. Infect Control Hosp Epidemiol 23(11):648–652
83. Manian FA, Meyer L, Jenne J (1996) Clostridium difficile contamination of blood pressure cuffs: a call for a closer look at gloving practices in the era of universal precautions. Infect Control Hosp Epidemiol 17(3):180–182
84. Kaatz GW et al (1988) Acquisition of *Clostridium difficile* from the hospital environment. Am J Epidemiol 127(6):1289–1294

85. Brooks S et al (1998) Reduction in vancomycin-resistant *Enterococcus* and *Clostridium difficile* infections following change to tympanic thermometers. Infect Control Hosp Epidemiol 19(5):333–336
86. Gaynes R et al (2004) Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis 38(5):640–645
87. Komatsu M et al (2003) High frequency of antibiotic-associated diarrhea due to toxin A-negative, toxin B-positive *Clostridium difficile* in a hospital in Japan and risk factors for infection. Eur J Clin Microbiol Infect Dis 22(9):525–529
88. Pulvirenti JJ et al (2002) Difference in the incidence of *Clostridium difficile* among patients infected with human immunodeficiency virus admitted to a public hospital and a private hospital. Infect Control Hosp Epidemiol 23(11):641–647
89. Talon D et al (1995) Use of pulsed-field gel electrophoresis for investigation of an outbreak of *Clostridium difficile* infection among geriatric patients. Eur J Clin Microbiol Infect Dis 14(11):987–993
90. McFarland LV, Surawicz CM, Stamm WE (1990) Risk factors for Clostridium difficile carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. J Infect Dis 162(3):678–684
91. Brown E et al (1990) Risk factors for *Clostridium difficile* toxin-associated diarrhea. Infect Control Hosp Epidemiol 11(6):283–290
92. Safdar N, Maki DG (2002) The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, *Enterococcus*, gram-negative bacilli, *Clostridium difficile*, and *Candida*. Ann Intern Med 136(11):834–844
93. Blot E et al (2003) Outbreak of *Clostridium difficile*-related diarrhoea in an adult oncology unit: risk factors and microbiological characteristics. J Hosp Infect 53(3):187–192
94. Gifford AH, Kirkland KB (2006) Risk factors for *Clostridium difficile*-associated diarrhea on an adult hematology-oncology ward. Eur J Clin Microbiol Infect Dis 25(12):751–755
95. McDonald LC et al (2005) An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 353(23):2433–2441
96. Warny M et al (2005) Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet 366(9491):1079–1084
97. Kuijper EJ et al (2008) Update of *Clostridium difficile* infection due to PCR ribotype 027 in Europe. Euro Surveill 13(31)
98. Boone N et al (1998) Evaluation of an interdisciplinary re-isolation policy for patients with previous *Clostridium difficile* diarrhea. Am J Infect Control 26(6):584–587
99. Hanna H et al (2000) Control of nosocomial *Clostridium difficile* transmission in bone marrow transplant patients. Infect Control Hosp Epidemiol 21(3):226–228
100. Delmee M et al (1987) Epidemiology and prevention of *Clostridium difficile* infections in a leukemia unit. Eur J Clin Microbiol 6(6):623–627
101. Sherertz RJ et al (1987) Impact of air filtration on nosocomial *Aspergillus* infections. Unique risk of bone marrow transplant recipients. Am J Med 83(4):709–718
102. Sehulster L, Chinn RY (2003) Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 52(RR-10):1–42
103. Haiduven D (2009) Nosocomial aspergillosis and building construction. Med Mycol 47(1):S210–S216
104. Maschmeyer G, Haas A, Cornely OA (2007) Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 67(11):1567–1601
105. Carter CD, Barr BA (1997) Infection control issues in construction and renovation. Infect Control Hosp Epidemiol 18(8):587–596
106. Gustafson TL et al (1983) Invasive aspergillosis in renal transplant recipients: correlation with corticosteroid therapy. J Infect Dis 148(2):230–238

107. Palmore TN et al (2009) A cluster of cases of nosocomial legionnaires disease linked to a contaminated hospital decorative water fountain. Infect Control Hosp Epidemiol 30(8):764–768
108. Meletis J et al (1987) Legionnaires' disease after bone marrow transplantation. Bone Marrow Transplant 2(3):307–313
109. Parry MF et al (1985) Waterborne *Legionella bozemanii* and nosocomial pneumonia in immunosuppressed patients. Ann Intern Med 103(2):205–210
110. Neill MA et al (1985) Nosocomial legionellosis, Paris, France. Evidence for transmission by potable water. Am J Med 78(4):581–588
111. Arnow PM et al (1982) Nosocomial Legionnaires' disease caused by aerosolized tap water from respiratory devices. J Infect Dis 146(4):460–467
112. Garbe PL et al (1985) Nosocomial Legionnaires' disease. Epidemiologic demonstration of cooling towers as a source. JAMA 254(4):521–524
113. Levin AS (2009) Nosocomial legionellosis: prevention and management. Expert Rev Anti Infect Ther 7(1):57–68
114. Fiore AE et al (2009) Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 58(RR-8):1–52
115. Talbot TR et al (2005) Influenza vaccination of healthcare workers and vaccine allocation for healthcare workers during vaccine shortages. Infect Control Hosp Epidemiol 26(11):882–890
116. Lemaitre M et al (2009) Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc 57(9):1580–1586
117. Hayward AC et al (2006) Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ 333(7581):1241
118. Carman WF et al (2000) Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 355(9198):93–97
119. Potter J et al (1997) Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis 175(1):1–6
120. Babcock HM et al (2009) Mandatory influenza vaccination: translating policy to practice, in Society for Healthcare Epidemiology of America 19th annual scientific meeting. San Diego, CA
121. Stone PW et al (2009) Staffing and structure of infection prevention and control programs. Am J Infect Control 37(5):351–357
122. Richards C et al (2001) Characteristics of hospitals and infection control professionals participating in the National Nosocomial Infections Surveillance System 1999. Am J Infect Control 29(6):400–403
123. Haley RW et al (1980) The SENIC Project. Study on the efficacy of nosocomial infection control (SENIC Project). Summary of study design. Am J Epidemiol 111(5):472–485
124. O'Boyle C, Jackson M, Henly SJ (2002) Staffing requirements for infection control programs in US health care facilities: Delphi project. Am J Infect Control 30(6):321–333
125. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36(5):309–332
126. Edwards JR et al (2008) National Healthcare Safety Network (NHSN) Report, data summary for 2006 through 2007, issued November 2008. Am J Infect Control 36(9):609–626

# Prevention of Infection in Cancer Patients

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**Abstract**

Patients with cancer vary regarding the nature and level of immunocompromise. Both the underlying malignancy and therapy can influence risk of infectious complications. Therefore, decisions about antimicrobial prophylaxis must be guided by a number of factors: (1) the risk of infection; (2) the potential severity of infection and the likelihood of response to therapy; and (3) the safety and efficacy of antimicrobial prophylaxis. The potential for selection for antibiotic-resistant pathogens should also inform decisions about prophylaxis. When assessing clinical trial data on antimicrobial prophylaxis, two major criteria should be considered: the quality of studies supporting prophylaxis (randomized, blinded studies are optimal) and the expected benefit of prophylaxis, measured in terms of prevention of morbidity and potentially mortality. This chapter reviews the epidemiology and clinical trial data on prophylaxis against the major bacterial, viral, and fungal diseases in patients with cancer. Gaps in knowledge and alternative approaches, such as the use of newer diagnostics, are discussed.

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Neutropenia · Transplant · Infections · Prophylaxis · Bacteria · Fungi · Viruses

## Contents



## 1 Risk Factors for Infectious Complications in Patients with Cancer

Patients with cancer comprise a heterogeneous group with regard to risk factors, predisposing to infectious diseases. The malignancy itself may increase the risk of infectious complications. As examples, hematological malignancies (such as myelodysplastic syndrome, leukemias) may result in either global leukopenia or a reduction in functional myeloid and lymphoid cells. Chronic lymphocytic leukemia (CLL) and multiple myeloma are associated with either hypogammaglobulinemia or an inability to produce protective immunoglobulin responses to pathogens, leading to an increased risk of infections by encapsulated bacteria (e.g., *Streptococcus pneumoniae*) [1, 2]. Hodgkin's lymphomas are associated with prolonged T-cell impairment [3]. Human T-cell lymphotropic virus-1 (HTLV-1)-associated leukemias and lymphomas are associated with a high risk of opportunistic infections (e.g., *Pneumocystis jiroveci, Cryptococcus neoformans,* mycobacteria) related to leukopenia and impaired T-cell immunity [4] (Table 1).

Solid tumor malignancies can also increase the risk of infectious complications based on anatomic location. As examples, endobronchial lung tumors can lead to post-obstructive pneumonia and obstructive hepatobiliary and pancreatic tumors, predisposing to cholangitis. Head and neck tumors that become necrotic from overgrowing their blood supply or from radiation therapy can become infected by skin and oral flora. Malnutrition and general debilitation associated with advanced cancer also increase the risk of infections.

**Table 1** Conditions predisposing to infectious complications in patients with cancer

| Patient populations | Major immune deficits | Bacterial infections | Viral infections | Fungal infections | Parasitic infections |
|---|---|---|---|---|---|
| Induction regimens for acute leukemia and myelodysplastic syndrome | Neutropenia and mucosal toxicity | Enterobacteriaceae, *Pseudomonas aeruginosa*, enterococci, viridans group streptococci, *Staphylococcus aureus*, intravenous catheter-related bacterial (e.g., coagulase-negative staphylococci) | Herpes simplex virus (I and II), community respiratory viruses | *Candida* species, *Aspergillus* species (usually when ANC < 100/ul for >10 days), and other molds (e.g., zygomycetes, *Fusarium* species) | |
| Chronic lymphocytic leukemia, multiple myeloma | Hypogammaglobulinemia or ineffective antibody responses | Encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae*, *Neisseria meningitides*) | | | |
| HTLV-1-associated leukemia and lymphoma | Leukopenia and T-cell impairment related to disease and chemotherapy | Infections associated with neutropenia plus T-cell impairment (e.g., *Listeria monocytogenes*, mycobacteria, nocardiosis) | Infections associated with neutropenia plus T-cell impairment (e.g., cytomegalovirus, varicella zoster virus) | Infections associated with neutropenia plus T-cell impairment (e.g., *Pneumocystis jiroveci, Cryptococcus neoformans,* endemic dimorphic fungi, such as histoplasmosis and coccidioidomycosis) | Toxoplasmosis, *Strongyloides* hyperinfection syndrome |

(continued)

**Table 1** (continued)

| Patient populations | Major immune deficits | Bacterial infections | Viral infections | Fungal infections | Parasitic infections |
|---|---|---|---|---|---|
| Acute lymphoblastic leukemia (induction), chronic lymphocytic leukemia (advanced or refractory), central nervous system tumors (treated with high-dose corticosteroids and/or temozolomide) | Depressants of T-cell immunity (e.g., high-dose corticosteroids for >4 weeks, calcineurin inhibitors, TNF-α inhibitors, alemtuzumab, purine analogues such as fludarabine, temozolomide, and T-cell-depleting antibodies) | Common bacterial infections plus those associated with T-cell impairment (e.g., *Listeria monocytogenes*, mycobacteria, nocardiosis) | Herpes simplex virus, varicella zoster virus, community respiratory viruses, Epstein–Barr virus-associated lymphoproliferative disease<br>Alemtuzumab: Cytomegalovirus | *Pneumocystis jiroveci, Cryptococcus neoformans,* endemic dimorphic fungi, such as histoplasmosis and coccidioidomycosis, invasive aspergillosis. Concurrent neutropenia increases the risk of invasive aspergillosis and other mold diseases | Toxoplasmosis, *Strongyloides* hyperinfection syndrome |
| | Asplenia | Encapsulated bacteria | | | |
| Multiple myeloma | Bortezomib | | Varicella zoster virus | | |
| AIDS-associated malignancies | Chemotherapy-induced immunosuppression and T-cell impairment associated with AIDS | Common bacterial infections plus those associated with T-cell impairment (e.g., *Listeria monocytogenes*, mycobacteria, nocardiosis), pneumococcal infections | Herpes simplex virus, varicella zoster virus, community respiratory viruses, cytomegalovirus disease (usually retinitis), Epstein–Barr virus-associated lymphoproliferative disease, progressive multifocal leukoencephalopathy | *Pneumocystis jiroveci, Cryptococcus neoformans,* endemic dimorphic fungi, such as histoplasmosis and coccidioidomycosis, invasive aspergillosis. Concurrent neutropenia increases the risk of invasive aspergillosis and other mold diseases | Toxoplasmosis, *Strongyloides* hyperinfection syndrome |

**Table 2** Infectious complications associated with allogeneic hematopoietic stem cell transplantation

| Time after transplant | Predominant immune impairment | Major infections |
|---|---|---|
| Conditioning to day 30 | Neutropenia, mucositis | Similar to induction regimens for acute leukemia; peripheral blood stem cells and reduced-intensity conditioning may reduce early infectious complications |
| Day 30–100 | T-cell impairment due to lack of reconstitution of T-cell immunity, acute GVHD, immunosuppressive therapy | *Bacteria* Common bacterial infections plus those associated with T-cell impairment (e.g., *Listeria monocytogenes*, mycobacteria, nocardiosis)<br>*Viruses* Cytomegalovirus, herpes simplex virus, varicella zoster virus, community respiratory viruses, Epstein–Barr virus-associated lymphoproliferative disease, HHV-6, progressive multifocal leukoencephalopathy<br>*Fungi* Invasive aspergillosis and other mold diseases, candidiasis, *Pneumocystis jiroveci, Cryptococcus neoformans,* endemic dimorphic fungi, such as histoplasmosis and coccidioidomycosis<br>*Parasites* Toxoplasmosis, Strongyloides hyperinfection syndrome |
| Day 100 to 180 | Deficits in T-cell and B-cell immunity, chronic GVHD, immunosuppressive therapy | Similar to days 30–100; pneumococcal sepsis is more common after day 100 |
| >Day 180 | Deficits in T-cell and B-cell immunity[1] | Grade of chronic GVHD and intensity of immunosuppressive therapy are the major determinants of risk of common and opportunistic infections |

[1]Donor-derived T-cell and B-cell immunity is expected to reconstitute within 2 years after transplant in the absence of chronic GVHD requiring persistent immunosuppression. T-cell-depleted allografts reduce GVHD, but are associated with a significant risk of invasive fungal diseases and cytomegalovirus disease

In addition to infectious complications resulting from the malignancy is the iatrogenic immunosuppression related to therapy for the malignancy (Table 2). Antineoplastic regimens result in different forms of immunosuppression—both quantitatively and qualitatively. Cytotoxic regimens increase the risk of infectious complications in two ways. First is the leukopenia related to chemotherapy- and radiation therapy-induced marrow suppression. Second is the mucosal toxicity that predisposes to infection by gastrointestinal flora. The risk of infectious complications is directly related to the intensity and duration of neutropenia, and the likelihood of recovery from infections is related to the rapidity of neutrophil recovery [5].

Opportunistic infections associated with severe T-cell impairment (e.g., *P. jiroveci*, *C. neoformans*, listeriosis) do not typically occur in patients receiving cytotoxic regimens alone. Rather, these infections occur more commonly in patients receiving prolonged high-dose corticosteroids, lymphocyte-depleting agents (e.g., purine analogues, alemtuzumab, T-cell-depleting antibodies), or a combination of these agents. Multiple risk factors for infectious diseases can exist simultaneously in patients with cancer. For example, standard induction regimens for acute lymphoblastic leukemia include cytotoxic agents and high-dose corticosteroids.

Patients with refractory hematological malignancies are at greater risk for infections than those with cancer in remission both because of the underlying disease and greater exposure to immunosuppressive regimens. CLL provides an illustrative example. Patients with early stage CLL frequently have hypogammaglobulinemia, predisposing to infections by encapsulated bacteria [6]. Although not cost-effective on a routine basis, intravenous immunoglobulin can decrease the incidence of infection by encapsulated bacteria in patients with CLL [7, 8]. Advanced CLL may lead to replacement of normal marrow with leukemic cells and neutropenia, further increasing the risk of infections. Fludarabine-based regimens used to treat CLL lead to prolonged CD4+ T-cell lymphopenia, increasing the risk of shingles (reactivated varicella zoster), listeriosis, and *P. jiroveci* [9, 10]. Alemtuzumab, an anti-CD52 antibody used to treat refractory CLL, leads to prolonged T-cell depletion and can also be complicated by neutropenia. Alemtuzumab increases the risk of bacterial, fungal, and viral infections, including a high frequency of reactivated cytomegalovirus (CMV) infection (detected by serum PCR or CMV antigenemia) and, less commonly, CMV organ disease [11].

In addressing the questions of whether antimicrobial prophylaxis is warranted and which agents are optimal, it is essential to consider the type and level of immunosuppression that exists in the individual patient. Indeed, the majority of patients with solid tumors do not require any antimicrobial prophylaxis. Data from the patient's history regarding prior infections, epidemiological exposures, and prior and anticipated antineoplastic regimens together with evidence-based review of the literature should be used to guide decisions on antimicrobial prophylaxis.

## 1.1 Hematopoietic Stem Cell Transplantation

Autologous hematopoietic stem cell transplantation (HSCT) can be considered a form of intensive chemotherapy. Neutropenia and mucositis following conditioning predispose to bacterial infections and candidemia. Autologous HSCT recipients also have a period of defective T-cell-mediated immunity of variable length, depending on the type of cancer (longer in hematological malignancies [12]), and age (more rapid reconstitution in children) [13]. CD34 enrichment of autografts ("T-cell-depleted" transplant) leads to a significant reduction in T cells, natural killer cells, and monocytes, compared with unmanipulated autografts, delaying immune reconstitution. Recipients of CD34-enriched autografts appear to

be at a similar level of risk as allogeneic HSCT recipients for CMV and other opportunistic infections [14].

The risk of infectious complications is higher in allogeneic compared to autologous HSCT recipients. The spectrum of pathogens to which allogeneic HSCT recipients are most susceptible follows a time line, corresponding to the predominant immune defects [15] (Table 2). In the first month of HSCT, neutropenia is the principal host defense defect, predisposing to bacterial, fungal, and viral (principally herpes simplex virus (HSV) and community-associated respiratory viruses) infections. After myeloid recovery, qualitative dysfunction of phagocytes persists due to corticosteroid and other immunosuppressive agents. Defects in cell-mediated immunity persist for several months even in uncomplicated allogeneic HSCT recipients, predisposing to opportunistic infections, including candidiasis, invasive mold diseases *P. jiroveci*, CMV, and herpes zoster. The intensity of immunosuppressive therapy for graft-versus-host disease (GVHD) is the major predictor of opportunistic fungal and viral infections. In addition, T-cell depletion of allografts to prevent GVHD is associated with a high risk of invasive aspergillosis and CMV disease [16].

Whereas mature and cooperative T- and B-cell functions are usually reconstituted by 1–2 years after engraftment, chronic GVHD is associated with persistently depressed cell-mediated and humoral immunity [17, 18]. Chronic GVHD is the major risk factor for pneumococcal infections, which most frequent occur from day 100 to years after HSCT [19–21].

Antimicrobial prophylaxis in HSCT recipients must be tailored to the nature and severity of immunosuppression. Authoritative guidelines on both antimicrobial prophylaxis and infection control measures to prevent infections in HSCT recipients have been published [22, 23].

## 2 Principles of Antimicrobial Prophylaxis

Decisions regarding antimicrobial prophylaxis can create, "The Doctor's Dilemma," the title of a play by Oscar Wilde. Ridgeon, the protagonist, is a prominent research physician who confronts the subjects of allocation of scarce medical resources as well as medical treatments of dubious value. Although today we have an armamentarium of medical treatments of proven value, the modern physician still faces the dilemma of who should receive prophylactic antimicrobials and at what cost. Cost not only refers to pharmacy acquisition costs, but also encompasses toxicity drug toxicity and selection for antimicrobial-resistant pathogens.

Antimicrobial prophylaxis entails administering an antibiotic to patients who have pre-specified factors that predispose to infection, when only a minority will benefit. For example, consider the scenario of a prophylactic drug that is 80 % effective in reducing the incidence of an infection (e.g., candidemia) expected to occur in 10 % of a specific group of patients (e.g., induction therapy for acute myelogenous leukemia) without prophylaxis. If administered to 100 patients, then the number of cases of candidemia would be expected to be reduced from 10 to 2.

Averting candidemia is clearly an important benefit for 8 of 100 patients, but we have insufficient evidence to judge the overall benefit of prophylaxis for the entire group of 100 hypothetical patients.

The most important goal relates to balancing benefit and toxicity. For example, averting 8 cases of candidemia per 100 patients may not be sufficient benefit if the antifungal drug in question causes substantial toxicity in 20 % or more of patients. In addition, adverse events related to a given drug may not be readily apparent. For example, a drug–drug interaction between the antimicrobial agent and an antineoplastic agent leading to accelerated or impaired metabolism of one of the agents may result in overall greater toxicity or diminished efficacy of the antineoplastic regimen. In this regard, phase III randomized, controlled trials that include an analysis of toxicity and overall survival provide the most definitive data about the overall benefit versus toxicity of an antimicrobial prophylactic strategy.

We also have to consider the risk of antimicrobial prophylaxis selecting for resistant pathogens. Indeed, a component of the Doctor's Dilemma unique to antimicrobial prophylaxis is the danger that such resistant flora poses not only to the individual patient receiving the antimicrobial drug, but also to the larger population. For example, widespread use of quinolone prophylaxis may select for quinolone-resistant bacteria [24, 25] that can be a source of health-care-associated infections with broad effects on a community of patients rather than solely the individual patients receiving the antimicrobial drug.

## 3 Antibacterial Prophylaxis

### 3.1 Neutropenia

In patients with cancer, antibacterial prophylaxis is principally administered to patients with chemotherapy-induced neutropenia. Antibacterial prophylaxis for neutropenia is largely restricted to quinolones and trimethoprim-sulfamethoxazole. In adults, quinolones (principally ciprofloxacin or levofloxacin) are used when the major risk factor is neutropenia (Table 3). Trimethoprim-sulfamethoxazole is most useful in patients with T-cell impairment (e.g., prolonged high-dose steroids, fludarabine, and alemtuzumab) that predispose to *P. jiroveci*.

There is a large randomized clinical trial database supporting the use of quinolones in patients with prolonged neutropenia. A meta-analysis of trials of fluoroquinolone prophylaxis in neutropenic patients showed a clear benefit in reducing aerobic gram-negative rod infections [26]. Engels et al. [26] evaluated 18 trials with 1,408 patients in which quinolones were compared to either placebo or trimethoprim-sulfamethoxazole. Patients who received quinolones had $\sim$80 % fewer gram-negative infections than those without prophylaxis, leading to an overall reduction in total infections. The reduction in fever was small, and in blinded trials, it was not significant. The frequency of quinolone-resistant gram-negative isolates, gram-positive infections, and fungal infections was not significantly affected by quinolone prophylaxis.

**Table 3** Antibacterial agents used as prophylaxis in patients with cancer

| Agent | Usual adult dose(s) as prophylaxis in patients with normal renal function | Spectrum of activity | Comments |
|---|---|---|---|
| Ciprofloxacin | 500 mg twice daily | Active against Enterobacteriaceae (coliforms) and *Pseudomonas aeruginosa*; variable activity against gram-positive organisms including *Staphylococcus aureus*; inactive against anaerobes | Effective in reducing gram-negative rod infections in neutropenic patients; prophylaxis may predispose to an increased frequency of quinolone-resistant gram-negative rods; may increase the risk of viridans group streptococcal infection in patients with acute leukemia receiving mycotoxic regimens |
| Levofloxacin | 500 mg daily | Similar to ciprofloxacin, but increased activity against gram-positive organisms, including *Streptococcus pneumoniae* | Effective in reducing the incidence of fever and hospitalization in neutropenic patients |
| Trimethoprim-sulfamethoxazole | Antibacterial prophylaxis: Studies of trimethoprim-sulfamethoxazole as antibacterial prophylaxis during neutropenia have generally used a dose of one double strength tablet twice daily [96–98] | Active against Enterobacteriaceae but not *P. aeruginosa*; active against *Staphylococcus aureus*, including the majority of community-acquired oxacillin-resistant strains; active against *Pneumocystis jiroveci* | Marrow suppression is a potential concern in patients receiving cytotoxic regimens; Effective as prophylaxis against *Pneumocystis jiroveci* |
| Penicillin | 500 mg twice daily | *Streptococcus pneumoniae* (penicillin-resistant strains are well documented) | In allogeneic HSCT recipients, generally administered from day 100 through the first year and possibly indefinitely in patients with chronic GVHD<br>Prophylaxis may be considered for the first 2 years after splenectomy, corresponding to the highest risk period for pneumococcal sepsis. When feasible, pneumococcal, H. influenzae and meningococcal immunization should be administered at least 2 weeks prior to splenectomy |

Two large randomized, placebo-controlled studies showed benefit of levofloxacin prophylaxis in neutropenic patients at different levels of risk of infectious complications [27, 28]. Levofloxacin has similar activity against gram-negative pathogens compared to ciprofloxacin and ofloxacin, but improved activity against certain gram-positive pathogens, including streptococci. Bucaneve et al. [28] evaluated levofloxacin prophylaxis in adult patients with cancer in whom chemotherapy-induced neutropenia (<1,000 neutrophils/ul) was expected to occur for more than seven days. This protocol excluded patients anticipated to have a short duration of neutropenia who would generally be candidates for outpatient management of neutropenic fever. Levofloxacin recipients had a lower rate of microbiologically documented infections, bacteremias, and single-agent gram-negative bacteremias than placebo recipients. The effects of prophylaxis were also similar between patients with acute leukemia and those with solid tumors or lymphoma. Mortality and tolerability were similar in the two groups.

Cullen et al. [27] evaluated levofloxacin prophylaxis after chemotherapy for solid tumors and lymphomas. The primary outcome was the incidence of clinically documented febrile episodes (temperature >38 °C) attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization. A total of 1,565 patients underwent randomization, 87 % with solid tumors and 13 % with lymphoma. During the entire chemotherapy course, 10.8 % of levofloxacin recipients had at least one febrile episode compared with 15.2 % of placebo recipients ($P = 0.01$). Hospitalization was required for the treatment of infection (suspected and documented) in 15.7 % of patients in the levofloxacin group and 21.6 % of patients in the placebo group ($P = 0.004$). The incidence of severe infections, infection-related mortality, and overall mortality were similar in both groups. Using the primary endpoint of prevention of neutropenic fever in the study by Cullen et al. [27], 1,000 hypothetical patients would have to receive prophylaxis during each cycle of chemotherapy-induced neutropenia to benefit only 44 patients. A secondary analysis of this trial suggested that prophylactic levofloxacin on cycle 1 only of cytotoxic chemotherapy and on subsequent cycles only if the first cycle is complicated by neutropenic fever may be an effective way to target antibacterial use to those patients who would derive the most benefit [29].

Taken together, the main advantage of levofloxacin prophylaxis in intermediate- and higher-risk patients with chemotherapy-induced neutropenia was a reduction in clinically significant bacterial infections, including gram-negative rod bacteremia. In contrast, the main advantage of prophylaxis in lower-risk neutropenic patients was a reduction in fever and hospitalization for neutropenic fever [27]. Neither study conducted a systematic long-term evaluation of antimicrobial resistance.

Gafter-Gvili et al. [30] conducted a meta-analysis of 95 randomized, controlled trials comparing antibiotic prophylaxis with placebo or no intervention or another antibiotic in afebrile neutropenic patients. Antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no treatment. Quinolone prophylaxis reduced the risk for all-cause mortality as well as infection-

related mortality, fever, clinically documented infections, and microbiologically documented infections. Most of the trials involved hospitalized patients with hematological malignancies, and data were inadequate to assess the relationship between duration and degree of neutropenia and relative risk of mortality.

The clinical trial database shows clear advantages of quinolone use in neutropenic patients at high risk for gram-negative rod infections. There are important downsides: potential for selection for quinolone-resistant gram-negative rod infections, increased risk for *Clostridium difficile* colitis, and limited options for outpatient management of neutropenic fever when neutropenic fever develops in patients receiving a quinolone as prophylaxis [31].

The National Comprehensive Cancer Network (NCCN) guidelines advise considering quinolone prophylaxis in patients with expected duration of neutropenia (absolute neutrophil count <1,000/ul) of >7 days [23, 31]. Trimethoprim-sulfamethoxazole should be used instead of a quinolone in patients at risk for *P. jiroveci*. In patients with neutropenia expected to last $\leq$7 days and not receiving immunosuppressive regimens (e.g., systemic corticosteroids), we suggest the strategy of no initial prophylaxis and consideration of outpatient empirical therapy for neutropenic fever in those who meet validated criteria for low risk.

### 3.2 Antibacterial Prophylaxis to Prevent Pneumococcal Sepsis

Patients at high risk for pneumococcal sepsis include those with asplenia (including functional asplenia following splenic irradiation in HSCT recipients) and allogeneic HSCT recipients with chronic GVHD. Penicillin remains the mainstay of anti-pneumococcal prophylaxis, with the understanding that in regions where penicillin-resistant pneumococcal infection is common, alternative agents might be considered (e.g., daily trimethoprim-sulfamethoxazole or a newer generation quinolone). Penicillin-resistant pneumococcal isolates can be cross-resistant to other classes of antibiotics, emphasizing the importance of being familiar with local susceptibility patterns.

## 4 Antiviral Prophylaxis

### 4.1 Herpes Simplex Virus

HSV reactivation occurs with greater frequency in patients with severe neutropenia (e.g., induction therapy for acute leukemia) and in patients with T-cell impairment (e.g., GVHD, T-cell-depleting agent, HIV-infected) (Table 4). Randomized studies have shown the benefit of prophylactic acyclovir in preventing HSV reactivation in patients with acute leukemia [32] and during the neutropenic period following conditioning for HSCT [33].

**Table 4** Antiviral agents used as prophylaxis in patients with cancer

| Agent | Usual adult dose(s) as prophylaxis in patients with normal renal function | Spectrum of activity | Comments |
|---|---|---|---|
| Acyclovir | Total daily dose of 800–1,600 mg, divided two or three times daily | Herpes simplex virus; varicella zoster virus; acyclovir-resistant strains are uncommon in patients with cancer, but should be suspected if breakthrough infection occurs | Effective as prophylaxis against herpes simplex virus (HSV) during neutropenia following induction chemotherapy for acute leukemia and following conditioning for allogeneic HSCT; effective as prophylaxis against varicella zoster virus (VZV) in the first year following allogeneic HSCT; should be considered in other patients at high risk for either HSV or VZV reactivation (e.g., patients receiving purine analogues, bortezomib, alemtuzumab, and other T-cell-depleting agents) |
| Ganciclovir | For cytomegalovirus (CMV) reactivation, dose is IV 5 mg/kg Q12 h for 2 weeks, followed by 5 mg/kg daily maintenance; administer for at least 2 weeks following CMV reactivation and until resolution of CMV antigenemia or PCR detection | Same as acyclovir, plus activity against CMV and HHV-6; acyclovir-resistant HSV or VZV will be cross-resistant to ganciclovir | Prophylaxis or pre-emptive therapy is targeted to allogeneic HSCT recipients and alemtuzumab recipients; ganciclovir is usually well tolerated, but marrow toxicity can be limiting |
| Foscarnet | For CMV reactivation, dose is IV 90 mg/kg Q12 h for 2 weeks, followed by 90 mg/kg daily maintenance; administer for at least 2 weeks following CMV reactivation and until resolution of CMV antigenemia or PCR detection | Same as ganciclovir; no cross-resistance with acyclovir- or ganciclovir-resistant strains | Similar efficacy as ganciclovir for CMV reactivation in allogeneic HSCT recipients; main toxicity is renal and electrolyte wasting |

(continued)

**Table 4** (continued)

| Agent | Usual adult dose(s) as prophylaxis in patients with normal renal function | Spectrum of activity | Comments |
|---|---|---|---|
| Valganciclovir | For CMV reactivation, dose is 900 mg orally twice daily | Same as ganciclovir | Valine ester of ganciclovir enhances oral bioavailability and achieves similar systemic exposure as standard IV ganciclovir regimen |
| Oseltamivir | 75 mg daily | Influenza (resistant strains may occur) | Prophylaxis should be considered during outbreaks of influenza or significant exposure to an index case |
| Zanamivir | 2 oral inhalations (5 mg/inhalation) daily | Influenza (resistant strains may occur) | Prophylaxis should be considered during outbreaks of influenza or significant exposure to an index case |
| Lamivudine | 100 mg daily | Hepatitis B, HIV | Pre-emptive therapy in patients with chronic hepatitis B infections undergoing chemotherapy or HSCT |

## 4.2 Varicella Zoster Virus

Risk factors for VZV differ from HSV in that neutropenia is not per se a significant risk factor for VZV reactivation; rather, impaired T-cell immunity is the major risk factor. In allogeneic HSCT recipients, VZV reactivation generally occurs after day 100 following transplantation. Acyclovir prophylaxis (800 mg orally twice daily) was effective in preventing VZV reactivation within the first year of allogeneic HSCT recipients in which either the donor or recipient was VZV seropositive [34].

T-cell-depleting agents (e.g., fludarabine) and systemic corticosteroids predispose to VZV reactivation. Another group of patients with cancer at high risk for VZV are patients with multiple myeloma treated with bortezomib-containing regimens [35]. As a proteasomal inhibitor, bortezomib may inhibit presentation of viral antigens via MHC-I molecules, thereby disabling VZV immunity.

## 4.3 Cytomegalovirus

Patients with severe T-cell immunodeficiency are at risk for CMV disease. In patients with cancer, allogeneic HSCT recipients are the classic high-risk group. Intensive immunosuppressive therapy for GVHD and T-cell-depleted allografts pose the highest risk of CMV reactivation and disease among allogeneic HSCT recipients [16, 36]. In uncomplicated allogeneic HSCT, the period of risk of CMV disease is generally between 1 and 6 months after HSCT; in the setting of GVHD and intensive immunosuppression, T-cell reconstitution is disabled and the risk of CMV disease persists.

A second group of oncology patients at risk for CMV disease is alemtuzumab recipients. Alemtuzumab treatment results in prolonged and severe lymphopenia. It can also cause neutropenia, as a toxic side effect, in up to one-third of patients. Infections, both opportunistic and non-opportunistic, have been reported in a significant fraction of patients receiving alemtuzumab [11]. CMV reactivation is seen in up to two-thirds of alemtuzumab recipients, although CMV disease seems to be uncommon.

Two approaches are used to prevent CMV disease: prophylaxis and pre-emptive therapy. Prophylaxis involves administering an anti-CMV agent based only on host factors, whereas pre-emption involves using surveillance for CMV reactivation prior to overt disease as a trigger to initiate anti-CMV therapy in high-risk patients. In the pre-emptive strategy, sensitive methods for early CMV diagnosis include detection of the CMV pp65 antigen from peripheral blood leukocytes and of CMV DNA by PCR. Triggers for pre-emptive antiviral therapy are either a single positive CMV antigenemia or two consecutive positive PCR results. Pre-emption is generally preferred over prophylaxis because it limits the use of potentially toxic agents to those patients at highest risk for developing CMV disease.

Intravenous ganciclovir and foscarnet have similar efficacy as pre-emptive CMV therapies in allogeneic HSCT recipients. Oral valganciclovir used as pre-emptive anti-CMV therapy was shown to have acceptable oral bioavailability and

was safe and effective in controlling CMV reactivation in allogeneic HSCT recipients (including in patients with grades I and II GI GVHD) [37–40] and in patients receiving alemtuzumab [41]. Therefore, valganciclovir is an acceptable oral alternative to IV ganciclovir as pre-emptive therapy. Ganciclovir (and valganciclovir) is associated with marrow suppression that may increase the risk of common and opportunistic infections. Foscarnet can cause nephrotoxicity but is generally well tolerated. Cidofovir (a second-line anti-CMV agent) is also associated with nephrotoxicity. Maribavir was safe and effective as pre-emptive anti-CMV therapy in allogeneic HSCT recipients [42], but is not yet FDA approved.

## 4.4 Seasonal and Pandemic Influenza

Community respiratory viruses (e.g., influenza, parainfluenza, adenovirus, respiratory syncytial virus, metapneumoviruses) can cause substantial morbidity and mortality in the highly immunocompromised. Respiratory viruses are of particular concern in patients receiving induction therapy for acute leukemia and allogeneic HSCT recipients. Of the respiratory viruses, influenza, both seasonal and pandemic (e.g., the novel H1N1 strain) is the major pathogen at the broader community level. During community and individual hospital outbreaks, anti-influenza agents (e.g., oseltamivir) administered prophylactically can limit the spread of sensitive influenza strains [43–46]. The database on antiviral prophylaxis against influenza in highly immunocompromised patients with cancer is limited, but suggests that oseltamivir is safe and effective [47, 48]. Since sensitivity to antiviral agents cannot be predicted based on prior seasonal influenza strains, it is important to be aware of the antiviral susceptibility of the specific strain implicated in a seasonal or pandemic outbreak in guiding prophylaxis. Emergence of antiviral resistance while on therapy may also occur [49].

## 4.5 Hepatitis B

Carriers of hepatitis B virus may develop severe hepatitis flares as a complication of cytotoxic chemotherapy. The immunosuppressive effect of the chemotherapy allows virus reactivation in the liver, and the subsequent immune reconstitution may result in hepatocellular damage. Patients with lymphoma seem to be at higher risk, but the phenomenon has been observed in solid tumors, particularly breast cancer [50]. Rituximab therapy can be complicated by severe hepatitis B reactivation. Both autologous [51, 52] and allogeneic [53, 54] HSCT recipients are at risk for hepatic complications from hepatitis B reactivation. Reverse seroconversion—hepatitis B reactivation in patients with immunity based on pre-transplant antibodies to hepatitis B surface antigen and to hepatitis B core antigen—has been reported in allogeneic HSCT recipients [55]. Immunization of donors with hepatitis B vaccine may in principle offer protection to allogeneic HSCT recipients with prior hepatitis B infection [56].

Pre-emptive lamivudine is recommended in patients who are hepatitis B surface antigen positive who will undergo intensive immunosuppressive therapy to avert hepatic complications of viral hepatitis [57]. Lamivudine has been shown to be safe and effective as therapy for patients with hepatitis B infection undergoing HSCT [58]. Lamivudine 100 mg daily started seven days before chemotherapy and continued for eight weeks after completion of chemotherapy significantly reduced the incidence of hepatitis B reactivation and the overall morbidity compared to historical controls [59].

A concern related to lamivudine is the frequent emergence of antiviral resistance with long-term therapy. Tenofovir, a nucleotide analogue and a potent inhibitor of hepatitis B virus polymerase, is likely the most effective drug from long-term control of chronic hepatitis B [60]; however, published data in patients with cancer and HSCT recipients are lacking. Therefore, lamivudine is probably the preferred agent as pre-emption in patients undergoing cytotoxic chemotherapy or HSCT.

## 5 Prophylaxis Against *Pneumocystis Jiroveci*

Defective T-cell immunity is the principal risk factor for *P. jiroveci* infection. The traditional groups of cancer patients at risk have been patients with acute lymphocytic leukemia, allogeneic HSCT, and those receiving prolonged high-dose corticosteroids (e.g., 20 mg of prednisone daily for more than a month) [61]. In allogeneic HSCT recipients, anti-*Pneumocystis* prophylaxis is typically administered from day 30 to 180 after transplant and until resolution of GVHD. Alemtuzumab causes prolonged CD4 lymphopenia, warranting prophylaxis according to the package insert. Prophylaxis should also be considered in patients receiving fludarabine and other purine analogues that cause T-cell depletion (particularly when combined with corticosteroids) and in patients with brain tumors receiving temozolomide and radiation or corticosteroids.

The most effective prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMX). Prophylactic TMP-SMX also has the potential to prevent listeriosis, nocardiosis, and toxoplasmosis. When TMP-SMX cannot be administered due to marrow intolerance or hypersensitivity reaction, second-line agents include: dapsone (100 mg po daily), inhaled pentamidine (300 mg every four weeks), and atovaquone (1,500 mg daily).

## 6 Antifungal Prophylaxis

The two major fungal pathogens in patients with cancer are *Candida* and *Aspergillus* species. *Candida* species are endogenous flora that colonizes the skin, gastrointestinal, and vaginal mucosa. Candidemia generally requires disruption of barriers of the skin (e.g., from a central venous or dialysis catheter) or bowel mucosa (e.g., from bowel trauma or mycotoxic antineoplastic chemotherapy) [62].

Patients with cancer at risk for invasive mold diseases fall into two major groups: prolonged neutropenia and allogeneic HSCT recipients. In neutropenic patients, the degree and duration of neutropenia predict the risk of invasive mold diseases. Patients with relapsed or refractory acute leukemia with prolonged neutropenic from both the underlying disease and multiple cycles of chemotherapy are at particularly high risk for invasive mold diseases. Among allogeneic HSCT recipients, the early period of risk of invasive mold diseases corresponds to neutropenia following the conditioning regimen and later periods correspond to the intensity of immunosuppressive therapy required to control GVHD [63–67].

Diseases by dimorphic fungi (e.g., histoplasmosis and coccidioidomycosis) occur in immunocompetent persons, but are more likely to be severe or disseminated in patients with compromised cellular immunity (e.g., HIV infection, transplant recipients) [68–70]. *C. neoformans* principally causes disease in patients with severe impairment in cellular immunity.

The majority of patients with cancer do not require antifungal prophylaxis. Antifungal prophylaxis is generally restricted to patient with hematological malignancies or HSCT recipients during periods of high risk. Systemic antifungal prophylaxis can be divided into two categories: fluconazole or mold-active agents.

## 6.1 Fluconazole

Fluconazole has activity against yeasts (e.g., *Candida* spp.), but not against *Aspergillus* species and other molds (Table 5). Fluconazole is a safe and effective as prophylaxis against candidemia. Two randomized studies showed the efficacy of fluconazole prophylaxis in the early period following HSCT [71, 72]. In the study by Slavin et al. [72] that included most allogeneic (as opposed to autologous) HSCT recipients, fluconazole prophylaxis administered from day 0 to 75 after HSCT resulted in improved overall survival. A follow-up analysis of patients enrolled in this trial showed that fluconazole conferred significant long-term improvement in survival, possibly by decreasing exposure to pro-inflammatory *Candida* constituents that may induce gastrointestinal tract GVHD [73].

The benefit of fluconazole prophylaxis in patients receiving induction chemotherapy for acute leukemia and in autologous HSCT recipients is not as well established as in allogeneic HSCT recipients. Fluconazole prophylaxis decreased fungal colonization, invasive infection, and fungal-infection-related mortality in non-transplant patients with leukemia and in autologous transplant recipients in a placebo-controlled trial [74]. However, only 30 % of the patients received growth factors, and the median duration of neutropenia was 14–16 days [74]. The benefit of fluconazole prophylaxis was greatest in autologous transplant recipients not receiving colony-stimulating growth factor support and in patients with leukemia receiving mycotoxic regimens consisting of cytarabine plus anthracycline. Other studies of non-transplant patients with acute leukemia showed no significant benefit of fluconazole [75, 76]. In a meta-analysis, antifungal prophylaxis with either azoles

**Table 5** Antifungal agents used as prophylaxis in patients with cancer

| Agent | Usual adult dose(s) as prophylaxis | Spectrum of activity | Comments |
|---|---|---|---|
| Fluconazole | 200–400 mg daily | *Candida* spp., *Cryptococcus neoformans*, dimorphic fungi; no activity against *Aspergillus* spp. and other molds | Effective as yeast-active prophylaxis, but breakthrough candidal infection with resistant strains may occur; dose adjustment required for severe renal impairment; potential for drug–drug interactions regarding hepatically metabolized agents[1] |
| Itraconazole | Total daily dose of 400 mg that can be administered once daily or divided into two equal doses; adjust dosing, aiming for serum trough level of at least 250 ng/ml | Same as fluconazole plus activity against *Aspergillus* species | Effective as anti-*Aspergillus* prophylaxis; solution has better oral bioavailability than capsules, but can be associated with significant gastrointestinal intolerance; negative inotropic properties making it contraindicated in patients with systolic dysfunction or a history of congestive heart failure; potential for drug–drug interactions regarding hepatically metabolized agents; IV formulation (but not the oral drug) should be used with caution in patients with significant renal impairment based on potential for accumulation of the cyclodextrin vehicle |
| Voriconazole | No standard prophylactic dosing given absence of published clinical trials on prophylaxis; 200 mg orally or intravenously twice daily used in a randomized trial in abstract form [91] | Similar to itraconazole, plus activity against some *Fusarium* species | Drug of choice as primary therapy for invasive aspergillosis; visual symptoms are common, but self-limiting potential for drug–drug interactions, regarding hepatically metabolized agents; IV formulation (but not the oral drug) should be used with caution in patients with significant renal impairment based on potential for accumulation of the cyclodextrin vehicle |

(continued)

**Table 5** (continued)

| Agent | Usual adult dose(s) as prophylaxis | Spectrum of activity | Comments |
|---|---|---|---|
| Posaconazole | 200 mg orally three times daily | Similar to voriconazole, plus activity against the majority of zygomycetes | Effective as prophylaxis during neutropenia following induction chemotherapy for acute myelogenous leukemia and myelodysplastic syndrome and in allogeneic HSCT recipients with significant GVHD; must be taken with food (ideally fatty meals) for optimal oral bioavailability |
| Echinocandins (caspofungin, micafungin, anidulafungin) | Prophylactic dose of micafungin is 50 mg/day | *Candida* sp. and *Aspergillus* sp. | Of the echinocandins, only micafungin has been evaluated as prophylaxis (see text); as a class, individual echinocandins have a similar spectrum of activity and good safety profile |
| Amphotericin B formulations | Different dosing for amphotericin B deoxycholate and lipid formulations | Similar to voriconazole, plus activity against azole-resistant *Candida* sp. and zygomycetes; inactive against *Aspergillus terreus* and certain rare molds, such as *Scedosporium* sp. and certain *Fusarium* strains | Given agents better safety profiles (azoles and echinocandins), amphotericin B products are better suited for treatment of proven or suspected invasive fungal infections rather than prophylaxis |

[1]All azoles inhibit cytochrome p450 3A4 isoenzyme, which mediates the metabolism of numerous drugs. The mold-active azoles are more potent inhibitors than fluconazole. Certain agents (e.g., calcineurin inhibitors) require dose adjustment when administered with mold-active azoles, whereas other agents must be used with caution or are contraindicated

or low-dose amphotericin B reduced the frequency of superficial and invasive fungal infection and fungal-infection-related mortality in HSCT recipients and in non-transplant patients with acute leukemia and prolonged neutropenia [77].

Selection of azole-resistant candidal strains is a risk of long-term use. In HSCT recipients receiving fluconazole prophylaxis, *Candida* strains colonizing the mouth and those causing bloodstream infection are likely to be fluconazole resistant [78]. Modes of azole resistance include modification of *ERG11* gene (gene mutation, conversion, and overexpression) that encodes the azole target enzyme, alteration in sterol biosynthesis, and increased expression of genes that encode efflux pumps in which azoles are substrates [79]. Fluconazole-resistant *Candida* strains are frequently cross-resistant to voriconazole and posaconazole [80]. Taken together, fluconazole prophylaxis reduces the frequency of candidemia and other form of invasive candidiasis in specific high-risk patients, but breakthrough candidiasis is likely to be caused by azole-resistant strains, requiring a switch in class of antifungal therapy (e.g., to an echinocandin).

## 6.2 Mold-Active Agents

Itraconazole formulations have been evaluated as prophylaxis in patients with leukemia and in HSCT recipients. The studies vary in design and study populations, including the frequency of invasive aspergillosis in the study arm not receiving a prophylactic mold-active agent. Two randomized trials compared itraconazole solution (the solution has better bioavailability than the capsule formulation) with fluconazole as prophylaxis in allogeneic HSCT recipients [81, 82]. In both trials, prophylaxis was administered during neutropenia following conditioning and during the period corresponding to acute GVHD. When viewed together, the trials showed that itraconazole was protective against aspergillosis, but had more toxicity than fluconazole. One of the trials showed that itraconazole can increase cyclophosphamide metabolites, which in turn are associated with hyperbilirubinemia and nephrotoxicity during the early transplant period [83]. The intravenous formulation of itraconazole is no longer marketed in the USA.

Intravenous formulations of amphotericin B are effective as prophylaxis, but entail a risk of infusional and renal toxicity. Inhalational amphotericin B formulation, which target drug delivery to the lung while avoiding systemic toxicity, would theoretically satisfy the major goal of prophylaxis: efficacy and safety. A randomized trial showed that inhaled liposomal amphotericin B was effective in preventing aspergillosis in patients with hematological diseases and prolonged neutropenia [84].

The echinocandin, micafungin, was superior to fluconazole based on prespecified criteria that included absence of a breakthrough fungal infection and the absence of modifying the antifungal regimen empirically due to neutropenic fever [85]. This randomized trail enrolled a similar proportion of allogenic and autologous HSCT recipients, and the duration of study drug encompassed the

neutropenic period only. The frequency of breakthrough candidemia was similar in both arms, but there was a trend to fewer episodes of invasive aspergillosis in allogeneic HSCT recipients receiving micafungin. Survival and drug-related toxicity were similar in both arms.

Posaconazole was evaluated in two prophylactic trials. The first involved neutropenic patients with MDS or AML receiving induction chemotherapy [86]. Posaconazole recipients had reduced incidence of invasive aspergillosis, fungal infection-related mortality, and overall mortality compared to the standard arm where either fluconazole or itraconazole (depending on the practice of individual study sites) was administered. There was no difference in the overall frequency of adverse events, but a greater frequency of investigator-attributed significant adverse events occurred in posaconazole recipients.

The second study involved allogeneic HSCT recipients with significant GVHD and compared posaconazole with fluconazole in a randomized blinded trial [87]. There was no significant difference in the overall frequency of invasive fungal diseases (the primary endpoint). Prophylaxis with posaconazole led to a reduction in the incidence of invasive aspergillosis, the total number of invasive fungal diseases while on treatment, and the number of deaths attributed to fungal infection. Adverse events were similar in the two arms.

Several limitations to prophylaxis with mold-active agents exist: (1) potential toxicity, including drug–drug interactions in the case of mold-active azoles; (2) sensitivity of serum galactomannan as a diagnostic adjunct is decreased; (3) in the case of posaconazole, patients are required to be able to take the drug orally and ingestion of food (ideally high-fat food) or enteral nutrition is required for optimal bioavailability; (4) added cost; and (5) lack of a clear standard of care for breakthrough aspergillosis in patients receiving a mold-active azole.

Prophylaxis refers to administration of an antifungal drug prior to the onset of fungal disease based on host factors (e.g., prolonged neutropenia or GVHD). Empirical antifungal therapy refers to initiation of antifungal treatment or modifying the antifungal regimen based on persistent neutropenic fever of unknown etiology unresponsive to antibacterial therapy. Both prophylaxis and empirical antifungal therapy can be incorporated into an algorithm; as an example, fluconazole may be initiated as prophylaxis and mold-active therapy may be initiated based on persistent neutropenic fever [88]. An alternative approach is a pre-emptive strategy, in which the use of a mold-active agent is targeted based on a combination of host factors and laboratory markers (e.g., fungal antigen detection or PCR) [89]. A randomized study showed that pre-emptive antifungal therapy was associated with an increased incidence of invasive fungal disease without increasing mortality as compared to empirical antifungal therapy in patients with persistent neutropenic fever [90]. Another study compared the strategy of fluconazole plus real-time serum galactomannan monitoring with voriconazole in allogeneic HSCT recipients [91]. No difference occurred with respect to fungal-infection-free survival and overall survival at six months after transplantation (the primary endpoint). There was a trend to reduced incidence of invasive aspergillosis in voriconazole recipients. This study has only been published in abstract form, but lends additional support to the

pre-emptive strategy in specific patient populations. More research is required to delineate which patients will benefit most from the pre-emptive versus prophylactic approach regarding mold-active agents [92, 93].

We are also learning more about genetic polymorphisms that may predispose to aspergillosis in HSCT recipients [94, 95]; this knowledge may be useful to stratify risk for invasive aspergillosis in patients with classic risk factors (e.g., prolonged neutropenia, GVHD). One of the important areas of future research is to incorporate algorithms that include host genetic factors as well as antigen-based and PCR-based laboratory markers to target patients most likely to benefit from prophylaxis or early treatment with broad-spectrum antifungal agents.

## References

1. Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG (1994) Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK group for immunoglobulin replacement therapy in multiple myeloma. Lancet 343:1059–1063
2. Tsiodras S, Samonis G, Keating MJ, Kontoyiannis DP (2000) Infection and immunity in chronic lymphocytic leukemia. Mayo Clin Proc 75:1039–1054
3. Fisher RI (1982) Implications of persistent T cell abnormalities for the etiology of Hodgkin's disease. Cancer Treat Rep 66:681–687
4. Rhew DC, Gaultier CR, Daar ES, Zakowski PC, Said J (1995) Infections in patients with chronic adult T-cell leukemia/lymphoma: case report and review. Clin Infect Dis 21:1014–1016
5. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328–340
6. Tsiodras S, Samonis G, Keating MJ, Kontoyiannis DP (2000) Infection and immunity in chronic lymphocytic leukemia. Mayo Clin Proc 75(10):1039–1054
7. CGftSoIiCL L (Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia) (1988) Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med 319:902–907
8. Weeks JC, Tierney MR, Weinstein MC (1991) Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia (see comments). N Engl J Med 325:81–86
9. Anaissie E, Kontoyiannis DP, Kantarjian H, Elting L, Robertson LE, Keating M (1992) Listeriosis in patients with chronic lymphocytic leukemia who were treated with fludarabine and prednisone. Ann Intern Med 117:466–469
10. Anaissie EJ, Kontoyiannis DP, O'Brien S et al (1998) Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Intern Med 129:559–566
11. Martin SI, Marty FM, Fiumara K, Treon SP, Gribben JG, Baden LR (2006) Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. Clin Infect Dis 43:16–24
12. Te Boekhorst PA, Lamers CH, Schipperus MR et al (2006) T-lymphocyte reconstitution following rigorously T-cell-depleted versus unmodified autologous stem cell transplants. Bone Marrow Transplant 37:763–772
13. Machatschek J, Duda J, Matthay K, Cowan M, Horn B (2003) Immune reconstitution, infectious complications and post transplant supportive care measures after autologous blood and marrow transplantation in children. Bone Marrow Transplant 32:687–693

14. Crippa F, Holmberg L, Carter RA et al (2002) Infectious complications after autologous CD34-selected peripheral blood stem cell transplantation. Biol Blood Marrow Transplant 8:281–289
15. Marty FM, Rubin RH (2006) The prevention of infection post-transplant: the role of prophylaxis, preemptive and empiric therapy. Transplant Int 19:2–11
16. van Burik JA, Carter SL, Freifeld AG et al (2007) Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. Biol Blood Marrow Transplant 13:1487–1498
17. D'Orsogna LJ, Wright MP, Krueger RG et al (2009) Allogeneic hematopoietic stem cell transplantation recipients have defects of both switched and igm memory B cells. Biol Blood Marrow Transplant 15:795–803
18. Fry TJ, Mackall CL (2005) Immune reconstitution following hematopoietic progenitor cell transplantation: challenges for the future. Bone Marrow Transplant 35(Suppl 1):S53–S57
19. Kulkarni S, Powles R, Treleaven J et al (2000) Chronic graft versus host disease is associated with long-term risk fro pneumococcal infections in recipients of bone marrow transplants. Blood 95:3683–3686
20. Winston DJ, Schiffman G, Wang DC et al (1979) Pneumococcal infections after human bone-marrow transplantation. Ann Intern Med 91:835–841
21. Youssef S, Rodriguez G, Rolston KV, Champlin RE, Raad II, Safdar A (2007) Streptococcus pneumoniae infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989–2005. Medicine (Baltimore) 86:69–77
22. Tomblyn M, Chiller T, Einsele H et al (2009) Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 15:1143–1238
23. Segal BH, Freifeld AG, Baden LR et al (2008) Prevention and treatment of cancer-related infections. J Natl Compr Cancer Netw 6:122–174
24. Carratala J, Fernandez-Sevilla A, Tubau F, Dominguez MA, Gudiol F (1996) Emergence of fluoroquinolone-resistant *Escherichia coli* in fecal flora of cancer patients receiving norfloxacin prophylaxis. Antimicrob Agents Chemother 40:503–505
25. Chen DK, McGeer A, de Azavedo JC, Low DE (1999) Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. Canadian bacterial surveillance network. N Engl J Med 341:233–239
26. Engels EA, Lau J, Barza M (1998) Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 16:1179–1187
27. Cullen M, Steven N, Billingham L et al (2005) Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 353:988–998
28. Bucaneve G, Micozzi A, Menichetti F et al (2005) Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353:977–987
29. Cullen MH, Billingham LJ, Gaunt CH, Steven NM (2007) Rational selection of patients for antibacterial prophylaxis after chemotherapy. J Clin Oncol 25:4821–4828
30. Gafter-Gvili A, Fraser A, Paul M, Leibovici L (2005) Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 142:979–995
31. Segal BH, Freifeld AG (2007) Antibacterial prophylaxis in patients with neutropenia. J Natl Compr Cancer Netw 5:235–242
32. Saral R, Ambinder RF, Burns WH et al (1983) Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. A randomized, double-blind, placebo-controlled study. Ann Intern Med 99:773–776
33. Saral R, Burns WH, Laskin OL, Santos GW, Lietman PS (1981) Acyclovir prophylaxis of herpes-simplex-virus infections. N Engl J Med 305:63–67

34. Boeckh M, Kim HW, Flowers ME, Meyers JD, Bowden RA (2006) Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation–a randomized double-blind placebo-controlled study. Blood 107:1800–1805
35. Chanan-Khan A, Sonneveld P, Schuster MW et al (2008) Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 26:4784–4790
36. Walker CM, van Burik JA, De For TE, Weisdorf DJ (2007) Cytomegalovirus infection after allogeneic transplantation: comparison of cord blood with peripheral blood and marrow graft sources. Biol Blood Marrow Transplant 13:1106–1115
37. Ayala E, Greene J, Sandin R et al (2006) Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 37:851–856
38. Einsele H, Reusser P, Bornhauser M et al (2006) Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. Blood 107:3002–3008
39. van der Heiden PL, Kalpoe JS, Barge RM, Willemze R, Kroes AC, Schippers EF (2006) Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. Bone Marrow Transplant 37:693–698
40. Winston DJ, Baden LR, Gabriel DA et al (2006) Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. Biol Blood Marrow Transplant 12:635–640
41. O'Brien S, Ravandi F, Riehl T et al (2008) Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. Blood 111:1816–1819
42. Winston DJ, Young JA, Pullarkat V et al (2008) Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood 111:5403–5410
43. Khazeni N, Bravata DM, Holty JE, Uyeki TM, Stave CD, Gould MK (2009) Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. Ann Intern Med 151:464–473
44. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M (2007) Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev CD002744
45. Welliver R, Monto AS, Carewicz O et al (2001) Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 285:748–754
46. Hayden FG, Atmar RL, Schilling M et al (1999) Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 341:1336–1343
47. Machado CM, Boas LS, Mendes AV et al (2004) Use of oseltamivir to control influenza complications after bone marrow transplantation. Bone Marrow Transplant 34:111–114
48. Vu D, Peck AJ, Nichols WG et al (2007) Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 45:187–193
49. Cohen-Daniel L, Zakay-Rones Z, Resnick IB et al (2009) Emergence of oseltamivir-resistant influenza A/H3N2 virus with altered hemagglutination pattern in a hematopoietic stem cell transplant recipient. J Clin Virol 44:138–140
50. Yeo W, Zee B, Zhong S et al (2004) Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 90:1306–1311
51. Lau GK, Leung YH, Fong DY et al (2002) High hepatitis B virus (HBV) DNA viral load as the most important risk factor for HBV reactivation in patients positive for HBV surface antigen undergoing autologous hematopoietic cell transplantation. Blood 99:2324–2330

52. Ma SY, Lau GK, Cheng VC, Liang R (2003) Hepatitis B reactivation in patients positive for hepatitis B surface antigen undergoing autologous hematopoietic cell transplantation. Leuk Lymphoma 44:1281–1285
53. Chen PM, Chiou TJ, Fan FS et al (1999) Fulminant hepatitis is significantly increased in hepatitis B carriers after allogeneic bone marrow transplantation. Transplantation 67:1425–1433
54. Seth P, Alrajhi AA, Kagevi I et al (2002) Hepatitis B virus reactivation with clinical flare in allogeneic stem cell transplants with chronic graft-versus-host disease. Bone Marrow Transplant 30:189–194
55. Dhedin N, Douvin C, Kuentz M et al (1998) Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. Transplantation 66:616–619
56. Lau GK, Liang R, Lee CK, Lim WL (1997) Is vaccination of donor adequate for clearance of hepatitis B virus after bone-marrow transplantation? Lancet 349:1626–1627
57. Liang R, How I (2009) Treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 113:3147–3153
58. Lau GK, He ML, Fong DY et al (2002) Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. Hepatology 36:702–709
59. Yeo W, Chan PK, Ho WM et al (2004) Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 22:927–934
60. Marcellin P, Heathcote EJ, Buti M et al (2008) Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 359:2442–2455
61. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D (1992) Pneumocystis carinii pneumonia among patients without AIDS at a cancer hospital. JAMA 267:832–837
62. Bow EJ, Loewen R, Cheang MS, Shore TB, Rubinger M, Schacter B (1997) Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. J Clin Oncol 15:2254–2261
63. Segal BH (2009) Aspergillosis. N Engl J Med 360:1870–1884
64. Wald A, Leisenring W, van Burik JA, Bowden RA (1997) Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 175:1459–1466
65. Jantunen E, Anttila VJ, Ruutu T (2002) *Aspergillus* infections in allogeneic stem cell transplant recipients: have we made any progress? Bone Marrow Transplant 30:925–929
66. Yuen KY, Woo PC, Ip MS et al (1997) Stage-specific manifestation of mold infections in bone marrow transplant recipients: risk factors and clinical significance of positive concentrated smears. Clin Infect Dis 25:37–42
67. Marr KA, Carter RA, Boeckh M, Martin P, Corey L (2002) Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 100:4358–4366
68. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC (2005) Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. Transpl Infect Dis 7:109–115
69. Wheat LJ, Freifeld AG, Kleiman MB et al (2007) Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the infectious diseases society of America. Clin Infect Dis 45:807–825
70. Galgiani JN, Ampel NM, Blair JE et al (2005) IDSA guidelines: Coccidioidomycosis. Clin Infect Dis 41:1217–1223
71. Goodman JL, Winston DJ, Greenfield RA et al (1992) A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation [see comments]. N Engl J Med 326:845–851

72. Slavin MA, Osborne B, Adams R et al (1995) Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation–a prospective, randomized, double-blind study. J Infect Dis 171:1545–1552
73. Marr KA, Seidel K, Slavin MA et al (2000) Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo- controlled trial. Blood 96:2055–2061
74. Rotstein C, Bow EJ, Laverdiere M, Ioannou S, Carr D, Moghaddam N (1999) Randomized placebo-controlled trial of fluconazole prophylaxis for neutropenic cancer patients: benefit based on purpose and intensity of cytotoxic therapy. The Canadian fluconazole prophylaxis study group [In Process Citation]. Clin Infect Dis 28:331–340
75. Kern W, Behre G, Rudolf T et al (1998) Failure of fluconazole prophylaxis to reduce mortality or the requirement of systemic amphotericin B therapy during treatment for refractory acute myeloid leukemia: results of a prospective randomized phase III study German AML cooperative group. Cancer 83:291–301
76. Winston DJ, Chandrasekar PH, Lazarus HM et al (1993) Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial [see comments]. Ann Intern Med 118:495–503
77. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S (2002) Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. Cancer 94:3230–3246
78. Marr KA, Seidel K, White TC, Bowden RA (2000) Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 181:309–316
79. Balkis MM, Leidich SD, Mukherjee PK, Ghannoum MA (2002) Mechanisms of fungal resistance: an overview. Drugs 62:1025–1040
80. Pfaller MA, Messer SA, Boyken L, Tendolkar S, Hollis RJ, Diekema DJ (2008) Selection of a surrogate agent (Fluconazole or Voriconazole) for initial susceptibility testing of posaconazole against *Candida* spp.: Results from a global antifungal surveillance program. J Clin Microbiol 46:551–559
81. Marr KA, Crippa F, Leisenring W et al (2003) Itraconazole versus fluconazole for prevention of fungal infections in allogeneic stem cell transplant patients. Blood 2:2
82. Winston DJ, Maziarz RT, Chandrasekar PH et al (2003) Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. Ann Intern Med 138:705–713
83. Marr KA, Leisenring W, Crippa F et al (2003) Cyclophosphamide metabolism is impacted by azole antifungals. Blood 22:22
84. Rijnders BJ, Cornelissen JJ, Slobbe L et al (2008) Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. Clin Infect Dis 46:1401–1408
85. van Burik JA, Ratanatharathorn V, Stepan DE et al (2004) Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 39:1407–1416
86. Cornely OA, Maertens J, Winston DJ et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359
87. Ullmann AJ, Lipton JH, Vesole DH et al (2007) Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 356:335–347
88. Segal BH, Almyroudis NG, Battiwalla M et al (2007) Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis 44:402–409

89. Maertens J, Theunissen K, Verhoef G et al (2005) Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 41:1242–1250
90. Cordonnier C, Pautas C, Maury S et al (2009) Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 48:1042–1051
91. Wingard JR, Carter SL, Walsh TJ et al (2007) The blood and marrow transplant clinical trials network. Results of a randomized, double-blind trial of fluconazole (FLU) versus voriconazole (VORI) for the prevention of invasive fungal infections (IFI) in 600 allogeneic blood and marrow transplant (BMT) patients. Blood 110: abstract 163
92. Gonzalez AV, Ullmann AJ, Almyroudis NG, Segal BH (2008) Broad-spectrum antifungal prophylaxis in patients with cancer at high risk for invasive mold infections: point. J Natl Compr Cancer Netw 6:175–182
93. Maertens J, Buve K, Anaissie E (2008) Broad-spectrum antifungal prophylaxis in patients with cancer at high risk for invasive mold infections: counterpoint. J Natl Compr Cancer Netw 6:183–189
94. Bochud PY, Chien JW, Marr KA et al (2008) Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med 359:1766–1777
95. Zaas AK, Liao G, Chien JW et al (2008) Plasminogen alleles influence susceptibility to invasive aspergillosis. PLoS Genet 4:e1000101
96. Bow EJ, Rayner E, Scott BA, Louie TJ (1987) Selective gut decontamination with nalidixic acid or trimethoprim-sulfamethoxazole for infection prophylaxis in neutropenic cancer patients: relationship of efficacy to antimicrobial spectrum and timing of administration. Antimicrob Agents Chemother 31(4):551–557
97. Lew MA, Kehoe K, Ritz J, Antman KH, Nadler L, Kalish LA, Finberg R (1995) Ciprofloxacin versus trimethoprim/sulfamethoxazole for prophylaxis of bacterial infections in bone marrow transplant recipients: a randomized, controlled trial. J Clin Oncol 13(1):239–250
98. Figueredo AT, Hryniuk WM, Strautmanis I, Frank G, Rendell S (1985) Co-trimoxazole prophylaxis during high-dose chemotherapy of small-cell lung cancer. J Clin Oncol 3(1):54–64