
Host Impairments in Patients with Neoplastic Diseases

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

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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

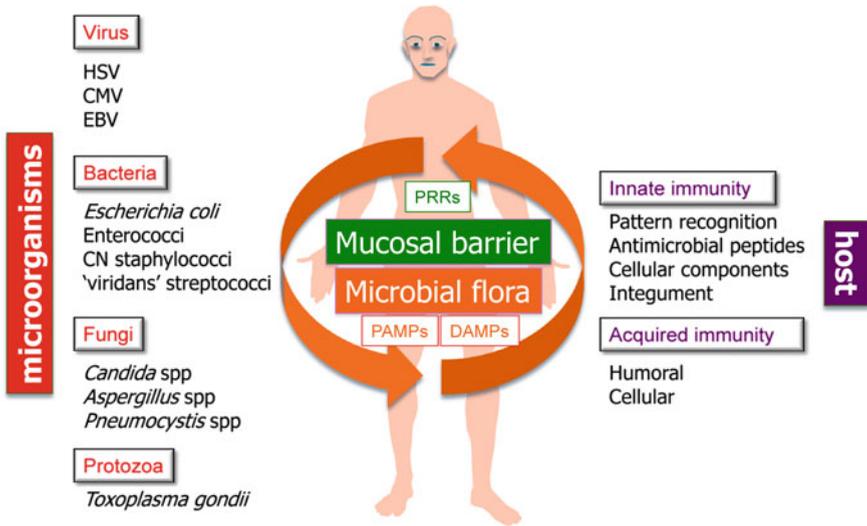


Fig. 1 The balance between the host and the indigenous microbial flora

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

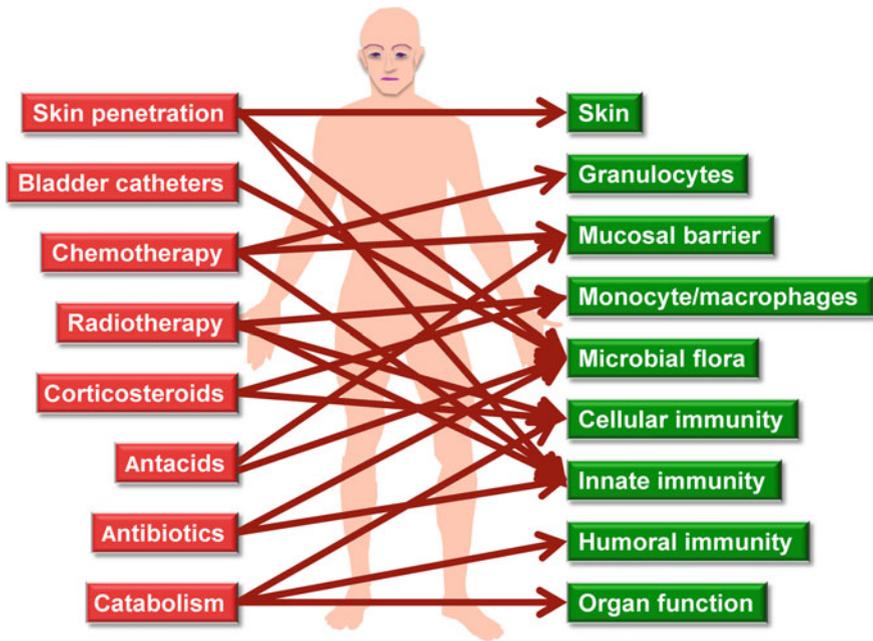


Fig. 2 Evolution of impairment of defense systems after treatment for malignancy

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 place 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 m² 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	<i>Staphylococcus</i> spp.	<i>S. epidermidis</i>
	<i>Micrococcus</i> spp.	
Gram-positive bacilli	<i>Corynebacterium</i> spp.	<i>C. jeikeium</i>
	<i>Brevibacterium</i> spp.	
	<i>Propionibacterium</i> spp.	
	<i>Acinetobacter</i> spp.	<i>A. baumannii</i>
Yeasts	<i>Pityrosporum</i> spp.	
	<i>Candida</i> spp.	<i>C. parapsilosis</i>

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

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	<i>Bacteroides</i> spp.	<i>B. fragilis</i>
	<i>Desulfomonas</i> spp.	
	<i>Leptotrichia</i> spp.	<i>L. buccalis</i>
	<i>Fusobacterium</i> spp.	<i>F. nucleatum</i>
	<i>Butyrivibrio</i> spp.	
	<i>Sucinimonas</i> spp.	
Gram-negative facultatively anaerobic bacilli	<i>Vibrio</i> spp.	
	<i>Escherichia</i> spp.	<i>E. coli</i>
Anaerobic bacilli	<i>Citrobacter</i> spp.	<i>C. freundii</i>
	<i>Klebsiella</i> spp.	<i>K. pneumoniae</i>
	<i>Enterobacter</i> spp.	<i>E. cloacae</i>
	<i>Morganella</i> spp.	<i>M. morganii</i>
	<i>Proteus</i> spp.	<i>P. mirabilis</i>
Gram-positive facultatively anaerobic bacilli	<i>Lactobacillus</i> spp.	<i>L. rhamnosus</i>
Gram-positive anaerobic bacilli	<i>Bifidobacterium</i> spp.	
	<i>Clostridium</i> spp.	<i>C. tertium</i> , <i>C. difficile</i> , <i>C. sporogenes</i>
	<i>Eubacterium</i> spp.	
	<i>Lachnospira</i> spp.	
	<i>Propionibacterium</i> spp.	<i>P. acne</i>
Gram-positive facultatively anaerobic cocci	<i>Enterococcus</i> spp.	<i>E. faecalis</i> , <i>E. faecium</i>
Anaerobic cocci	<i>Staphylococcus</i> spp.	<i>S. epidermidis</i>
	<i>Streptococcus</i> spp.	<i>S. milleri</i> , <i>S. mitis</i> , <i>S. oralis</i> , <i>S. bovis</i>
Gram-positive anaerobic cocci	<i>Peptococcus</i> spp.	
	<i>Peptostreptococcus</i> spp.	
	<i>Acidaminococcus</i> spp.	
	<i>Megasphaera</i> spp.	

(continued)

Table 3 (continued)

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

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 be 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

monocytes, 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 led 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 β -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- β , TSLP, and retinoic acid, epithelial cells contribute to the induction of tolerogenic dendritic 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

<i>Causes of thrombocytopenia</i>	
Disease related	Leukemia and lymphoma, bone marrow metastasis
Treatment related	Chemotherapy, radiotherapy
<i>Causes of thrombocytopathy</i>	
Disease related	Leukemia and myeloma, renal insufficiency
Treatment related	Chemotherapy, β -lactam antibiotics, anti-inflammatory drugs, anti-histamines, 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- α 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 indispensable 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 γ . 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 β -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 γ and Th2 (GATA-3) under the influence of IL-4 and IL-5. Recently, a third subset was discovered, named Th17 (ROR γ t) generated by IL-1, IL-6, TGF- β , and IL-23 [92]. In their effector functions, these Th subsets also differ. Th1 cells release IL-2, IFN γ , and TNF α 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 γ 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

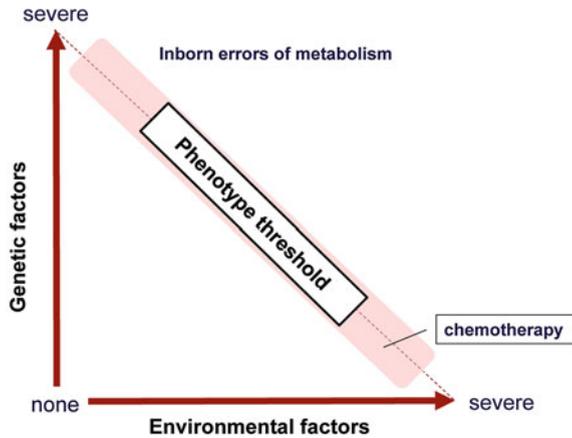
Chemotherapy and radiotherapy inflict severe damage upon the different components of the immune system. Physiologic barriers are breached, immune cells decreased in number resulting in neutropenia, monocytopenia, and various degrees of lymphopenia, often accompanied by functional impairment, and the 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- κ B [99], resulting in the production and release of pro-inflammatory cytokines and chemokines (IL-1, IL-6, IL-8, TNF α , IFN γ) 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/ μ L 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- κ B, is involved in the production of the pro-inflammatory cytokines, TNF- α 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

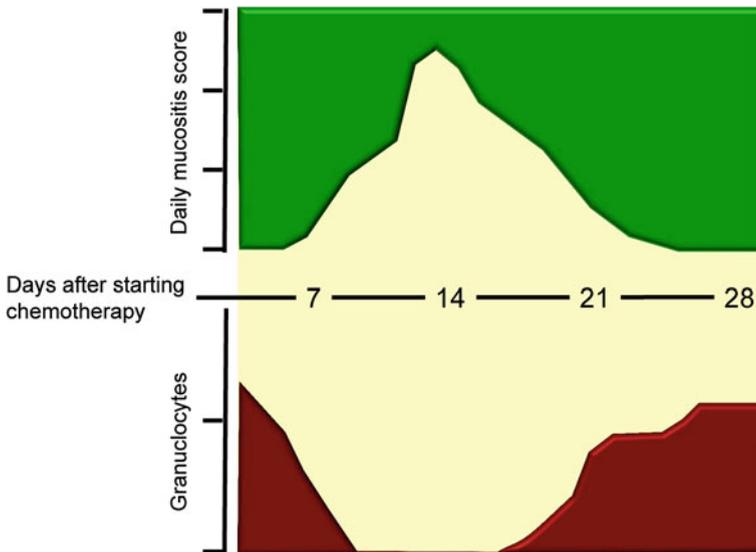


Fig. 4 Oral mucositis and its relationship to neutropenia. Mucositis and bone marrow aplasia, leading to profound neutropenia, are both manifestations of toxicity frequently occurring together with gut toxicity manifested by nausea, vomiting, and diarrhea. As with neutropenia, mucosal changes normally 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*, *Campylobacter* 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.

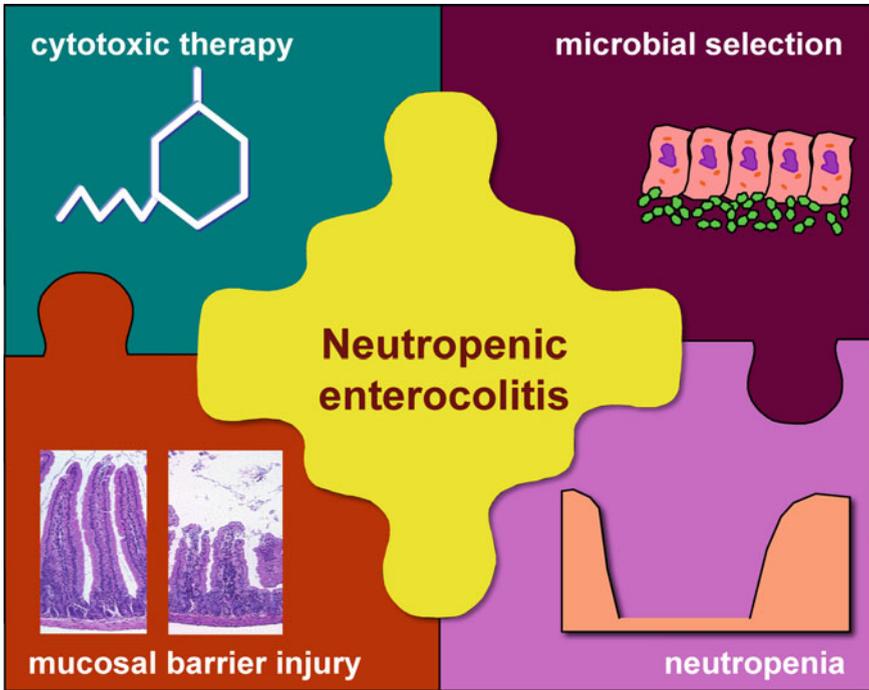


Fig. 5 Neutropenic enterocolitis—an example of MBI-related infection. Neutropenic enterocolitis (also known as typhlitis) is an example of the interplay between the nature of the chemotherapeutic regimen, the mucosal barrier injury it induces, the indigenous microbial flora that remains after exposure 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.

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