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## Keywords

Infection • Prevention • Neutropenia • Immunosuppression

## Introduction and General Principles: A Risk-Targeted Approach

Infection is a frequent complication and a leading cause of morbidity and mortality in patients with hematological malignancies. Problems associated with the management of infections in these patients include difficulties in early diagnosis because the clinical signs of infection are subtle, the low performance of diagnostic tests, and suboptimal response to treatment because recovery of host defenses is a key factor for resolution of infection. Preventing these infections relies on infection control measures and antimicrobial chemoprophylaxis. While infection control measures are safe (but not always effective), the use of antimicrobial agents for prophylaxis of infection is not devoid of problems. Its wide use may

increase the possibility of the development of resistance, select for resistant organisms, and increase toxicity and cost. Therefore, any attempt to administer an antimicrobial agent should be accompanied by a reflection of the potential benefits and risks of prophylaxis.

In general the higher is the incidence of infection the more beneficial is likely to be antimicrobial prophylaxis. Likewise, the shorter is the period at risk (and therefore the predicted duration of prophylaxis) the higher is the possibility that prophylaxis will work. However, the prediction of an incidence of infection is not simple, and requires an analysis of various factors including patient's prior exposure to pathogens, underlying disease, previous and current treatment, comorbidities, geographic area and others. Therefore, three questions are critical in defining the appropriateness of antimicrobial prophylaxis: what is the risk for infection; what are the pathogens that predominate in this setting; and what is the period at risk.

Table 51.1 provides a risk-targeted approach to prophylaxis of infections in patients with hematological malignancies and Table 51.2 presents the most frequent pathogens responsible for infection according to the type of immunodeficiency present. In this chapter, we describe various strategies directed at the prevention of infections in patients with hematological malignancies, according to this risk-based strategy.

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## Infection Control Measures

Patients and healthcare workers should be educated about the risk of and methods to prevent acquisition of pathogens. These methods are discussed in this section.

**Table 51.1** Risk factors for infection in patients with hematological malignancies

Risk factor for infection	Risk category	
	Low	High
<i>General condition including organ function</i>		
Performance status	Good	Poor
Renal failure	No	Yes
Liver failure	No	Yes
Lung disease	No	Yes
Diabetes mellitus	No	Yes
Nutritional status	Normal	Impaired
Iron stores	Normal or decreased	Increased
Age	Younger (<40 years)	Older (>65 years)
Smoking	No	Yes
<i>Underlying disease and its treatment</i>		
Tumor burden	None	Large
Likelihood of obtaining control of the underlying disease <sup>a</sup>	High	Low
Disease-related immunosuppression <sup>b</sup>	Absent	Present
Prior chemotherapy	None or minimal	Extensive
Receipt of purine analogues (fludarabine, cladribine, clofarabine) or monoclonal antibodies (rituximab, alemtuzumab)	No	Yes
<i>Exposure to pathogens</i>		
Prior history of infection <sup>c</sup>	No	Yes
Colonization with pathogens (bacteria, fungi)	No	Yes
Nosocomial exposure to potential pathogens (water and airborne pathogens such as <i>Legionella</i> , <i>Aspergillus</i> spp., and other molds, resistant bacteria, respiratory viruses)	No	Yes
Community-acquired infections, especially respiratory viruses	No	Yes
History of living or visiting areas of endemic infections	No	Yes
<i>Immunogenetics</i>		
Deficiency of MBL	No	Yes
Polymorphism of TLR	Absent	Present
<i>Duration of neutropenia</i>		
	Short (<7 days)	Long (>10 days)
<i>Severity of oral and gastrointestinal mucositis</i>		
	Absent or mild	Severe
Chemotherapy regimen	Less intensive	Intensive
Polymorphisms of genes associated with metabolism of chemotherapeutic agents (pharmacogenetics)	Absent	Present
Renal failure <sup>d</sup>	Absent	Present
<i>T-cell immune reconstitution after HCT</i>		
	Fast	Delayed
Prior chemotherapy	Minimal	Extensive
CMV serostatus	Negative	Positive
Need for additional chemotherapy to control the underlying disease <sup>e</sup>	No	Yes
In vitro manipulation of stem cells <sup>f</sup>	No	Yes
Graft versus host disease and its treatment (in allogeneic HCT)	No	Yes

MBL mannose-binding lectin; TLR toll-like receptors; HCT hematopoietic cell transplantation; CMV cytomegalovirus

<sup>a</sup>Risk assessment in each underlying disease (e.g. age, initial white blood cell count, cytogenetics, immunophenotype, rapidity of cytoreduction in acute lymphoid leukemia; advanced age, de novo vs. secondary leukemia, prior myelodysplasia, cytogenetics, gene mutation profile in acute myeloid leukemia; mutational status of immunoglobulin Vh gene and chromosomal abnormalities in chronic lymphocytic leukemia)

<sup>b</sup>Most common disease-related immunosuppression include: hypogammaglobulinemia (multiple myeloma, low-grade B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukemia), T-cell mediated immunodeficiency (Hodgkin's lymphoma and certain types of non-Hodgkin's lymphoma) and neutrophil dysfunction (acute myeloid leukemia with myelodysplasia)

<sup>c</sup>Infections with higher risk of recurrence include: mycobacteriosis (tuberculosis and others), aspergillosis, pneumocystosis, cytomegalovirus, Herpes simplex and Varicella-zoster virus, toxoplasmosis and strongyloidiasis

<sup>d</sup>Renal failure increases the risk of severe mucositis in patients with multiple myeloma receiving melphalan-based conditioning regimens

<sup>e</sup>Need for additional chemotherapy in lymphoma and acute myeloid leukemia is usually related to relapse of the underlying disease, whereas in multiple myeloma additional chemotherapy is usually part of the treatment strategy

<sup>f</sup>In vitro manipulation of stem cells decreases the content of CD34+ and T-cells, increasing the duration of neutropenia in the early post-transplant period and delaying T-cell immune reconstitution after transplant

**Table 51.2** Pathogens likely to cause infection in patients with hematological malignancies according to the predominant type of immunodeficiency

	Skin and mucous membrane disruption	Hypogammaglobulinemia	T-cell mediated immunodeficiency	Neutropenia and neutrophil dysfunction
<i>Bacteria</i>				
Gram-positive cocci				
Coagulase-negative staphylococci	+++	–	–	++
<i>Staphylococcus aureus</i>	+++	–	–	++
Viridans streptococci	+++	–	–	++
Enterococci	++	–	–	++
<i>Streptococcus pneumoniae</i>	–	+++	–	–
Gram-positive bacilli				
<i>Bacillus</i> spp.	++	–	+	++
<i>Corynebacterium jeikeium</i>	++	–	+	++
<i>Listeria monocytogenes</i>	–	–	+++	–
Gram-negative bacilli				
Enterobacteria <sup>a</sup>	++	–	–	+++
<i>Pseudomonas aeruginosa</i>	++	–	–	+++
Other non-fermentative bacteria <sup>b</sup>	++	–	–	+++
<i>Salmonella</i> spp.	+	+	++	+
<i>Legionella</i> spp.	–	++	++	–
Anaerobes				
<i>Clostridium difficile</i>	++	–	–	++
<i>Clostridium septicum</i>	++	–	–	++
<i>Fungi</i>				
Yeasts				
<i>Candida</i> spp., <sup>c</sup> mucosal disease	+	–	+++	–
<i>Candida</i> spp., <sup>c</sup> invasive disease	++	–	–	+++
<i>Cryptococcus neoformans</i>	–	–	+++	–
<i>Trichosporon</i> spp.	++	–	+	++
Molds				
<i>Aspergillus</i> spp. <sup>d</sup>	–	–	++	+++
<i>Fusarium</i> spp.	–/+	–	++	+++
Zygomycetes	–	–	++	+++
<i>Scedosporium</i> spp.	–	–	++	+++
Agents of phaeohyphomycosis	–	–	+	+
Other				
<i>Pneumocystis jirovecii</i>	–	–	+++	–
<i>Histoplasma capsulatum</i>	–	–	+++	–
<i>Viruses</i>				
Herpes simplex	++	–	+++	++
Varicella-zoster	–	–	+++	–
Cytomegalovirus	–	–	+++	–
Epstein–Barr virus	–	+	+++	–
Respiratory viruses <sup>e</sup>	+	+	++	–
Hepatitis A, B and C	–	+	+	–
Parvovirus	–	++	++	–
<i>Parasites</i>				
<i>Strongyloides stercoralis</i>	–	–	++	–
<i>Toxoplasma gondii</i>	–	–	++	–
<i>Cryptosporidium parvum</i>	–	+	++	–
<i>Mycobacteria</i>				
<i>Mycobacterium tuberculosis</i>	–	–	+++	–
Rapid growing mycobacteria	++	–	+	–
<i>Mycobacterium avium</i> complex	–	–	+++	–

– no; + occasional; ++ frequent; +++ very frequent

<sup>a</sup>Most frequent: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp.

<sup>b</sup>Most frequent: *Acinetobacter* spp., *Stenotrophomonas maltophilia*

<sup>c</sup>Most frequent: *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*

<sup>d</sup>Most frequent: *A. fumigatus* (~90%), *A. flavus*, *A. terreus*, *A. niger*

<sup>e</sup>Most frequent: Respiratory syncytial virus, Influenza A and B, Parainfluenza 1–3, Adenovirus, rhinovirus, coronavirus, metapneumovirus

## Personal Hygiene

### Handwashing

Handwashing remains the simplest and most effective measure to prevent the acquisition of organisms by patients [1]. Patients and healthcare workers (HCW) should wash their hands before eating, smoking, or inserting or removing contact lenses, and after using the restroom, blowing their nose, coughing, sneezing, handling dirty items such as soiled gaussees, or garbage and after touching an animal. In addition, healthcare workers should also wash their hands between patients. All surfaces should be thoroughly cleaned, including wrists, palms, back of hands, fingers and under the fingernails, preferably with an alcohol-based hand rub [2]. However, if hands are visibly dirty or soiled with blood or body fluids, soap and water are best for cleaning hands [3]. Additional recommendations include the removal of rings prior to handwashing, keeping nails short and clean, and avoiding the use of artificial nails as they may carry pathogens [4].

### Skin and Mucosal Care

The skin flora could potentially be a source of infections. Patients should keep their skin clean with daily baths using an antiseptic solution with special attention to potential portals of infection such as the perineum, and catheter sites.

The oral flora can lead to infection especially in the setting of severe mucositis, after radiotherapy, or in patients with graft vs. host disease (GVHD). Recommendations to maintain a good oral and dental hygiene include (a) oral rinses 4–6 times a day with sterile water, normal saline, or sodium bicarbonate; (b) tooth brushing at least twice a day

with a soft or ultrasoft toothbrush. Swabs are less effective, but should be used if the patient cannot tolerate brushings.

### Handling Pets

Pet owners should follow the following recommendations [3, 5]: (a) avoid contact with young animals as pets (higher risk of shedding *Salmonella* spp. and *Campylobacter* spp. because of a higher incidence of diarrhea); (b) obtain veterinarian consultation when a new pet is adopted and yearly thereafter; (c) keep pet's vaccinations current; (d) keep pet's feeding areas clean and its litter box away from kitchen and eating areas; (e) feed pets only with high-quality commercial pet foods, cooked egg, poultry and meat products, and pasteurized dairy products, and avoid access to bowl toilettes and garbage; (f) supervise pets when they are outdoors to prevent contact with other pet's feces; (g) prevent animals from roaming through tick-infested woods; (h) wash hands after handling pets and avoid contact with pet's feces and bird droppings; (i) avoid contact with animals with diarrhea, dogs exposed to shows or kennels, wild birds (especially pigeons), birds with avian tuberculosis, reptiles (high carriage and shedding of *Salmonella* spp.), and swine (source of *B. bronchiseptica*); (j) keep pets away from face and wounds; (k) trim pet's nail short; (l) notify physician immediately if patient is bitten or injured by a pet; (m) instruct kids not to share kisses with the classroom pet; and (n) when cleaning cages, wear a particulate mask and avoid shaking cages.

### Other Personal Hygiene Items including Food Handling

High risk patients should follow additional precautions to prevent serious infections as summarized in Table 51.3.

**Table 51.3** Instructions to give to patients with hematological malignancies

*Apply during periods of severe immunosuppression:* maintain precautions for up to 3 months after last dose of chemotherapy or discontinuation of immunosuppression

#### Personal hygiene

Bathe regularly using a mild soap and shampoo and rinse well

Don't share razors (electric or blade) as they may retain particles of blood

Wash hands frequently, preferably with liquid soap before eating and after contact with contaminated materials. If not washed, keep hands away from eyes nose and mouth

Maintain good dental hygiene, by brushing teeth with soft bristle toothbrush, after meals and floss daily. Do not share toothbrushes and change toothbrush every 3 months

Use disposable vaginal douches, and when menstruating, avoid tampons change sanitary napkins frequently

Use sitz baths or soothing lotion for irritations of the rectum or vagina

Prevent skin dryness (use moisturizing creams)

Keep nails short and clean and avoid nail clippers used by others

Clip toenails straight across to prevent them from becoming ingrown

Try to avoid trauma to and irritation to the nails

Wear cotton gloves for chores that don't involve water and rubber gloves for chores involving water

Avoid unprotected sexual exposure (HIV, *Human papillomavirus*, *Herpes simplex*, *Hepatitis B*)

(continued)

**Table 51.3** (continued)

Environment
Discourage visits by individuals with respiratory infections
Avoid crowded places
Don't share towels with others
Keep house and rooms well ventilated and change air-filters regularly
Encourage household members to get influenza vaccine
Avoid swimming (particularly in stagnant water)
Ask your doctor for preventive measures before travel
Avoid exploring caves, cleaning chicken coops (histoplasmosis)
Other patients
Avoid close contact with infected patients (tuberculosis, herpes zoster, herpes simplex, other)
Medication/Vaccination
Before traveling, consult your physician and take all medications
Have vaccines according to recommendation of your clinician
Food/Water
<i>Precautions for food handling</i>
Cook food thoroughly, wash fruits/vegetables before eating
Wash dishes and silverware in hot soapy water and dry then very well
Keep uncooked meats separate from vegetables, fruits and wash hands, knives, and cutting boards after handling uncooked foods & clean kitchen surfaces that have come in contact with raw meat
Avoid using tap water for drinking or making juices, other food items
Refrain from skinning animals or cleaning seafood
Use plastic bags in all trash cans for proper disposal
At the supermarket, pick up perishables last and take them home promptly
Defrost meat, turkey, chicken in the refrigerator
Wash the meat before cooking
Cook thoroughly eggs and meat (use thermometers)
Clean your refrigerator regularly discarding food of >3–4 days age, especially salad dressings, sauces, milk and egg products, condiments, processed meats, bacon
Never use canned foods if the can is swollen dented, or rusted
Toss out any cheese or food that's moldy. Cut up fresh cheeses into small portions and store separately in the freezer, taking out only what can be used up quickly
Keep cold foods cold (<40 °F) and hot foods hot (>140 °F)
When preparing foods, the hands should be kept away from the hair, mouth and nose. If possible, rings and jewelry should be removed, because they may harbor germs. Try to limit touching food with the hands at all; use tongs or a fork if possible. After cutting up raw meats, soak the cutting board and all utensils for 30–40 min in solution of one part bleach and eight or nine parts water. One ounce of bleach to a cup of water. All foods that are not going to be cooked should be prepared first; only after those are out of the way, can any raw meat and poultry be prepared
Wash all fruits and vegetables well
Keep food preparation surfaces clean, and use a good dishwashing detergent on the work surface often, especially while handling raw meat, chicken or fish
Never let cats or other animals up on the work surface
Do not prepare food if you have diarrhea or vomiting, or have an open infected sore
Put leftover foods into the fridge right away and divide large leftovers into individual containers (to avoid repeated warming)
<i>Food restrictions</i>
Raw eggs (sometimes used in restaurant-prepared Caesar salad dressing or homemade mayonnaise, eggnog)
Dried, uncooked or undercooked meats, seafood and poultry (to include medium or rare steaks, game, pickled fish or oysters), or food from delis such as cold cuts, hot dogs, tofu, sausage, bacon, cold smoked fish and lox
Unpasteurized commercial fruit and vegetable juices
Unpasteurized milk or cheese products
Soft and aged cheeses such as Feta, Brie, Camembert, blue-veined; Mexican-style cheese, refrigerated cheese-based salad dressings (e.g., blue cheese). <i>Cream cheese, cottage cheese or yogurt (provided they do not contain Lactobacillus.spp) are ok to eat</i>
Unwashed raw vegetables and fruits end those with visible mold
Unpasteurized honey or beer or raw, uncooked brewers yeast
All miso products (e.g., miso soup); tempe (tempeh); mate'tea
All moldy and outdated food products
Herbal preparations and nutrient supplements

## Environmental Precautions

### Hospital Environment

#### Air Precautions

Air quality is important to prevent infections in high-risk patients by airborne organisms such as molds (*Aspergillus* spp or other filamentous fungi), *Legionella* spp. and *Mycobacterium tuberculosis*. Patients at very high risk for invasive aspergillosis (IA) should be placed in sealed rooms with HEPA filters (central or point-in-use) and positive pressure. Air flow should be direct (air intake at one side of the room and air exhaust at the opposite side), and the system should be able to make  $\geq 12$  air exchanges per hour [6]. This group is represented mostly by patients receiving induction chemotherapy for acute myeloid leukemia (AML) and in the pre-engraftment period post-allogeneic hematopoietic cell transplantation (HCT).

The conidia levels in outdoor air vary widely, from 1–5 cfu/m<sup>3</sup> [7] to 2,400 in winter and fall in certain areas [8]. The safe concentration of airborne fungi is not established and probably depends on the patient's immune status. The efficacy of HEPA filters in preventing the entry of contaminated outside air into the hospital was confirmed after the demolition of a building. Despite the increase in the number of conidia of filamentous fungi, no conidia were found in most HEPA-filter equipped areas [9]. Because construction and renovation may increase the concentration of airborne fungi, guidelines have been developed when such activities are taking place close to areas where high-risk patients are cared for [10].

Portable HEPA filters decrease the concentration of airborne fungal spores [11] and their use has successfully prevented the occurrence of fungal infections during building construction [12]. However, it is generally agreed that they are less efficient than central or point-in-use HEPA filters [3].

Airborne fungi have been shown to secondarily aerosolize from a water source [13]. Therefore, preventive measures to limit exposure to water can decrease the airborne concentration of fungal pathogens (see the section on "Antifungal Prophylaxis").

#### Diet

Although no data exist to support a role for sterile or low-level microbial-content (<1,000 CFU/ml of non-pathogenic organisms) diets for patients with hematological malignancy, this practice is generally recommended [3]. A recently published randomized study compared cooked and uncooked diet for patients undergoing induction remission for AML. There were no differences in the rates of episodes of major infection and death [14].

#### Water

The hospital water system can be a reservoir for *Legionella* spp [15], bacteria [16–18], and the opportunistic molds,

especially *Aspergillus* spp [13, 19–21], *Fusarium* spp [22, 23], and *Exophiala jeanselmei* [24]. Potential modes of acquisition of infection include contamination of intravenous solutions, direct contact with skin breakdowns, and aerosolization of fungal spores. Measures to prevent the occurrence of infection depend on the mode of acquisition. It is generally recommended that patients at risk for such infections should avoid direct exposure to contaminated water. In addition, specific measures have been tested, including the use of point-in-use water filters for *Legionella* spp [25] and cleaning water-related structures to prevent aerosolization of fungi [26].

#### Healthcare Workers

Infections can be transmitted from the HCW to the patient. The risk of transmission is high for *Varicella zoster* (VZV), viral conjunctivitis, measles, and tuberculosis, and intermediate for influenza, mumps, *Parvovirus B19*, pertussis, respiratory syncytial virus (RSV), rotavirus, and rubella. Therefore, HCW with any of the previously mentioned infections or with Herpes Simplex Virus (HSV) lesions in lips or fingers should not be in contact with patients [3].

HCW who care for patients with hematological cancer should be immunized against rubella, measles, mumps, influenza, and chickenpox, in addition to the already recommended tetanus and hepatitis B immunization [3].

#### Household Exposure

The recommendations for immunization and precautions that apply to the HCW also apply to close contacts of patients with hematological cancer [3]. Immunization against hepatitis A and B is highly recommended for sexual contacts of patients. In addition, immunization against hepatitis A should be considered for all households of patients with chronic liver disease or living in endemic areas. Oral polio vaccine is contraindicated for all households of patients with hematological cancer since live polioviruses can be transmitted to and cause disease in immunocompromised patients, especially during the first month after vaccination [27]. Patients with hematological cancer should also avoid exposure to individuals with vesicular rash secondary to chickenpox immunization to prevent VZV disease [3].

#### Sexual Partners

Sexually active patients should avoid unprotected sex during the periods of significant immunosuppression to reduce the risk of exposure to CMV, HSV, HIV, HPV, HBV, HBC, and other sexually transmitted infections [3].

#### Invasive Procedures

Procedures that break the integrity of natural barriers such as skin and mucosa should be avoided when possible. Fixed orthodontic appliances and space maintainers should not be

worn during any period of neutropenia to avoid oral trauma and infection. Enemas, suppositories, rectal temperature check or/and rectal examination are contraindicated. Necessary dental procedures should be performed prior to chemotherapy to allow proper healing before neutropenia and mucositis develop [28]. Bone marrow biopsies should be done aseptically to avoid cellulitis and osteomyelitis.

Recommendations for the insertion of indwelling devices include careful cleaning and sterilization of instruments and devices (particularly reusable ones) and guidelines for the prevention of intravascular device-related infections [29]. However, solid evidence to support some of the guidelines for the prevention of intravascular device-related infections is lacking.

## Antimicrobial Prophylaxis

Antimicrobial prophylaxis may be primary, when prevention targets an individual that has not been infected in the past, and secondary, when prevention is used to avoid recurrence of infection in an individual who has been previously infected.

## Antibacterial Prophylaxis

Bacterial infections occur frequently in two settings: neutropenia and hypogammaglobulinemia. As shown in Table 51.2, common bacterial infections in patients with neutropenia include staphylococci, enterococci and viridans streptococci among the Gram-positive bacteria, and enterobacteria and non-fermentative bacteria (especially *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas* spp. among the Gram-negative bacteria.

Because Gram-negative bacteremia may be associated with high mortality rates, strategies of antibacterial prophylaxis during neutropenia have been focused mostly to prevent the occurrence of Gram-negative bacteremia, and the quinolones have been extensively studied. A meta-analysis pooling data from 95 trials showed that quinolones reduced the incidence of fever, documented infections, and mortality associated with infection [30]. A major concern is the development of resistance. Another meta-analysis examined the effect of quinolone prophylaxis on microbial resistance. There was no difference in the incidence of colonization by resistant organisms, or in the rates of infection caused by resistant pathogens [31]. These data, however, must be interpreted with caution, because rates of resistance are very different among different institutions, cities, and countries. As a general rule, once the clinician decides to give prophylaxis with a quinolone for neutropenic patients, a careful attention to the development of resistance is advised.

**Table 51.4** Dosage schedule of antimicrobial agents used in the prophylaxis of infection in patients with hematological malignancies

Disease	Prophylaxis
<i>Bacterial infections</i>	
Neutropenic	Quinolone <sup>a</sup>
Non-neutropenic	TMP–SMX—800 mg/160 mg PO daily or daily quinolone
<i>C. difficile</i> diarrhea	Consider metronidazole prophylaxis (500 mg PO TID) if prior history of CDAD
Tuberculosis	Isoniazid—300 mg PO daily
<i>Fungal infections</i>	
Invasive candidiasis	Fluconazole—200–400 mg PO daily
Invasive aspergillosis	Posaconazole—200 mg TID
Oral and/or esophageal candidiasis	Clotrimazole troches (10 mg, ×5 per day) or fluconazole—100–200 mg PO daily
<i>Pneumocystis jirovecii</i> pneumonia	TMP–SMX—800 mg/160 mg PO daily or ×2 per week, pentamidine—300 mg aerosol monthly, dapsone—100 mg PO daily, atovaquone 1,500 mg PO daily
<i>Viral infections</i>	
Herpes simplex	Acyclovir—200–400 mg PO BID or TID, valacyclovir—500 mg PO TID or famciclovir—500 mg PO TID
Herpes zoster	Acyclovir—400 mg PO BID or TID, valacyclovir—500 mg PO TID or famciclovir—500 mg PO TID
Cytomegalovirus	Ganciclovir—5 mg/kg IV BID or valganciclovir—900 mg/d PO or foscarnet—60 mg/kg IV BID
Influenza virus	Oseltamivir—75 mg PO daily for the duration of the Influenza season. Zanamivir is more appropriate in the presence of viral resistance

TMP–SMX trimethoprim–sulfamethoxazole; PO per os; TID three times a day; QID four times a day; BID twice a day

<sup>a</sup>Includes ciprofloxacin—500 mg PO BID, levofloxacin—500 mg PO daily, moxifloxacin—400 mg PO daily, others

Another concern when using quinolone prophylaxis is the increase in the incidence of infections caused by Gram-positive organism, notably viridans streptococci [32, 33]. A great concern related to such infections is that they may occasionally evolve to shock and respiratory failure [34]. Although most of such infections may be prevented by penicillin or macrolides [35], some strains are resistant to these agents [36]. The use of glycopeptides is not generally recommended for prophylaxis [3]. Table 51.4 shows the usual doses of quinolones in the prophylaxis of bacterial infections in neutropenic patients.

Hypogammaglobulinemia is frequent in chronic lymphocytic leukemia (CLL), multiple myeloma, and in allogeneic HCT recipients who develop GVHD. These patients are at greater risk of developing bacterial infections, particularly by encapsulated bacteria. Intravenous immunoglobulin (400 mg/kg) every 4 weeks may be effective for the prevention of bacterial infections, and this recommendation is supported by randomized controlled studies [37–39].

However, since its use is costly, intravenous immunoglobulin should be reserved to a selected population of patients with repeated episodes of severe infections. A cheaper alternative to immunoglobulin is to give quinolone prophylaxis with levofloxacin (500 mg/day), moxifloxacin (400 mg/day) or sulfamethoxazole–trimethoprim (TMP–SMX) (Table 51.4) [40].

## Antifungal Prophylaxis

Primary prophylaxis against invasive candidiasis is not indicated in all neutropenic patients. In allogeneic HCT recipients, two randomized clinical trials (RCTs) showed that fluconazole reduced the frequency of superficial and systemic candidiasis, as well as infection-related mortality [41, 42]. In one of these trials, fluconazole was given until day +75 post-transplant, and a post hoc analysis of the trial has shown that fluconazole was associated with prolonged protection against invasive candidiasis, even beyond the period of prophylaxis [43].

The benefit of prophylaxis against invasive candidiasis was not as apparent in other settings, such as in patients with acute leukemia [44]. However, the ineffectiveness of fluconazole in non-HSCT neutropenic patients is probably related to the heterogeneity of the populations of neutropenic patients studied (with different incidences of invasive candidiasis) rather than an absence of efficacy. In general, the higher is the risk for the patient to develop severe mucositis during neutropenia, the higher is the risk for invasive candidiasis.

Fluconazole is the drug of choice, usually at a dose of 400 mg daily. Fluconazole is not effective in preventing infection caused by all *Candida* species. *Candida krusei* is intrinsically resistant to fluconazole, and *Candida glabrata* exhibits minimal inhibitory concentrations (MIC) higher than other species. As a consequence, fluconazole is not recommended for the prevention of infection due to these two species.

Other than fluconazole, itraconazole oral solution (but not capsules) [45], voriconazole [46], posaconazole [47], and micafungin [48] and voriconazole [46] effectively prevent the occurrence of invasive candidiasis during neutropenia.

IA usually occurs in the context of prolonged (>15 days) and profound (<100/mm<sup>3</sup>) neutropenia in patients receiving induction therapy for AML or myelodysplasia (MDS), or after myeloablative conditioning regimen for allogeneic HCT [49]. In addition, HCT recipients with GVHD are at high risk for IA. In these patients, severe T-cell mediated immunodeficiency rather than profound and prolonged neutropenia is the main risk factor [50]. More recently, cases of IA have been diagnosed in patients with other hematological malignancies, including patients with CLL receiving treatment with alemtuzumab, and patients with multiple myeloma [51–54].

In the setting of AML/MDS, posaconazole (200 mg 3× per day) was superior to fluconazole or itraconazole oral solution in a large randomized controlled trial, and is considered the drug of choice for anti-*Aspergillus* prophylaxis [47]. By contrast, a reduction in the incidence of IA was not observed in trials comparing itraconazole with fluconazole, and itraconazole was associated with more adverse events [45, 55]. A recent meta-analysis of itraconazole trials suggest that there is a reduction in *Aspergillus* infections but only if a certain threshold of bioavailable dosing is used [56]. Its ability to prevent invasive fungal infections has been associated with trough itraconazole concentrations >500 ng/mL, best achieved with the IV formulation (followed by the oral solution if the gastrointestinal function is intact). The oral capsule formulation suffers from erratic bioavailability and is best avoided.

In allogeneic HCT recipients, itraconazole oral solution resulted in a reduction in the frequency of IA in two trials, but about 25 % of patients discontinued itraconazole because of gastrointestinal side effects [57, 58]. In these trials, prophylaxis was used both in the early pre-engraftment and in the post-engraftment period. Another RCT compared posaconazole to fluconazole in allogeneic HCT recipients who developed GVHD. Although the primary endpoint (incidence of invasive fungal infection from randomization to day 112 of prophylaxis) was not achieved, posaconazole significantly reduced the incidence of IA [59]. Micafungin given during the pre-engraftment period was associated with a trend suggesting ability to prevent aspergillosis. In this trial the incidence of IA was 0.2 % among 425 patients receiving micafungin and 1.5 % among 457 patients receiving fluconazole ( $p=0.07$ ) [48].

Taken together, it seems that mold-active azoles indeed reduce the incidence of IA. These findings, however, should be balanced against our significantly improved ability for the early detection of fungal infections and the potential undesirable consequences including toxicities, drug–drug interactions, costs, emergence of resistance [60]. The application of serial serum galactomannan monitoring has enabled us to make the diagnosis of IA much earlier, with a significant impact in reducing mortality [54]. Indeed, this strategy has been applied in a recently published RCT. In this study, allogeneic HCT recipients were randomized to receive fluconazole or voriconazole from conditioning until day +100 (or more, if patients developed GVHD). Different from previous studies, screening with twice-weekly serum galactomannan was part of the protocol in the two arms, and appropriate antifungal therapy was started based on positive galactomannan tests. In the primary endpoint (fungal-free survival) there were no differences between the two arms, but there was a trend for a lower incidence of IA in the voriconazole arm, with similar survival rates [46]. Therefore, these data suggest that giving an anti-mold agent as prophylaxis or giving fluconazole plus



serial monitoring with serum galactomannan result in similar outcomes. Therefore, several factors should be taken into consideration in determining if prophylaxis is appropriate at a specific treatment center, for a given patient or patient population to target a specific infection or if prophylaxis should be withheld and a diagnostic-based preemptive strategy used instead.

Secondary prophylaxis is indicated for patients who developed an invasive mold infection and will receive treatment for the underlying malignancy that results in immunosuppression, particularly neutropenia and/or T-cell immunodeficiency [61]. Options for secondary prophylaxis include amphotericin B and its lipid formulations, caspofungin, itraconazole, voriconazole and lipid amphotericin B followed by voriconazole [62–66]. In addition to secondary chemoprophylaxis, strategies to abbreviate the duration of neutropenia, such as the use of reduced-intensity conditioning regimens and peripheral blood stem cells, and the use of granulocyte transfusions may be employed [67, 68]. The antifungal agents and doses given as prophylaxis are summarized in Table 51.4.

## Antiviral Prophylaxis

Most viral infections that complicate the course of chemotherapy in patients with hematological malignancies represent reactivation of latent infections, while a minority are due to exogenous acquisition (such as respiratory viruses).

### Cytomegalovirus

Until the early 1990s, Cytomegalovirus (CMV) seropositive allogeneic HCT recipients had a 70–80 % risk of viral reactivation, and one-third of these patients developed CMV disease (mainly pneumonia) [69] with a high fatality rate [70]. The application of preemptive therapy guided by serial monitoring with CMV antigenemia has markedly reduced the incidence of patients who develop overt manifestations and/or die of CMV pneumonia [71]. More recently, quantitative PCR for the detection of CMV DNA and CMV RNA have been introduced as alternatives for the antigenemia [72, 73]. Since these techniques are more sensitive than antigenemia, a threshold for starting preemptive therapy should be established for every group of patients; in other words, a specific number of copies of CMV DNA above which triggers the institution of preemptive therapy in allogeneic HCT may not be the same for patients with less severe immunodeficiency. Indeed, the application of these sensitive biomarkers has revealed that hosts not thought to be at risk for CMV reactivation may indeed have positive CMV PCR quite frequently [74]. Outside the setting of allogeneic HCT, patients at higher risk to develop CMV reactivation include patients with CLL receiving fludarabine or (especially) alemtuzumab [75],

patients with multiple myeloma receiving highly intensive therapies [76], and autologous HCT recipients treated previously with rituximab [77].

Two strategies were reported effective for the prophylaxis of CMV disease in allogeneic HCT recipients: universal prophylaxis and preemptive therapy. Universal prophylaxis is not usually given because this strategy may lead to a significant increase in the incidence of bacterial and fungal superinfections associated with ganciclovir-induced neutropenia and immunosuppression [78], and the occurrence of late CMV disease [70]. Ganciclovir, administered intravenously, is the drug most often used for preemptive therapy. The usual duration of therapy is 2 weeks, provided antigenemia (or PCR) becomes promptly negative. Otherwise, a prolonged course of ganciclovir or maintenance therapy is indicated. Alternatives to ganciclovir include foscarnet and oral valganciclovir [3].

### Herpes Simplex Virus

Reactivation of HSV is frequent in patients with hematological malignancies, especially after induction chemotherapy for acute leukemia, and following conditioning regimens for HCT, and manifests as oral lesions indistinguishable from chemotherapy-induced mucositis [79]. Less frequent manifestations include genital ulcers, esophagitis, hepatitis, and pneumonia. Antiviral prophylaxis against HSV is administered if the patient is seropositive for HSV or conveys a history of recurrent fever blisters, cold sores, or other indications of recurrent HSV infections, particularly if the CD4 counts are low ( $<50/\text{mm}^3$ ). The drug of choice is acyclovir, and should be given prior to or at the time of cytotoxic or myeloablative chemotherapy and continued until bone marrow recovery and/or resolution of mucositis [79]. Alternatives to acyclovir are valacyclovir and famciclovir (Table 51.4).

### Varicella-Zoster Virus

Patients at highest risk for VZV reactivation are those with severe lymphopenia and/or CD4 cytopenia such as patients with lymphoma, leukemia (mainly CLL), heavily treated myeloma patients, HCT recipients and patients receiving fludarabine or alemtuzumab. Without acyclovir prophylaxis, reactivation of VZV is common and can be complicated with severe post-herpetic neuralgia. Visceral dissemination (pneumonitis, meningoencephalitis, and hepatitis) may rarely occur in severely immunocompromised patients [80].

Patients at high risk should avoid contact with persons with VZV disease, as well as vaccine recipients who develop a rash after vaccination. In addition, contact and airborne precautions are recommended if an immunocompromised patient develops VZV disease, in order to decrease the risk of transmission to other patients and to HCW [3].

High-risk patients with a history of recent contact with any person with VZV disease should receive varicella-zoster

immunoglobulin (VZIG) or, as an alternative, acyclovir or valacyclovir [81]. Acyclovir is indicated as prophylaxis against VZV reactivation in allogeneic HCT recipients, usually given for 1 year [82]. In addition, patients with multiple myeloma receiving regimens containing bortezomib should receive prophylaxis because of the high risk of VZV reactivation [76]. The use of VZV prophylaxis in other settings is more debatable, and should be reserved for severely immunosuppressed patients, especially when they develop herpes zoster.

### Epstein–Barr Virus

Patients with Epstein–Barr Virus (EBV) disease may present fever and mononucleosis syndrome. In addition, HCT recipients may present post-transplant lymphoproliferative disease (PTLD). Patients at high risk for PTLD include recipients of matched unrelated, mismatched, or T-cell depleted transplants, recipients of high dose antithymocyte globulin or anti-T-cell monoclonal antibodies, patients with acute and chronic GVHD, and those receiving radiation as part of the conditioning regimen [83].

High risk patients who are EBV seronegative should be advised to avoid close contact with EBV seropositive individuals. Increases in EBV viral load following PPSCT/BMT are common, and are highest in patients at risk for PTLD. The best strategy to prevent PLTD is to serially monitor high-risk patients with serum quantitative PCR technique and giving rituximab preemptively for patients who present EBV replication [84].

### Hepatitis B Virus and Hepatitis C Virus

Patients with hematological malignancies undergoing cytotoxic chemotherapy while infected with Hepatitis B Virus (HBV) have a higher risk for severe liver dysfunction [85]. During therapy-induced aplasia, the possibility of viral replication increases dramatically resulting in acute HBV infection that may be mild, asymptomatic, or chronically progressive leading to fulminant hepatitis. Fulminant hepatitis usually coincides with discontinuation of immunosuppression [86]. Risk factors for reactivation include male gender, younger age, a diagnosis of lymphoma, and positive HBV e antigen [87]. In HCT recipients, the risk of reactivation is as high as 50 % [88]. Although any chemotherapy regimen may result in HBV reactivation, the risk is particularly higher after exposure to corticosteroids, rituximab, and alemtuzumab [89, 90].

Patients with circulating HBV DNA should receive preemptive therapy with lamivudine (100 mg/day). This regimen is effective and relatively nontoxic. However, prolonged exposure to lamivudine may result in the development of resistance. The optimal duration of preemptive therapy is not established, but is usually recommended to be at least 6 months after discontinuation of chemotherapy, to avoid viral reactivation and the development of hepatitis [88, 91].

Patients infected with Hepatitis C Virus (HCV) may receive chemotherapy or HCT without major complications except for a higher risk for sinusoidal obstruction syndrome; the risk for such patients is the development of late cirrhosis, several years after HCT [92]. Patients with HCV should be assessed for the evidence of chronic liver disease. Patients with cirrhosis who are selected for receipt of HCT should not receive conventional conditioning regimens. Although oral ribavirin may clear HCV viremia, its routine use as prophylaxis is not recommended.

### Respiratory Viruses

The respiratory viruses Adenovirus, Influenzae, Parainfluenza, RSV, Rhinovirus, Coronavirus, and Metapneumovirus may cause infections in patients with hematological malignancies. Most of these infections appear to be self-limited, although progression to severe lower respiratory infection may occur [93–96]. The main strategy for prophylaxis of infections by respiratory viruses is to prevent exposure of patients with hematological malignancies to individuals with symptoms of respiratory infections.

Vaccination of household contacts and HCWs for Influenza is recommended during each Influenza season [3]. In addition, patients receiving chemotherapy should also receive the vaccine, considering that they may respond to vaccination and the intervention is safe [97]. However, considering that the response to vaccination may be suboptimal, chemoprophylaxis with neuraminidase inhibitors during a community outbreak has been recommended [3].

Regarding RSV, parainfluenza virus, and adenovirus, while highly immunosuppressive patients may be at risk for severe pneumonia, no formal prophylaxis is available and approved. Therefore prevention of severe disease is best approached by early diagnosis and therapy.

### Other Pathogens

#### Mycobacteria

The incidence of tuberculosis in patients with hematological malignancies is low, even in highly endemic regions. In a study from Spain, the incidence of tuberculosis was significantly higher than the general population among allogeneic but not autologous HCT recipients [98]. In another study, 917 patients with hematological malignancies from Brazil were retrospectively reviewed for a diagnosis of tuberculosis. The prevalence was 2.6 % only; risk factors were an underlying disease associated with significant impairment in CMI (e.g., receipt of fludarabine and corticosteroids) and malnutrition [99]. The problem is that most patients who develop tuberculosis have not had clearly identified risk factors.

Patients should avoid contact with persons with active tuberculosis, as well as environments that may potentially have patients with tuberculosis, such as healthcare facilities and shelters for the homeless. There are no studies testing

antimicrobial prophylaxis in high risk patients. Recently published guidelines for infection prophylaxis in HCT recipients recommend the use of isoniazid (5–10 mg/kg, maximum, 300 mg/day) with pyridoxine 25 mg daily for >9 months and until immunosuppression dosages are substantially reduced in patients with past history of tuberculosis or exposure to someone with active tuberculosis, patients with positive tuberculin test or interferon-gamma release assays without a history of BCG vaccination [3].

### **Pneumocystis Jirovecii**

Reactivation of latent infection is the most common mechanism of pneumonia by *Pneumocystis jirovecii* among immunocompromised patients. Patients at high risk for *Pneumocystis jirovecii* pneumonia (PJP) are those with chronic T-cell immunodeficiency, particularly: children with acute lymphoid leukemia (ALL), HCT recipients, patients receiving purine analogues, monoclonal antibodies, or corticosteroids for long periods [100].

The most effective drug for prophylaxis is TMP–SMX. Accepted dosages include one double-strength tablet (trimethoprim 160 mg + sulfamethoxazole 800 mg) bid 2 days a week, one double-strength tablet (daily or 3 times a week), and one single-strength tablet (trimethoprim 80 mg + sulfamethoxazole 400 mg) daily. The time of initiation and the duration of prophylaxis should be individualized according to the underlying disease and type of treatment. For example, in ALL patients, prophylaxis is usually started at the end of the induction period and discontinued 3 months after completion of maintenance therapy; in HCT recipients it should be started after engraftment and continued as long as immunosuppressive therapy is ongoing, extensive GVHD is present and CD4 count is <200 cells/mm<sup>3</sup>. Alternative agents include: aerosolized pentamidine (given with Respigard II nebulizer 300 mg every month after an initial loading dose given every other week), atovaquone suspension (1,500 mg/day), and dapsone (50 mg bid or 100 mg/day) [3].

### **Toxoplasmosis**

Seropositive patients are at risk of reactivation of toxoplasmosis following HCT. When the recipient and donor are seronegative, special precautions should be taken to avoid primary infection. Those precautions include eating only well-cooked meats (>66 °C), well washed vegetables, cooked eggs, pasteurized milk, sterile water, handwashing after outdoor activities or after handling raw meat or vegetables, using gloves for contact with soil or gardening, avoiding contact with cat litter, and having someone change litter box daily and soak it in boiling water for 5 min.

Reactivation of toxoplasmosis is highest among recipients of T-cell depleted allogeneic PSCT/BMT (5–15 %) and is otherwise rare among other allogeneic recipients (<1 %). The potential toxicities of effective agents preclude routine

prophylaxis against toxoplasmosis. However, preemptive therapy of high-risk patients (positive serology prior to transplantation, T-cell depleted allogeneic transplants) with PCR-based tests is recommended. Primary prophylaxis may be considered in patients with history of ocular toxoplasmosis. Effective prophylaxis includes TMP–SMX, one double-strength tablet daily or 3 times a week, or one single-strength tablet daily, Clindamycin 300–450 mg thrice daily plus pyrimethamine 25–75 mg/day plus leucovorin 10–25 mg, pyrimethamine–sulfadoxine (Fansidar) one tablet (25 mg pyrimethamine/500 mg sulfadoxine)/20 kg weight on day 1 with folinic acid, 50 mg/20 kg on day 2, then daily following engraftment, atovaquone (750–1,500 mg/day), and dapsone 50 mg/day plus pyrimethamine 50 mg/week plus folinic acid 25 mg/week. Fansidar is associated with significant toxicities [101].

### **Other Parasites**

*Strongyloides stercoralis* may cause a fatal disseminated syndrome with intestinal larval invasion and bacterial superinfection. Patients at high risk are those with T-cell immunodeficiency [102]. Patients at risk should avoid contact with outhouses and cutaneous exposure to soil or other surfaces that might be contaminated with human feces. In addition, patients with unexplained eosinophilia, or those who live in, have resided, or traveled to endemic areas should be screened with either stool examinations (≥3 stool examinations), or an enzyme-linked immunosorbent assay (ELISA) [103]. Patients whose screening is positive should receive empiric treatment with ivermectin (200 µg/kg/day for 2 days, repeat after 2 weeks) [104].

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## **Immune Reconstitution**

### **Passive Immunization (IV Immunoglobulin, IVIG)**

Intravenous immunoglobulins may benefit patients with CLL, non-Hodgkin lymphoma, and myeloma who have severe hypogammaglobulinemia (serum IgG levels <500 mg/dL) and recurrent and/or severe infections despite appropriate antimicrobial prophylaxis and immunizations [37–39]. Doses of IVIG of 250 mg/kg every 4 weeks were shown to be as effective as 500 mg/kg every 4 weeks. However, the role of IVIG in the prevention of infections among patients with hematological malignancies is not clear and is unlikely to be superior to that of antibiotic prophylaxis (see the earlier section on “Antibacterial Prophylaxis”).

Among HCT recipients, the major benefit of IVIG is the reduction of acute GVHD in allogeneic HCT. The administration of IVIG for the prevention of infections among these patients with severe hypogammaglobulinemia (serum IgG <400 mg/dL) is commonly practiced but is of unproven value.

**Table 51.5** Immunization after hematopoietic stem cell transplantation (HCT)

Vaccine	Time after HCT (months)	Number and interval of doses	Comments
Diphtheria, tetanus toxoid, pertussis	6–12	3	Acellular pertussis vaccine preferable
Pneumococcal 7-valent conjugate vaccine	3–6	3	The 7-valent pneumococcal conjugate vaccine is preferable; the polysaccharide vaccine can be given subsequently to broaden the immune response
Pneumococcal 23-valent polysaccharide	12	1	
H. influenzae type B	6	3	
Meningococcal	6–12	1	Follow recommendations for the general population in the country/region
Hepatitis B	6	3	
Influenza	4–6	1	Repeat every fall
Measles	24	2	All children and post-transplant seronegative adults
Mumps, Rubella	24	1	
Inactivated polio virus (Salk)	6–12	3	Inactivated polio vaccine should also be used in household contacts
Varicella vaccine	24	1	Limited data regarding safety and efficacy. Should be given only to seronegative patients

*HCT* hematopoietic cell transplantation

*AVOID live vaccines until* patient in complete remission, *and* not receiving immunosuppressive therapy for 6 months *and* has a CD 4+ count >400/ $\mu$ L *and* does not have chronic graft versus host disease

*Live vaccines:* (a) Adenovirus, BCG, Measles-Mumps-Rubella, Oral typhoid, Oral polio, Yellow fever, Varicella zoster; (b) *AVOID* oral polio in household contacts (the polio virus may spread and cause uncontrolled infection)

*AVOID vaccines until CD 4+ counts >200/ $\mu$ L* (unlikely to be effective)

*Consider measuring antibody titers* after vaccination to ensure efficacy and repeat doses until optimal titers achieved

## Active Immunization

The immunization of patients with hematological malignancies undergoing cytotoxic chemotherapy has three goals (a) maintaining the appropriate adult immunization schedule; (b) restoring the immunity that could have been lost after the immunosuppressive treatment; and (c) protecting the patient from the receipt of live vaccines. A suggested schedule for immunization in HCT is shown in Table 51.5.

## Colony-Stimulating Factors (CSF)

Granulocyte colony-stimulating factor (G-CSF) has been shown to reduce the incidence of fever, and duration of antibiotic therapy and hospitalization in some studies. However, a significant reduction of culture-proven infections or mortality has not been shown. The best cost-effective prophylactic use of G-CSF is in settings when the risk of febrile neutropenia is >20 % [105–107].

## Granulocyte Transfusions

Prophylactic GM-CSF or G-CSF elicited granulocyte transfusions remain investigational and may be considered in patients with a history of a neutropenia-related invasive mold

infection (such as aspergillosis or fusariosis) who are expected to be neutropenic for >14 days [108].

## Summary

Infection is a frequent complication and a leading cause of morbidity and mortality in patients with hematological malignancies. In general the higher is the risk for a certain infection the more beneficial is likely to be prophylaxis. Likewise, the shorter is the period at risk (and therefore the predicted duration of prophylaxis) the higher is the possibility that prophylaxis will work. The decision of giving prophylaxis should take into account its potential benefits, but also side effects, costs, induction of resistance, and the potential for drug interactions with antineoplastic drugs. Risk assessment is a key element in defining prophylactic strategies.

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